C H A P T E R - I

SULFA DRUGS : A REVIEW

1

CHAPTER - I

SULFA DRUGS : A REVIEW

1.1 INTRODUCTION :

Specific chemical compounds have been used for the treatment of human diseases of protozoal origin with some success for many years. The usefulness of quinine in maleria[1,2,3] dates from the 17th century. The most important development in the history of chemotherpy was the discovery of antibacterial powers of p-aminobenzene sulfonamide, and its derivatives. This compound is better known as Sulfanilamide, a name long recognised in dye chemistry.

"Sulfadrugs" are found to be effective in the treatment of number of bacterial infections, among them blood poisioning pneumonia, genoorrhe.[4] However, a fair number of such bacterial diseases eg. Tuberculosis,[5-7] typhoid, cholera and the main body of protozoal and viral deseases resist the treatment by sulfadrugs.

The sulfadrugs have a favourable chemotherapeutic Index (C.I.) which is defined.

$$C.I. = \frac{\text{Minimum effective dose (M.E.D.)}}{\text{Maximum tolerated dose (M.T.D.)}}$$

A small numerical value of C.I. indicates an effective drug. Sulfadrugs are widely used drugs because they are effective in cheap and free of the side effects, superinfection and problems of the broad spectrum antibiotics. They are quite safe even when widely used in ambultory patients.

1.2 NOMENCLATURE :

In the naming of such sulfanilamides, the following numbering system has been designated (1.1). The amide nitrogen atom has been designated as N^1 and the amine nitrogen as the N^4. The nomenclature radical is designated as a sulfanilamido group (1.2). N^4 substituted sulfonamide have been prepared by N^1- substituted sulfanilamide and acylchloride or anhydrides. The bacteriostatic actions are present in the parent sulfanilamide. If the N^4-aminogroup is replaced by groups which can be converted into the body to a free amino group, then activity is maintained.

The substitution of N^1-amide nitrogen with various groups result in a wide fluctuation in an activity. The fluctuation is correlated with acid dissociation constant. The sulfonamide, which is non substituted or monosubstituted N^1 amido nitrogen is acidic which readily form salt. The maximum activity shown by those compounds having a pKa value about 6.7 and activity destory if the compounds are either more or less acidic[8].

Substitution of a free sulfonic acid ($-SO_3H$) group for the sulfonamide function destorys activity. But replacement by a sulfinic acid ($-SO_2H$) group and acetylation of N^4-position gives an active compound[9].

N^1-mono and N^1, N^1-dimethyl sulfanilamide are almost as active as sulfanilamide itself in vitro and vivo[10]. The ethyl derivative is less active and activity is negligible in higher alkyl, cycloalkyl and N-cyclopolymethylene compounds.

Hydroxy alkyl derivatives are more active in vivo than the corresponding alkyl analogs, but the blood levels are not maintained due to rapid metabolic oxidation.[10,11]

The presence of halo, hydroxy, alkoxy and mercapto groups in the N^1-alkyl does not change the activity. However, the presence of sulfonic, sulfinic phosphoric, carboxyl and amino groups cause loss of activity.

N^1-phenyl sulfanilamide is 3 to 6 times as active in vitro as sulfanilamide against streptococci, pneumococci and E. coli but is only as active in vivo against streptococci infection.[11] This observation of greater activity in vivo led to intensive study of N^1-hetrocyclic substitution with the hope of decreasing the high toxicity of the phenyl compound.

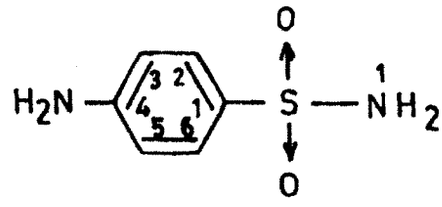
1.3 SULFANILAMIDE :

Sulfanilamide[12,13] (1.3) (P. aminobenzene sulfonamide) is the parent compound of this important class of chemotherapentic agent, because it is used as a drug. Sulfanilamides are discovered by late in 1935 by Trefouel, Nitti and Bovel[14] in posteur institute. They have prepared and tested different products with the help of coupling of diazotised p-aminobenzene sulfonamide with mono or polyphenol. They show antistereptococcic action. The protective action of p-aminobenzene sulfonamide derivatives differing by the substitution on the amide, by the position on the benzene ring of the substituted amines, phenols, halogens etc.

