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LITERATURE SURVEY

Novel Anti-Inflammatory Agents

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The nonsteroidal anti-inflammatory (NSAI) drugs currently in use are characterized by their ability to relieve the pain, fever, and inflammation associated with inflammatory disorders; to inhibit the synthesis of endogenous prostaglandins (PG's) by blocking the action of the cyclooxygenase (CO) enzyme; and, in relation with this inhibition, to cause GI irritation. As useful as they are, they do not interfere fundamentally with the progression of the disease. The question of the relevance of PG's on the course and/or the regulation of the disease has not been settled [for review see (1, 2)].

In the past few years, anti-inflammatory (AI) compounds having a profile of action on the arachidonic acid cascade metabolism distinct from that of the classical NSAI drugs have been reported. Some affect both pathways of arachidonic acid metabolism, while others have no effect on these endogenous mediators.

A nonexhaustive survey of these nonclassical NSAI agents along with the recently disclosed AI immunomodulators and of the classical agents currently in clinical trial is presented. Excluded are the steroids, the disease-modifying antirheumatic drugs (DMARD) such as penicillamine and gold salts, and the cytotoxic agents such as cyclophosphamide.

NONCLASSICAL, NONSTEROIDAL ANTI-INFLAMMATORY AGENTS

Inhibitors of Both Pathways of Arachidonic Acid Metabolism—3-Amino-1-[(*m*-trifluoromethyl)phenyl]-2-pyrazoline (I)[1] (3, 4), timegadine (5), and benoxaprofen (6) (Fig. 1) have in common AI activity and the capacity to inhibit both the cyclooxygenase (CO) pathway leading to the PG's and the lipoxygenase (LO) pathway leading *inter alia* to 5,12-dihydroxy-eicosatetraenoic acid (5,12-HETE), a potent chemotactic agent for polymorphonuclear leukocytes (7). The dual inhibition property of compound I, is reported to be of the same order both for CO and LO, while timegadine shows superior inhibitory activity for the CO system (5, 8). In the case of benoxaprofen, published data indicate a lower inhibition for CO and actually the low ulcerogenic activity of this product was related to this finding (9).

The activity profile of substances blocking both pathways of arachidonic acid should in some respects at least parallel that of the steroids. In fact, like dexamethasone, I was found to cause a dose-dependent reduction in leukocyte migration into inflammatory sponge exudate (3, 10). Benoxaprofen also inhibits migration of cells into inflammatory sites (6, 11). Moreover, the latter was found equipotent with hydrocortisone in the granuloma pouch test—in contrast to most NSAI agents (9) which are not active or weakly active in that test.

According to a recent paper (12), the action of I on the CO enzyme is selective: it inhibits PG production in inflammatory exudate but not in the GI tract—thus explaining its nonulcerogenicity as compared with aspirin and indomethacin.

Benoxaprofen, it is claimed, has the convenience of once-a-day dosage. It has been launched in Great Britain, Germany, and France (13), and it was currently being introduced in the United States when it was voluntarily recalled by the manufacturer after reports of deaths associated with the drug (14). The product, it was reported, induced photosensitivity and onycholysis in 10% of the patients (15).

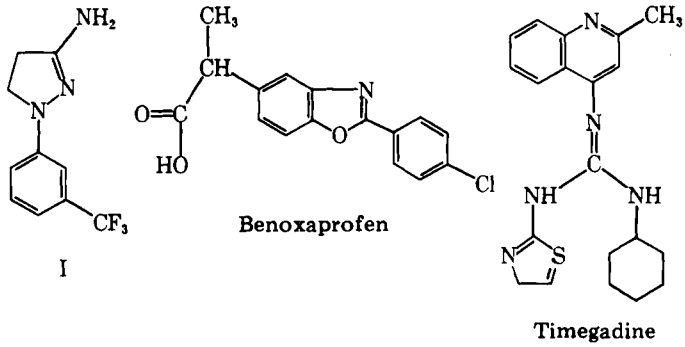

Figure 1.

