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# Aspirin (II)

## Structure-Activity Relationship of Salicylates and Improvements of Their Therapeutic Value through Structural Modification[1]

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Since the introduction of aspirin as a therapeutic agent in 1899, there have been numerous attempts at the improvement of its therapeutic value through molecular modification. These endeavors have centered mainly around the following two approaches: (a) improvement of the potency by introduction of a suitable group or groups on the benzene ring; and (b) modification of the carboxylic acid group, which is thought to be an immediate cause of the irritant effect.

Whitehouse studied the relationship between chemical structures of over 80 salicylate analogs and their pharmacological activities using *in vivo* measurements of their phosphorylation uncoupling properties in cartilage and rat liver mitochondria.[2] Several important and interesting conclusions emerged from this study. The presence of the hydroxy group *ortho* to the carboxylic acid group is an essential requirement, although sometimes the hydroxy group could be replaced by other groups such as mercapto or liphophilically substituted amino groups, with retention of the activity. The increase in lipophilic character improved the activity, and the hydrophilic character affected it adversely.[2] A similar conclusion was arrived at by Northover who reported that alkyl-substituted salicylic acids were in general active and that most of the halogenated congeners were active but toxic.[3]

The two isomers of salicylic acid, i.e., 3- and 4-hydroxy-benzoic acids (**2** and **3**, respectively, Figure 2) were inactive in rheumatic fever and in animal antiinflammatory tests.[4,5,6] The lack of activity was thought to be due to inability of the hydroxy group to form a chelate ring with the carboxylic acid group in such compounds.[7] Buss found that *o*-cresotinic acid *(**4**)* is effective in rheumatic conditions,[7] but others[8,9] reported it to be inferior to the salicylate. *m*-Cresotinic acid *(**5**)* had an effect similar to that of sodium salicylate.[8] Amatin *(**6**)* showed analgesic and antipyretic actions without gastric irritation and marked perspiration.[9]

Flufenisal *(**7**)* is a compound chosen for clinical trial after screening some 250 sub-

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stituted salicylic acid derivatives.[10] Although the results of its preliminary clinical trials made with patients suffering from episiotomy pain was very promising,[11] the agent did not show sufficient advantage over aspirin in antiinflammatory trials.[12] Continued and persistent search, however, resulted in the discovery of diflunisal *(**8**)*[13] which was approximately ten times as potent as aspirin in antiinflammatory and analgesic effects in animal tests and was relatively free of gastric hemorrhage.[14] Initial clinical trials in human have shown it to be more potent and to have fewer side-effects than aspirin. Jones, *et al.*[15] synthesized close to one hundred of 4- and 5-substituted heteroaryl salicylic acids. Only a few, however, showed respectable activity. 5-(1-pyrryl) salicylic acid *(**9**)* and its *o*-acetyl derivative which were most active in the series showed antiinflammatory activity almost twice as potent as aspirin. 4-thiazole derivative, **11** was also active. Interestingly, in the case of 5-aryl or heteroaryl salicylic acids, the activities of the free phenolic compounds and their *o*-acetyl derivatives are often comparable *in vivo*.[13] Diflunisal *(**8**)* was slightly more active than its *o*-acetyl congener in animal model.

Recently Lassman, *et al.*[16] reported that 3-(3-carboxy-4-hydroxyphenyl)-2-phenyl-4, 5-dihydro-3H-benzeindole (fendosal, **12**) which is structurally related to 5-(1-pyrryl) salicylic acid possesses an antiinflammatory and analgesic activities superior to aspirin with very low gastric-irritating property compared with aspirin.