Grey and Stephenson[9] suggest the effectiveness of sulfanilamide and its derivatives against streptococcal and meningococal infection in mice. The results were so convincing that almost any large medical research institute and pharmaceutical manufacturing concern in the world started research on derivatives of sulfanilamide. Intensive pharmacological and clinical work rapidly broadened the field of usefulness of parent compound and its derivatives.

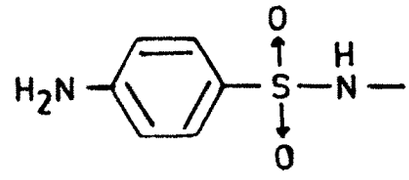
Sulfanilamide is usually prepared by the acetylation method.[15,16] However, the acetylation method involving the four separate steps. It is quite tedious but shorter preparation method[17,18] has been described for sulfanilamide

CHART-I



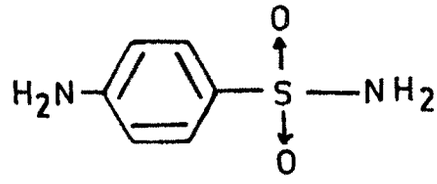
(1·1)

Nomenclature



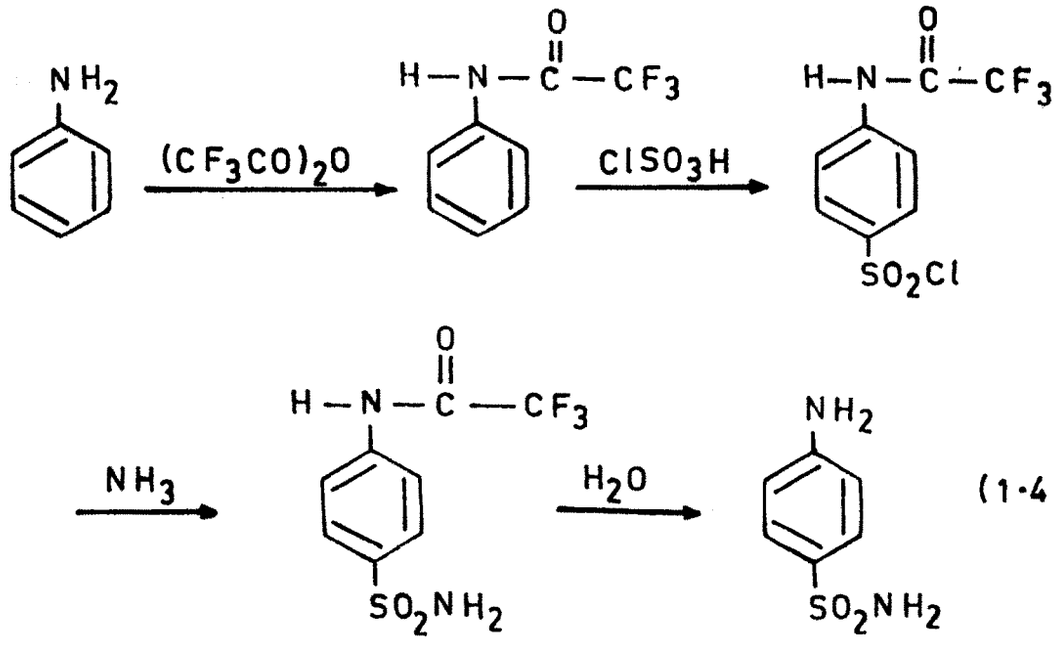
(1·2)

Sulfanilamido group



(1·3)

p-amino benzene sulphonamide



(1·4)

using trifluoroacetyl group as a protective group. In the trifluoroacetylation method (1.4), the first step goes rapidly in non aqueous solution and needs no dry intermediate. The complete process carried within three hours.