[1] Code name: BW-755.

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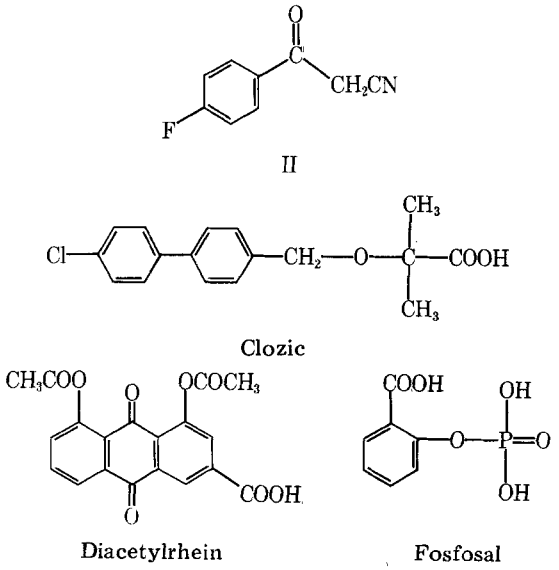


Figure 2.

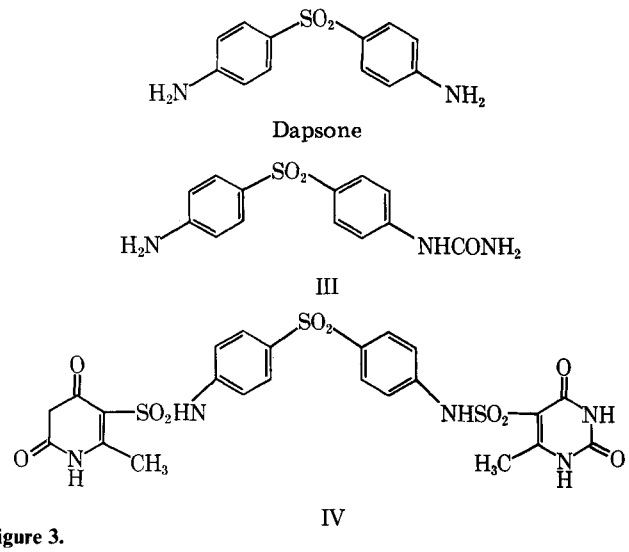


Figure 3.

Timegadine, which had been chosen out of a series of more than 100 guanidine derivatives, has only recently been submitted for clinical evaluation. In animal studies it showed low acute toxicity, low gastroulcerogenic effect, and high AI activity in both acute and chronic assays (16). Noteworthy is the fact that it can suppress the development of secondary lesions in the adjuvant arthritis (AA) screen when given only for a short period after the adjuvant injection (17). The tuberculin hypersensitivity reaction is enhanced by timegadine. Experimental allergic encephalomyelitis (EAE) (a model for cell-mediated immune response) is not inhibited by this product. Because of these results, it was concluded that the effect of timegadine in AA is not due to an immunosuppressive action (17).

Agents Having AI Effects not Mediated through Inhibition of Prostaglandins—*p*-Fluorobenzylacetonitrile (II)[2], (18, 19), clozic (20) and diacetylrhein (21) (Fig. 2) are novel agents which have in common, as opposed to the classical NSAI drugs, a markedly reduced potency in blocking the synthesis of PG's.

The acetonitrile II and clozic possess minimal acute AI or analgesic activity but are reported to be very potent in chronic assays. They produce little or no GI irritation in laboratory animals. For clozic, activity in type II collagen-induced arthritis is also claimed (22).

Clozic has been compared with penicillamine and gold salt clinically in a double-blind study testing 30 and 40 rheumatic patients, respectively, over a 6-month period. Similar activity to gold and penicillamine was found with substantial lowering of the biochemical markers of disease activity and with no serious side effects (23). If this result is confirmed in a long-term, larger clinical trial, then clozic would be the first example of a penicillamine-like drug susceptible to detection by conventional screening in animal models.