Many studies were carried out with dihydroxybenzoic acids because some of them (**13** and **15**) were then thought to be active metabolites of salicylic acid. In general, hydroxy derivatives of salicylic acid, i.e., **13, 14, 15,** and **16** showed favorable therapeutic values[17,18,19] (although there were some contradictory reports), but other dihydroxybenzoic acids such as 3, 4-dihydroxybenzoic acid and 3,5-dihydroxybenzoic acid were inactive. Higher antirheumatic potency (5–10 times) than that of salicylic acid was observed with $\gamma$-resorcylic acid *(**16**)* which has a second hydroxy group *ortho* to the carboxylic acid group.[6,8] Clarke *et al.* claimed that 2,3,6-trihydroxybenzoic acid *(**18**)* was 10 times and 2,4,6-trihydroxybenzoic acid *(**19**)* 8 times more active than salicylic acid in rheumatic fever patients without toxic effect.[18] The enhanced

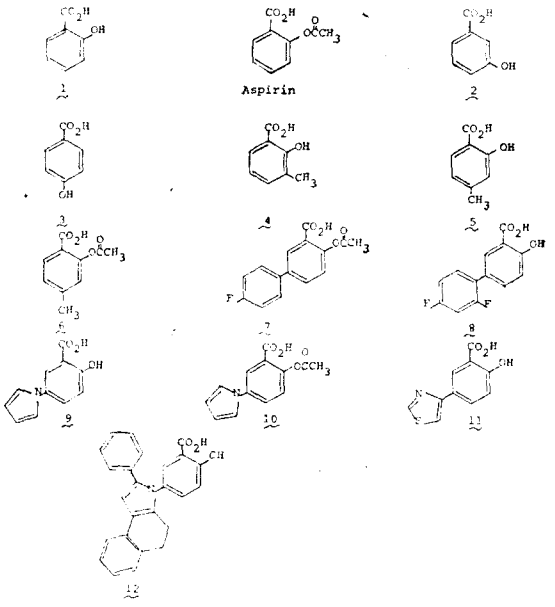


Fig. 1: Hydroxybenzoic acids and derivatives.

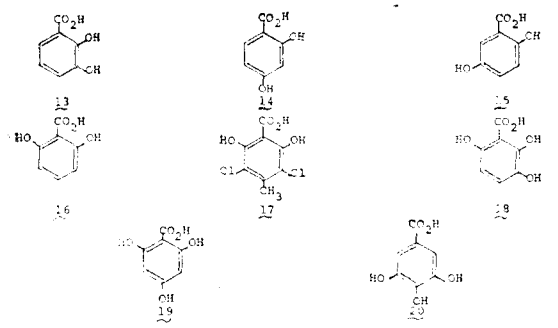

Fig. 2: Dihydroxybenzoic acids and derivatives.

activities of **16, 18** and **19** were viewed as supports for the hypothesis that a chelate ring formation of the *o*-hydroxy group with the carboxylic acid group is an important and necessary feature for the antirheumatic action of hydroxybenzoic acids.

Analgesic and antipyretic actions were retained by the introduction of an additional carboxylic acid group, but antiinflammatory activity appeared to be lost. Antipyretic and analgesic activities comparable to those of aspirin were observed with 4- and 2-hydroxyisophthalic acids.[20]

Methyl salicylate *(**28**)* which is used mainly as a flavoring and perfumery agent has only limited usage as an antirheumatic agent. It is used topically for painful muscles or joints in the form of salves and liniments.[21] Methyl acetoxybenzoate *(**29**)*, the methyl ester of aspirin showed antiedemic activity comparable to aspirin without producing gastric damage when tested in rats.[22]

Salicylamide *(**21**)* had analgesic and antipyretic activities, the potencies of which were no greater than those of aspirin, but showed depression of the central nervous system and smooth muscle in laboratory animals.[23] Although there was no clear indication that salicylamide was a clinically effective antirheumatic agent, it was once used in place of salicylate, particularly for those who were sensitive to aspirin.[24] 2-Acetoxybenzamide was, however, inactive when tested against paw edema in rats.[22]

Among a large number of salicylamide derivatives, a few showed salicylate-like activities comparable to or better than those of salicylate.[25] 2-Allyloxybenzamide *(**22**)* was about three times as potent as salicylamide. *N,N*-Dimethyl-3-phenylsalicylamide *(**23**)* was less toxic and more potent than salicylamide. In general, *N*-methylation, *N*-ethylation, or *N,N*-diethylation increased toxicity. Substitu-