Other processes[4,19] for making a variety of sulfisomides are known. Sulfanilamide derivatives commonly used a drug.

Sulfamethyoxydizine[19-21] (2.1) :

It should be protected from light. It is readily absorbed from gastrointestinal tract. It is administered orally as a single daily dose after breakfast.

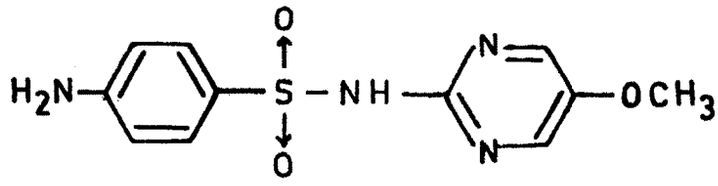
Sufamethoxazole[22-23] (2.2) :

It's acetyl derivatives is testless and, therefore, suitable for oral administration especially in liquid preparation of the drug. The acetyl compound is in the intestinal tract and absorb as sulfamethoxazole.

Sulfapyridine[24] (2.3) :

It was independently synthesised and tested before Whitby's publication by Crossley, Northy and Hutguis.[25] It is prepared by reacting dry acetylsulfonyl chloride with 2-aminopyridine in presence of pyridine as a solvent and

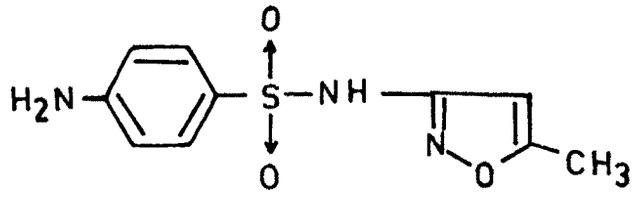
CHART–II



(2·1)

Sulfamethoxydiazine

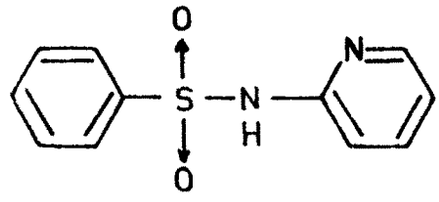
2 (4–aminobenzene sulphonamide) 5 methoxy pyrimidine



(2·2)

Sulphamethoxazole

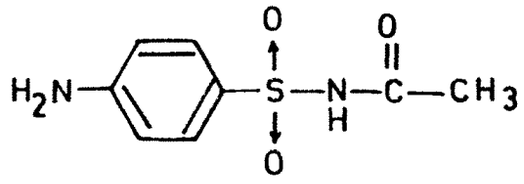
3–(4–aminobenzene sulphonmido)–5–
–methylisoxazolyl sulfonilamide



(2·3)

Sulfapyridine

($\overset{1}{N}$–2–Pyridylsulfanilamide)



(2·4)

Sulfacetamide

($\overset{1}{N}$–acetylsulfanilamide)

hydrochloric acid at 60^{o} to 100^{o}. The reaction mixture may be diluted with water and acidified to precipitate 2-(N^4-acetylsulfanilamide) pyridine and hydrolyse with excess of boiling sodium hydroxide. The soln of sodium sulfapyridine from the hydrolysis is acidified with SO_2 gives the crude sulfapyridine filtered and recrystalisation from alcohol or acetone. Other methods[26,27] are also known.

Its outstanding effect in curing pneumonia because of its high toxicity. The drug is readily acetylated in the body and it results into kidney damage. It is more potent than sulfanilamide in the treatment of streptococcal and gonococcal infections.

Sulfacetamide[28,29] (2.4) :

It is prepared by Dohrn and Diedrich[29] and also independently by Crossley, Northey and Hutquist[30] because of low toxicity it has found favour in the treatment of urinary infections and in the form of its highly soluble neutral sodium salt for ophthalmic and other topical uses.

Sulfaguanidine[30] (3.1) :

It is prepared by condensation of acetylsulfonyl-chloride with guandine nitrate in the presence of excess of sodium hydroxide in an aqueous acetone medium[31] gives sulfaguanidine.