Diacetylrhein does not block PG production, on the contrary, it stimulates its synthesis. In *in vivo* experiments with rat inflamed exudate it produced, at 4 mg/kg po, an increase (69%) in total PG-like substances, while indomethacin, at 0.2 mg/kg, under the same conditions, produced a decrease (−72%) of the same substances. A confirmation of this is the ability of diacetylrhein to counteract indomethacin-induced gastric damage in a dose-dependent manner. The product has the same AI potency as aspirin in experimental animal models. In the retinoic acid-induced rabbit ear cartilage degeneration assay, it was shown to have the potency of hydrocortisone (21). In a short-term clinical study it was found to be well tolerated and effective, the therapeutic effect persisting for several weeks after suspension of therapy (24, 25). A controlled double-blind clinical evaluation confirmed the therapeutic value of this drug in the treatment of osteoarthritis of the hip and knee (26). It is assumed that the drug exerts its action through its ability to inhibit the release of proteases (21). It also forms water soluble Cu-complexes, and this may also contribute to its mode of action (25).

Another drug potentially belonging to this group is fosfosal, a compound analogous to aspirin except for the acetyl function, which has been replaced by a phosphono group. This results in substantial modification of the activity profile. Indeed, contrary to aspirin, fosfosal does not inhibit PG synthetase even at very high doses, and probably because of that, produces no significant ulcerogenic effect in rats in spite of its very high acidity. In animal models it was found equipotent to aspirin in analgesic assays and slightly less so in AI tests (27). In a double-blind clinical study with 60 patients, the AI action was confirmed with no sign of serious side effects and good tolerance (28). The compound is reported to produce negligible effect on platelet aggregation induced by ADP (a much smaller effect than aspirin). Another facet of fosfosal is the fact that it is 6 times more potent than aspirin in inhibiting phosphodiesterase activity (27).

Dapsone and Derivatives—It was observed in a clinical study that dapsone (Fig. 3), a well-established antileprotic drug, given at 100 mg/d improved the clinical state of RA patients while reducing some of the biomedical markers of the disease (C-reactive protein and erythrocyte sedimentation rate). Compared with gold, its efficacy was judged slightly less pronounced and its toxic side effects were less severe [for review see (29)]. The fact that dapsone has apparently no effect on the immune system, and that its experimental AI profile is akin to that of the classical NSAI drugs, does not concur with the above findings (30). However, doses at which activity was seen in animals were much higher than the ones used clinically [NB: results of two different assays in AA regarding activity and toxicity are at odds in the literature (30, 31)]. Also,

[2] Code name: CL-224385.

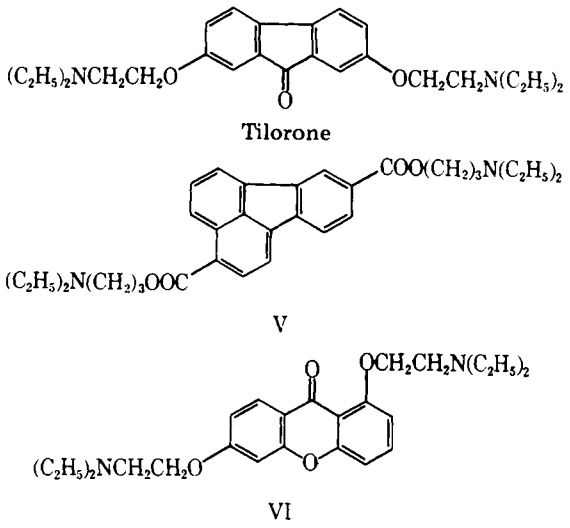


Figure 4.

contrary to the classical drugs, dapsone does not inhibit the PG-dependent ultraviolet-induced erythema, nor does it induce GI irritation in rats. The product has activity in zymosan, anti-IgG, and reversed passive Arthus models of inflammation, and in relation to these effects, it was suggested that dapsone could exert its AI effect by inhibiting complement activation. On the other hand, part of its mode of action must be related to its ability to inactivate the release (and the activity) of lysosomal enzymes from macrophages. It has been reported that dapsone and its urea derivative, (1-[4-(4-sulfanilyl)phenyl]-urea)[3] (III), specifically block *in vitro* incorporation of choline into phosphotidylcholine (lecithin) (32).