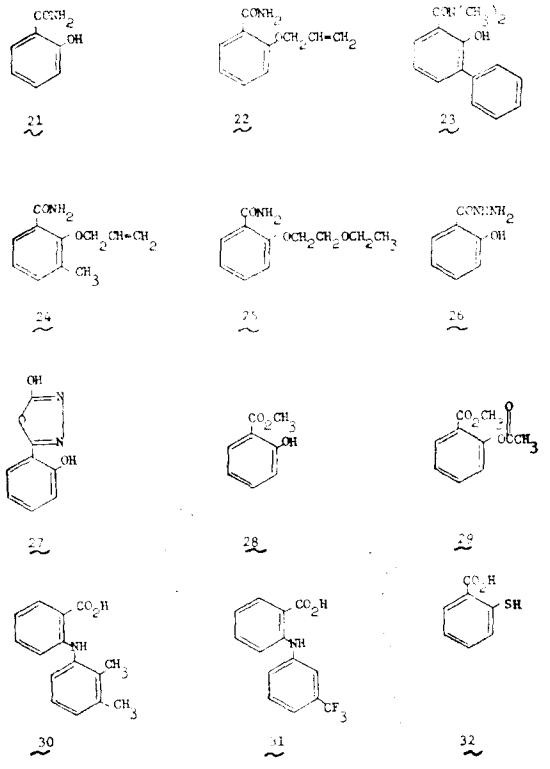

Fig. 3: Various analogs of salicylic acid and aspirin.

tion on the benzene ring at position 3,4 or 5 with phenyl, bromo, hydroxyl, or methoxyl groups generally decreased toxicity but also potency.[25] 3-Methylsalicylamide-2-allylether *(24)* showed antiinflammatory and extremely high analgesic activity when tested in the rat and showed clinical promise.[26] Salicylamide-2-ethoxyethylether *(25)*, once used in Europe as an antirheumatic drug, was later shown to be ineffective.[27]

Since certain benzoic acids, for example, p-aminobenzoic acid, could be converted into the corresponding hydrazide without much change in pharmacologic property, Smith *et al.* prepared salicylhydrazide *(26)* and 5-(*o*-hydroxyphenyl)-1,3,4-oxadizaol-2-01 *(27)* in the hope of reducing the gastric irritating property of salicylic acid. During this change the analgesic and antipyretic properties appeared to remain substantially unchanged, but the antiinflammatory activity was lost.[28]

Although anthranilic and acetylanthranilic acids were inactive, many of the *N*-arylanthranilic acids, such as mefenamic *(30)* and flufenamic *(31)* acids, are therapeutically important antiinflammatory agents.[29]

Recently, Thompkins and Lee studied the analgesic activity of salicylic acid, aspirin, and their isosteres by intraarterial injection in rats treated with bradykinin. In this study none of the isosteres, i.e., anthranilic acid, *N*-acetylanthranilic acid, thiosalicylic acid, or 2-acetonylbenzoic acid, were active. Thiosalicylic acid *(32)* and its acetyl derivatives were toxic.[30]

2-Hydroxypyridine-4-carboxylic acid *(33)* and 3-hydroxypyridine-4-carboxylic acid *(34)* did not show antiinflammatory activity when

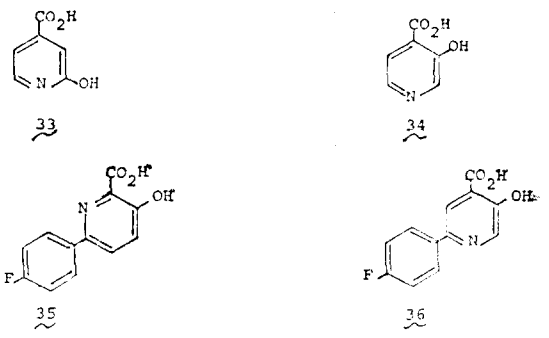


Fig. 4: Heterocyclic analogs of salicylic acid.

tested in guinea pigs.[31] In the carrageenin-induced foot-edema test in rats, the antiinflammatory activity of 35, an aza isostere of flufenisol (7), was better than aspirin, but **32** was inactive.[32]

Numerous salts of aspirin or salicylic acid have been introduced into clinical practice. Aluminum aspirin N.F. *(37)* obtained by maxing aluminum hydroxide gel, water and aspirin, has the advantage of being free of odor and taste, but is poorly absorbed in comparison with aspirin.[33]

Aloxiprin *(38)* is a water-insoluble neutral aluminum aspirin in polymeric form. In human trial this compound was found to cause less gastrointestinal bleeding[34] and much less gastric irritation[35] than aspirin. Aloxiprin is therapeutically as effective as aspirin.