Other methods are also reported for its preparation[32,33].

Large amounts are tolerated by human body without developing of high blood levels and toxic side effect. It is used to infections in intenstine. Having low toxicity used for the treatment of coccidiosis in chickens and for other veterinary purposes.

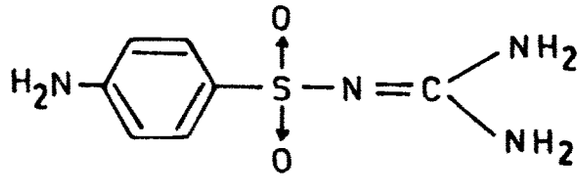
Sulfadiazine[34-38] (3.2) :

2-Aminopyrimidine is condensed with dry acetylsulfanyl chloride in pyridine give 2-(N^4-acetyl sulfanylamide) pyrimidine which is hydrolysed to sulfadiazine with sodium hydroxide. In vivo sulfadiazine is slightly less potent than sulfanilamide. It is absorbed slowly but completely in the intestine. It is also used in number of infections including pneumococcal, meningococcal and H. influenzae infections, cyanosis, acidosis, fever etc.

Sulfamerazine[39-42] (3.3) :

It is prepared by condensing ethylacetoacetate with guanidine which gives 6-methylisocytosine and further procedure of the reaction is similar to sulfadiazine. It maintains high blood levels. It is less toxic and less potent than sulfadiazine.

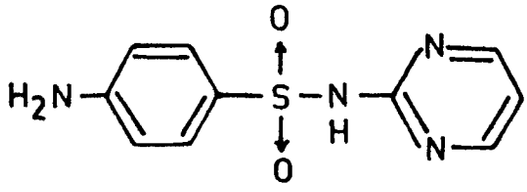
CHART–III



(3·1)

Sulfaguanidine

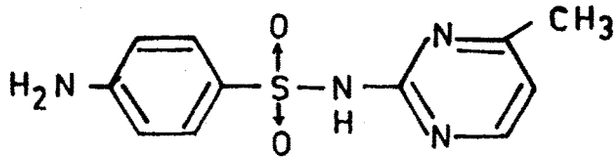
(^{1}N–Guanyl sulfanilamide)



(3·2)

Sulfadiazine

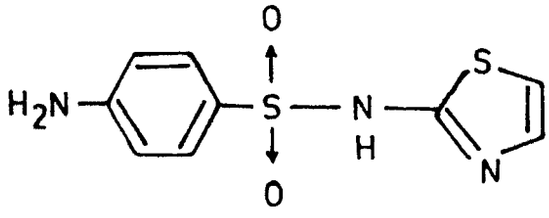
(^{1}N–2–Pyrimidinyl sulfanilamide)



(3·3)

Sulfamirazine

^{1}N–(4 Methyl–2–Pyrimidinyl) sulfanilamide



(3·4)

Sulfathiozole

(^{1}N–2–thiazolylsulfanilamide)

Sulfathiazole[43-45] (3.4) :

It is synthesised from 2-aminothiazole with acetylsulfonyl chloride in dry pyridine and the resulting N^4-acetylsulfathiazole is hydrolysed with sodium hydroxide.

The other process[46] is also known for the preparation of sulfathiazole. It is acetylated rapidly in body tissues and excreted rapidly by the kidney. It is more potent than staphylococcal, pneumococcal and gonococcal infections. It causes less nausea diziness and cyanosis than sulfanilamide.

Sulfisoxazole[47] (4.1) :

It is synthesised from Claisen condensation of propionitrile ethylacetate in the presence of sodium ethoxide gives cyclobutanone further on treatment with hydroxyl amine which undergoes cyclisation gives isoxazole acetylation of isoxazole with sulphonyl chloride gives sulfixazole.

Its solubility is high in body fluid so that it is not deposited in the kidney. It has low toxicity does not require alkalizer on administration. It is more effective in the treatment of gram negative urinary infections.