In clinical tests with 69 RA patients, 4,4′-bis-[(6-methyluracyl-5-sulfonyl)aminophenyl]sulfone (IV) led to a reduction of morning torpidity, after oral administration of 100–200 mg doses, and to the disappearance of pain syndrome after 10–12 d of treatment, for the majority of the patients (33).

IMMUNOMODULATORS

There seems to be little doubt that RA diseases are directly related to a deficiency in the regulation of the immune system (34). Substances capable of affecting any part of the complicated immunological network may present a potential for more efficacious treatment.

Tilerone-Like Agents—One of the first agents that demonstrated that selective manipulation of the two limbs of the immune system was possible is tilerone (35). A few laboratories have looked upon this interferon inducer as a worthwhile lead. Two examples of this line of research are bis-[3-(diethylamino)propyl] fluoranthene-3,9-dicarboxylate (V)[4] and 1,6-bis[2-(diethylamino)ethoxy]-9H-xanthen-9-one (VI)[5] (Fig. 4).

Like tilerone, these two compounds are able to suppress cell-mediated immune responses and, at the same time, to enhance antibody production (36, 37). Both compounds are effective in several of the cell-mediated immune response assays (EAE, tuberculin skin reaction, developing adjuvant-induced arthritis (D-AA), *etc.*). However, only compound VI is active orally in these tests. Another difference is the fact that VI is devoid of activity in the acute models of inflammation

[3] Code name: MK 241.
[4] Code name: RMI-9563.
[5] Code name: WY-15297.

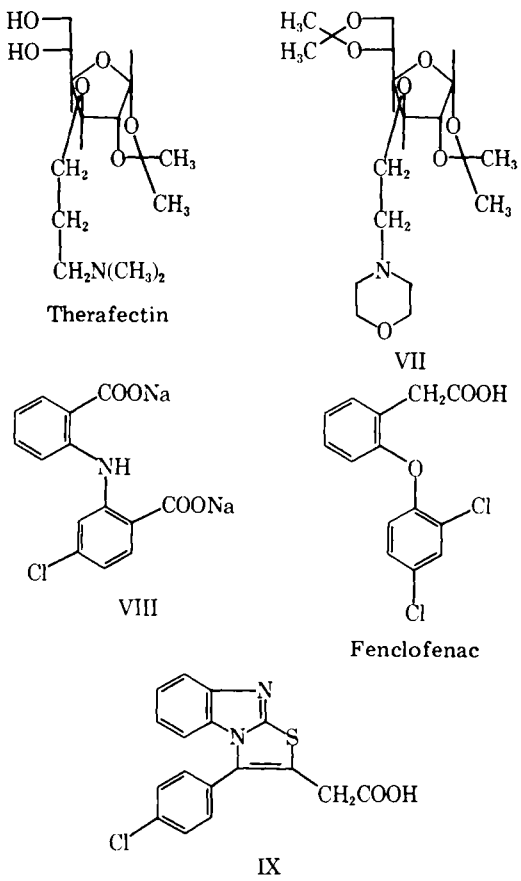


Figure 5.

(carrageenan-induced paw edema (CPE), Na urate, Randall-Sellito yeast tests), while V is active.

Like the steroids and the NSAI drugs, but contrary to immunosuppressive agents, VI is active in established adjuvant arthritis (E-AA) and also in the early phase of D-AA. However in E-AA, unlike the steroids and NSAI drugs, no rebound is observed up to 24 d after the last dosing. The product on the other hand, like the immunosuppressive drugs, is highly active in the EAE (a model in which the NSAI drugs are not active). This agent, it seems, does not fit the standard pattern of either the classical NSAI drugs nor the immunosuppressive agents. This mode of action might reflect selective stimulation of B-cells and suppression of T-cells (37).