Choline salicylate *(39)* is an extremely water-soluble salt of salicylic acid.[36] Preliminary clinical trial indicated the compound has therapeutic value comparable to that of aspirin, with lesser side effects.[37] Broh-Kahn reported that the agent is absorbed about four times as rapidly as aspirin, and peak plasma levels are reached in 10 minutes.[38]

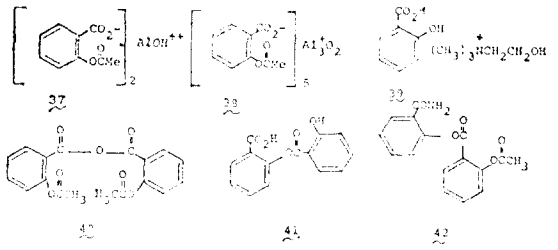

Fig. 5: Neutral salicylates.

Effervescent aspirin preparation, which contains a large excess of sodium bicarbonate and yields a solution of sodium aspirin, on disolution in water did not cause fecal occult blood loss in 31 out of 32 patients and showed good plasma levels.[34] Several other forms of buffered aspirin have been introduced in the past, but none have shown distinctive advantages over plain aspirin in overall therapeutic efficacy.

Enteric-coated aspirin tablets are prepared with a special coating that does not dissolve until it reaches the small intestine, where much of the ingested aspirin is absorbed. In time-released aspirin preparations, small particles of aspirin are encapsulated and bound together in a tablet, thus causing slightly delayed but prolonged absorption.

Recent studies made with rats indicated that the gastric irritancy of aspirin is primarily associated with the carboxylic acid group in aspirin. Rainsford and Whitehouse[39] showed that esterification of the aspirin is one way to attenuate the gastric irritancy while retaining the antiinflammatory activity. Thus when given orally to starved rats, aspirin methyl ester (methyl 2-acetoxy benzoate, **29**) which was absorbed rapidly did not cause gastric damage after 7 daily doses.

Aspirin anhydride (**40**) is an old compound originally prepared by the Bayer Company in 1908; they claimed that it was a superior salicylate. Recently Garrett predicted, based on its physicochemical properties, that aspirin anhydride should be a superior form of aspirin for oral administration.[40] However, in a limited clinical trial this compound was less effective than aspirin as an analgesic and antiinflammatory agent and produced as much gastrointestinal bleeding and dyspepsia.[41] The gastrointestinal absorption of aspirin anhydride was found to be slow and incomplete.[42] Salicylcalicylic acid, **41** which was formed by the self-esterification of salicylic acid had no significant blood loss liability,[43] and salicylamide ester of acetylsalicylic acid, **42** does not possess analgesic activity but is rapidly hydrolyzed in the blood to aspirin and salicylamide.[44]

Recently, copper chelates received considerable attention as potential therapeutic agent for rheumatoid and degenerative diseases. Sorenson reported that copper complexes with a variety of ligands including proven antiathritic drugs possess antiinflammatory acitivity greater than the ligand itself.[45] He claimed that cupric aspirinate [Tetrakis (acetylsalicylato)-$\mu$-dicopper(II)], (**43**) was 20 times more active than aspirin when tested in rats by subcutaneous injection. Furthermore, the copper aspirinate showed potent antiulcer acitivity in contrary to aspirin which causes peptic ulcer in long term use. Similar observations were also made by others with the copper aspirinate.[46,47] Copper salicylate **44**

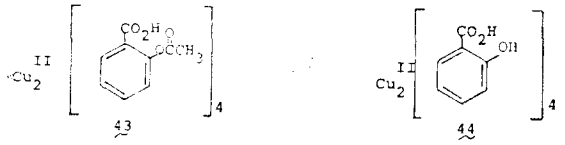

Fig. 6: Copper complexes of aspirin and salicylic acid.