Sulfisomidine[48] :

Only 10 % of the sulfisomidine in the urine is in the

acetylated form. The side effect of sulfisomidine is similar to those of other sulflonamides.

Sulfadimethoxine[49] :

It absorbs rapidly and causes kidney damage. Sulfameter[50] (4.2) is readily absorbed from the gastrointestinal tract. It is given orally as a single dose preferably after breakfast sulfaethidole.[51] It is useful in urologic therapy.

Sulfa Chloropyridine[52] (4.3) :

This sulfonamide is well tolerated absorb and excreated rapidly in the urine. It is valuable in chronic infection which involves only the urinary tract. Similarly very effective in infections due to proteus vulgaris.

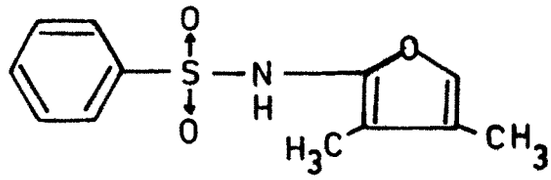
Sulfaphenazole[53-56] (4.4) :

It is readily absorbed from the gastrointertinal tract used in the treatment of urinary tract infections caused by suceptible organism.

Sulfamethizole[57-60] (5.1) :

It is useful for the treatment of urinary tract infection. It is administered to patients for infections who are sensitive to other sulfonamides.

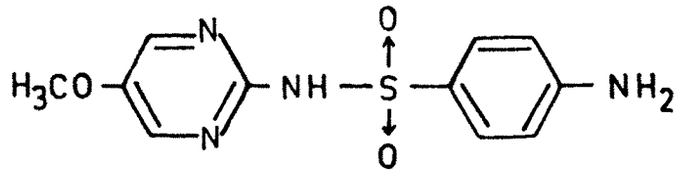
CHART-IV



(4·1)

Sulfisoxazole

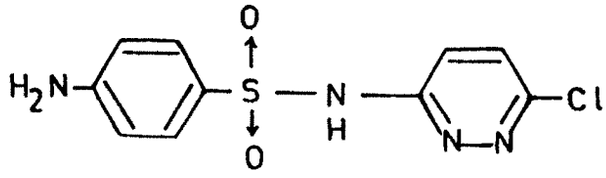
^{1}N-(3-4-Dimethyl-5-isoxalyl) sulfanilamide



(4·2)

Sulfameter

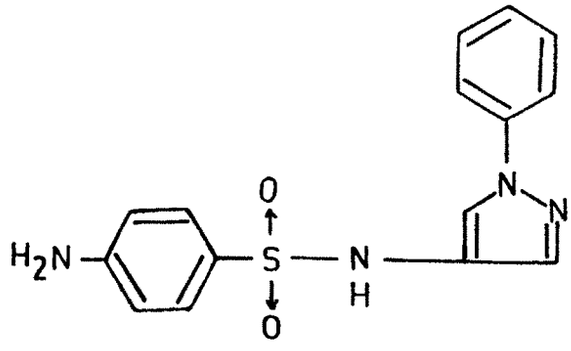
(^{1}N-5-methoxy-2-Pyrimidinyl sulfanilamide)



(4·3)

Sulfachloropyridazine

^{1}N-(6 Chloro-3-Pyridazinyl) sulfanilamide



(4·4)

Sulfaphenazole

(1-Phenyl-5-sulfanilamidopyrazole) sulfanilamide

1.4 N^4-SUBSTITUTED SULFONAMIDE :

N^4-methyl and dimethyl sulfonamides are active in man and mice as dealkylation gives arylamines[61]. Both methyl and dimethyl derivatives are active in vitro, without arylamine formation. The N^4-benzyl and 4-nitrobenzyl derivatives are active in vivo.[62] The N^4-glycosyl derivatives of sulfanilamido hetrocycles active in vitro and vivo.[63]

Succinylsulfathiazole[64,65] (5.2) :

It is prepared from sulfathiazole with succinic anhydride under vigorous controlled condition. It gives the succinyl sulfathiazole. It is less absorbed in gastrointestinal tract and 5 % present in urine and less toxic than sulfaguanidine and used in intestinal infection. It is inactive in vitro.