Other Compounds—Novel compounds of various chemical classes, unrelated to tilerone, have also been recognized as immunomodulators. Drugs such as the anthelmintic levamisol (38) and more recently the H_2-antagonist cimetidine (39, 40), used in the treatment of peptic ulcers, have been found more or less by serendipity to have an effect on rheumatoid arthritis.

Other agents like therafectin (Fig. 5) first claimed as antiviral, antibacterial, and/or antitumor agents (41) were later discovered to respond positively to AI screening in animal models. Still others, which one would have classified as classical NSAI agents on the basis of their chemical structures, such as Chugai's *N*-(2-carboxyphenyl)-4-chloroanthranilic acid disodium salt (VIII) (42) and fenclofenac (44), were found in fact to have immunomodulating capability.

Therafectin is currently in Phase II of clinical trials in this country. The product is practically devoid of toxicity (in rats $LD_{50} > 10$ g/kg) and active in both the acute and chronic

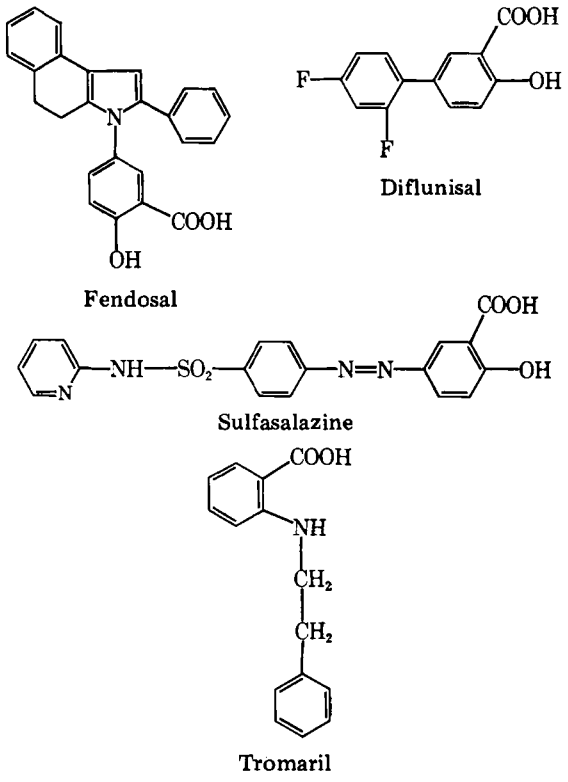


Figure 6.

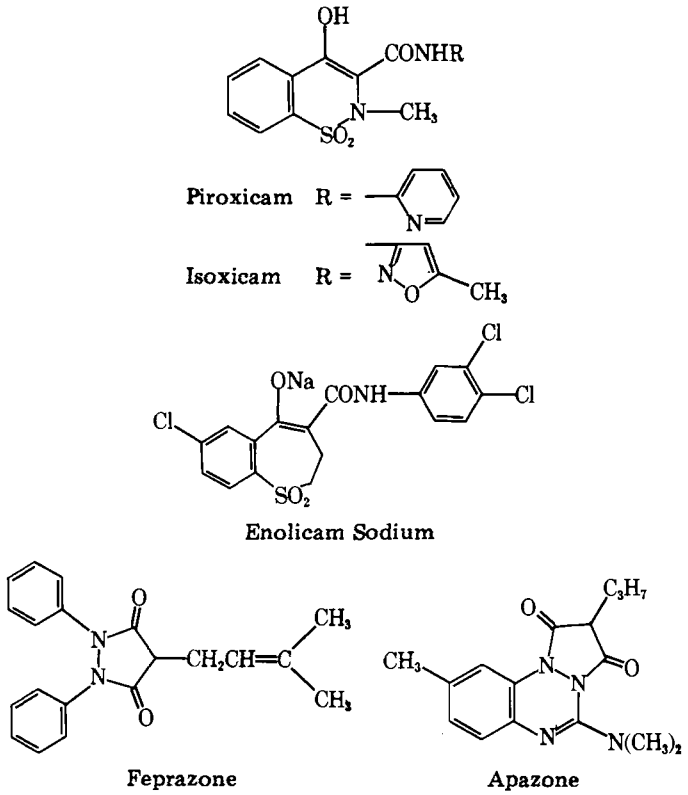


Figure 7.