is a therapeutically effective antirheumatic agent: Hangarter[48] used copper salicylate solution (Permalon) for 21 years, from 1950 to 1971 when the manufacture was discontinued for economic reasons, for treatments of many patients with a variety of rheumatic and degenerative diseases. The treatment was accomplished by intravenous administration of Permalon without pathological changes, abnormal reactions or gastrointestinal disturbances.[48]

Dittert, *et al.*[49] studied carbonate esters of salicylic acid as forms of prodrug. It was expected that such ester would be hydrolyzed rapidly in the blood to generate free salicylic acid. Hexylcarbonate of salicylic acid, **45**, one of the carbonate esters prepared by Dittert, *et al.* was equipotent as aspirin in antipyretic, analgesic and antiinflammatory activities. Its acute toxicity was less than that of aspirin and its gastric irritation potential was markedly lower in rats and dogs.[50]

2-Aspirin-1, 3-didecanoyltriglyceride (**46**) which was studied by Paris, *et al.* did not cause gastric lesions and had essentially all of the systemic activity associated with aspirin.[51] Anhydromethylenecitric acid disalicylic acid ester (**47**) which may also be considered as an aspirin prodrug was patented by the Bayer Company in 1907.[52]

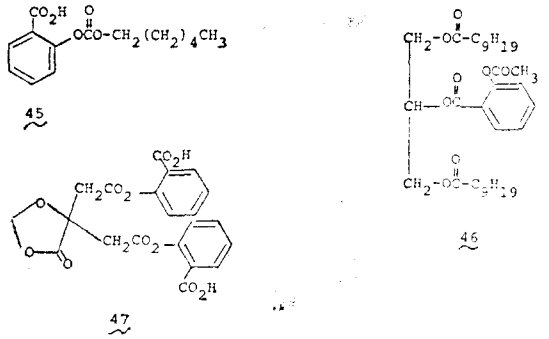

Fig. 7: Aspirin derivatives as prodrug forms.

Recently, acetaminophen (4-acetaminophenol, **48**) has been reintroduced to the market by several pharmaceutical firms.[53,54] Acetaminophen is the major metabolite of phenacetin (**49**) which was widely used as an analgesic-antipyretic agent during the first half of the century but was withdrawn from the market because of its serious side effects.[53] Acetaminophen has about the same analgesic and antipyretic effects as aspirin. It lacks, however, the ability to reduce inflammation and is not useful in the treatment of arthritis.[54] The major advantage of acetaminophen over aspirin is that it does not cause gastric bleeding or interfere with platelet function.[55] It is especially useful in those individuals who

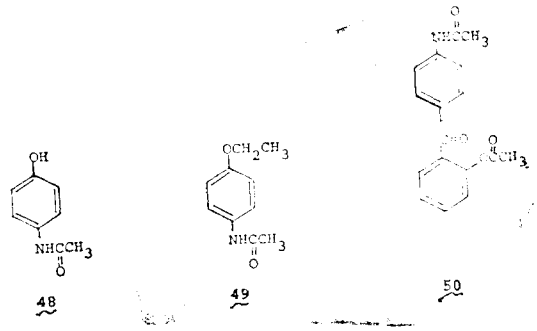

Fig. 8: Acetaminophen and Derivatives.

are sensitive to aspirin. In overdose, however, it may cause hepatic necrosis, and the treatment of acetaminophen overdosage is much more difficult than that for aspirin.[56,57,58,59]

Benorylate (4-acetamidophenol 2-acetoxybenzoate, **50**) is a lipid-soluble tasteless compound obtained by condensing aspirin with acetaminophen. The agent is well absorbed when taken orally, and after absorption it hydrolyzes to salicylic acid and acetaminophen. Excellent gastrointestinal tolerance in rats and dogs was noted. Benorylate showed an antipyretic action[60] and an analgesic action[61] superior to aspirin in some instances. Double blind between-patient clinical comparisons of benorylate with aspirin in rheumatoid arthritis patients demonstrated that the compound is as effective as aspirin or better in alleviating arthritis with fewer side effects than aspirin.[61,62,63,64,65,66]

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