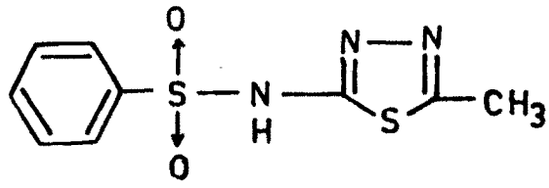
Pthalyl Sulfathiazole[66] (5.3) :

It is synthesised from sulfathiazole with pthalic anhydride under controlled conditions. It is less absorbed in the intestinal tract.

Pthalic Sulfacetamide[66] (5.4) :

It is synthesised from pathalic acid sulfanilamide and acetyl chloride under controlled condition. It diffused in intestinal wall and absorbed into blood stream. It is used an itenstinal antibacterial agent in gastrointestinal infection and abdominal surgery.

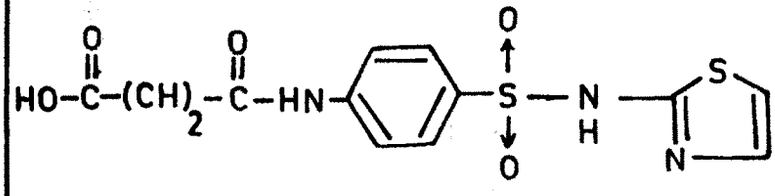
CHART-V



(5·1)

Sulfamethizole

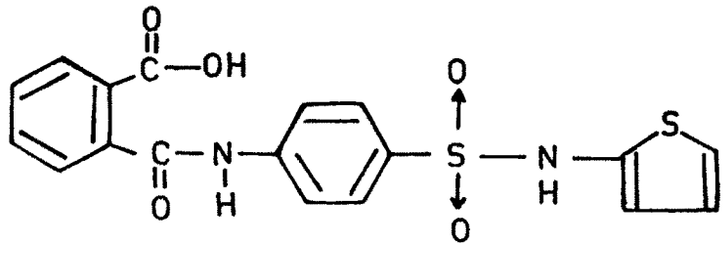
(^{1}N – 5 Methyl – 1,3,4 thiadiazole – 2 yl) Sulphanilamide



(5·2)

Succinyl Sulfathiazole

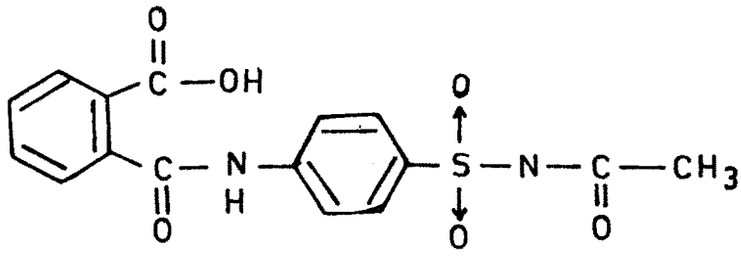
2–(^{4}N–Succinyl sulfanilamido) thiazole



(5·3)

Pthalyl sulfathiazole

2–(^{4}N – Pthalyl sulfanilamido) thiozole



(5·4)

Pthalyl sulfacetamide

^{1}N – acetyl – ^{4}N – pthaloyl Sulfanilamide

1.5 ACTION OF SULFA DRUGS :

Sulfa drugs are bacteriostatic. Several theories of the mechanism are put forth. These theories are such as:

1) Metabolite theories[67]
2) Kuhnand Harris[68]
3) Schmelkes[69]
4) Kuhler[70] resonance theory

Out of which theory the metabolite theory is most attractive due to relatively simple way in which molecular structure is related to drug action.

It has been found that p-amino benzoic acid (PABA) is the most powerful sulfonamide antagonist are inhibitor. PABA is considered to be catalyst in an essential stage of bacterial metabolism. The structural similarity between PABA and sulfonamides suggest that sulfonamide molecule may assume the place of the formal in the metabolite processes.

1.6 APPLICATION OF SULFONILAMIDE DRUGS :

1. All β-homolytic streptococcal infection of ear, nose, throat, other body organs and blood stream, eg. mastoditis, sinusitis, tonsillitis laryngitis, pharyngitis, meningitis, streptococcal pnenumonia, ulcer septicemia etc.

2. Meningococcal infections.

3. Gonococcal infections.

4. Urinary tract infections caused by the above organism or by *E. coli*.

5. Skin infection such as impetigo and erysipelas.

6. Trachoma and gonococcal opthalmia.

7. Surgical incisions, reactions, war wounds etc.

1.7 REFERENCES

1. Cogeshall, L.T., Proc. Soc., Exptl. Biol. Med., 38 768-73 (1938).

2. Peters W. Ann.,Trop. Med. Parasital, 62 (4) 488-94 (1968).

3. Flippin H.F., Schwart Z. L. and Domm A.M., Sulfanilamide and related compounds in general Practice, 2nd Ed. The Year Book Publishers, Inc., Chicago. 121 230-7 (1943).

4. Plaskon Co. U.S. 2, 237-372 (App. 8, 1947).

5. Tabini, Giovanni, Int. Congr. Chemother, Proc. 5th Ed. 2 (2) 909-14 (1967).

6. Vaichnlis J.A.U.S. Patent, 3272352 (6th Sept.,1966).

7. Gertraude, Nebert Bock, Arzneimitted Forsch, 8, 79(1958).

8. Bell P.H. and Roblin R.D.,Jr. J. Am. Chem. Soc. 64 2905 (1942).

9. Gray W.H. Buttle B.A. and Stephenson D.,Biochem. J. 31, 724 (1937).

10. Willeinson S. Antimicrob, Agents Chemotheraph 1966, 651 (1967).

11. Brokmann H.J. Bratton, A.C. Litchfield, J.T. Jr. and Marshall E.K. Jr. J. Pharmacol Exptl. Therap, 72, 112 (1941).

12. Gelmo P.J.,Pract. Chem. 77, 369 (1908).

13. Erdtman H. Progress in Organic Chem. Vol. I Ed. J.N. Cook, Butterworth, London.

14. Rao B.S. Panicker P.B. and Sudbrough J.J. Indian Inst. Sci. 8, 39 (1925).

15. Fieserr Lousis F. 'Organic Experiment' (2nd Ed.) Raytheon Education Compa Lexington, Mass, p.182 (1968).

16. Adams Roger, Jonson J.R. and Wilcox charles F.J.R., Lab. Experiment in Organic Chem. (5th Ed) MacMillan Co. New York, 317, 325 (1963).

17. Weygand Friedrich, and Csendes Ernest, Angew Chem. 64, 136 (1952).

18. Schallenberg Elmer, Eand Calvin, J. Am. Chem. Soc. 77, 2779 (1955).

19. Krememar J. et al Pharmazie 30, 447 (1975).

20. Oster K.A., Drills Pharmacology in Medicine (1971). Magraw Hill, N.Y. 4th Ed. 131 (1971).

21. Balosecuc, Farmacia (Bucharest) 20, 151 (1972).

22. H. Kano and K. Oganta Ann. Rept. Shiongo Res. Lab. 7, 1(1957).

23. C. Rudy and B.Z. Senkowski, Analytical profile of drug substances, 2, 467(1973).

24. R. Winterbottom, J. Am. Chem. Soc., 62, 160 (1940).

25. Crossley M.L. and Northy E.H. and Huttquist M.E., 62 372-4 (1940).

26. Brit. Chem. Abst. 33, 216 (1941).

27. Chem. Abst. 36, 3808 (1941).

28. M.L. Crossley, E.H. Northey and M.E. Hultquist, J.Am. Chem. Soc. 61, 2950 (19

29. Erdlman H., "Perspectives in Organic Chem. Ed. A. Todd, Intersione, N.Y. (1956).

30. Edtman H. Proc. Intern. Congr. Biochem, 4th Congress Vienna, Vol. 2, Pergame Press, London (1958).

31. Swiatowski H. and Zellner, J. Monatsch Chem. 48, 475 (1927).

32. Power F.B. and Chestnut V.K.J., Agr. Res. 26, 69 (1923).

33. Jamieson G.S. Gegetable fats and oils Reinhold Publishing Corporation, N.Y. 1943.

34. R.O. Roblin Jr. J.H. Williams P.S. Winnek and J.P. English J. Am. Chem. Soc. 62, 2002 (1940).

35. Bass A.D. Drills Pharmacology, in Medicine, 1971, MacGraw Hill N.Y. 4th Ed. 1957 (Rev.Pharmacol).

36. Chang C.J. et al J. Mech. Chem. 18, 505 (Pmr) 1975.

37. Kracmar J. et al pharmazie, 30, 447 (1975).

38. Przybylski M. Adv. Mass Spectrum Biochem. Med. 1, 309 (1976).

39. H.J. Backer and A.B. Grevenstuk Rec. Trave. Chim. pays Bas. 61, 291 (1942).

40. Moriguchi I. et al chem. pharmacol 17, 2554 (1969).

41. Chang C.J. et al J. Med. Chem. 18, 505 (1975).

42. Przybylski M. Adv. Mass Spectrum Biochem. Med. 1, 309 (1976).

43. R.J. Fossibinder and L.A. Walter, J. Am. Chem. Soc., 61, 2032 (1939).

44. Kruger G.J. et. al. Acta Crystallogr. Sect. A (Cryst Struct) 28, 272 (1972).

45. Kramcmar J. et. al. Pharmazie, 30, 447 (1975).

46. Foldi Z.U., S. 342, 190 (1943).

47. H.M. Wuest and M. Hoffer, U.S. Patent, 2, 094, 430 (1947).

48. W.T. Coldwell E.C. Kornfeld, and C.K. Donnel, J. Am. Chem. Soc., 63, 2188 (1941).

49. Anon Belg Patent, 618, 639 (1962) Chem. Abst. 59, 7, 540 C (1963).

50. B. Camerino and G. Palmidessi U.S. Patent, 3, 098, 069 (1963).

51. H.Wojahn and H. Wuckel, Arch. Pharm. 284 (19510α

52. M.M. Lester and J.P. English, U.S. Patent.

53. P. Schimidt and J. Druey Helv. Chim. Acta, 41 306(1958).

54. Kracmer J. Pharmazie, 21, 460 (UV) 1966.

55. Moriguchi I. et. al. Chem. Pharm. Bull 17, 2554 (1969).

56. Kracmer J. et.al. Pharmazie, 30, 447 (1975).

57. O. Hubher, U.S. Patent, 2, 447, 702 (1948).

58. Scudi J.V. et. al. J. Org. Chem. 23, 67 (1958).

59. Edwards D.J., Pharm. Pharmacol, 23, 956 (1971).

60. Kracmar J. et. al. Pharmzie, 30, 447 (UV) 1975).

61. R. Lewis and M. Tager Yale, J. Biol. Med. 13, 111 (1940).

62. H.J.White, A.C., Braton, J.T., Litchfield, Jr. and E.K. Marshall Jr. J. Pharmacol Exptal. Therap, 72, 112 (1941).

63. J.Druey, Helv. Chim. Acta, 31, 179 (1948).

64. M.L. Moore and C.S. Miller J. Am. Chem. Soc. 64, 1572 (1942).

65. Miller Rock and Moore, J.A.C.S. 61, 118 (1939).

66. M.L. Moore, U.S. Patent, 2, 324, 013 (1943).

67. Woods D.D. and Fildes, P. Chemistry and Industry, 59, 133-4 (1940).

68. Kuhn R., Weygand F. and Moller E.F., 76 B, 1044-51 (1943).

69. Schmelkes F.C., Wyss O., Marks H.C., Ludwig, B.J. and Strandskav F.B. Proc. Soc. Exptl. Biol. Med. 50, 145-8 (1942).

70. Kumbler W.D. and Daniels, T.C., J.Am, Chem. Soc.65 2190-6(1943).