animal assays of inflammation (CPE, D-AA and E-AA). It is an immunomodulator which primarily stimulates the activity of macrophages (45, 46). Another closely related glucofuranose in which the 5,6-dihydroxy functions are still protected with the isopropylidene group and described as 3-*O*-(2-morpholinoethyl)-1,2,5,6-di-*O*-isopropylidene-α-D-glucofuranose (VII) (47) has been claimed to have immunomodulatory properties.

Contrary to diclofenac sodium (to which it is closely related) the anthranilic acid (VIII) shows no activity in the acute assays, has no effect on tuberculin skin reaction, and no effect on passive cutaneous anaphylaxis in rats. The product is, however, quite active in the D-AA and E-AA assays. It has no immunosuppressive activity, but it enhances antibody levels in immune-deficient animals (42, 48).

As mentioned before, fenclofenac [a close analogue of fenoprofen (Lilly)], first thought to be of the classical type (49) has now been found to modulate the immune system (43). Again in animal studies, this product was found to have minimal activity in the acute but strong activity in the chronic assays. In AA the suppression of edema was seen to persist after treatment was discontinued. The product is 8 times as potent as aspirin in inhibiting PG synthetase. In a 1-year clinical study with 54 rheumatic patients, the effect of fenclofenac was compared with those of penicillamine and placebo (44). It was concluded that fenclofenac can indeed alter the disease profile of rheumatoid arthritis (RA) and, that on the basis of this result, a larger long-term study was warranted. An NDA for this compound has been filed recently in the United States (50).

In the same line, according to recent results of clinical trials, the NSAI agents sulfasalazine (51, 52) (Fig. 6), proquazone (53–55), and diftalone (56) (Fig. 13) would also have some of the characteristics of the disease-modifying agents, since besides improvement in the patient's physical condition, reduction in the RA abnormal parameters was observed. However, these claims have yet to be substantiated. As exemplified in the case of alclofenac (57), preliminary observations are not necessarily confirmed through long-term clinical studies (58–60).

3-(*p*-Chlorophenyl)thiazolo[3,2-*a*]benzimidazole-2-acetic acid (IX)[6] (Fig. 5), contrary to its immediate precursor the 3-hydroxy-2,3-dihydro compound (61), was not transformed *in vivo* to toxic metabolites. Although the product elicited weak inhibition of rat CPE (ED_{50} 200 mg/kg) (inhibition which was not abolished in adrenalectomized animals), it was found to be twice as active as aspirin in inhibiting PGE_2 biosynthesis in sheep seminal vesicles. In the rat AA model, it paralleled levamisole in enhancing the secondary paw edema on days 2–4, but it differs in being quite effective when given therapeutically (on days 16–28) (62).

CLASSICAL NONSTEROIDAL ANTI-INFLAMMATORY AGENTS

Including fenclofenac, sulfasalazine, proquazone, and diftalone [which may be working at a more fundamental level than most of the NSAI drugs in current use (*vide supra*)], there are at present, in clinical trials at one stage or another, more than 40 compounds related to the classical type of AI drugs. The unifying claim here is an improved therapeutic ratio. Several of these new agents are prodrugs of known substances.

Carboxylic Acids—Fendosal (Fig. 6), an indole derivative of salicylic acid, is undergoing Phase III clinical evaluation (63). In animal models this drug was 7–9 times more active than aspirin in the chronic assays (D- and E-AA). It was only slightly more active in the acute tests, but the duration of action was substantially longer than with aspirin (64).

[6] Code name: WY-18251.

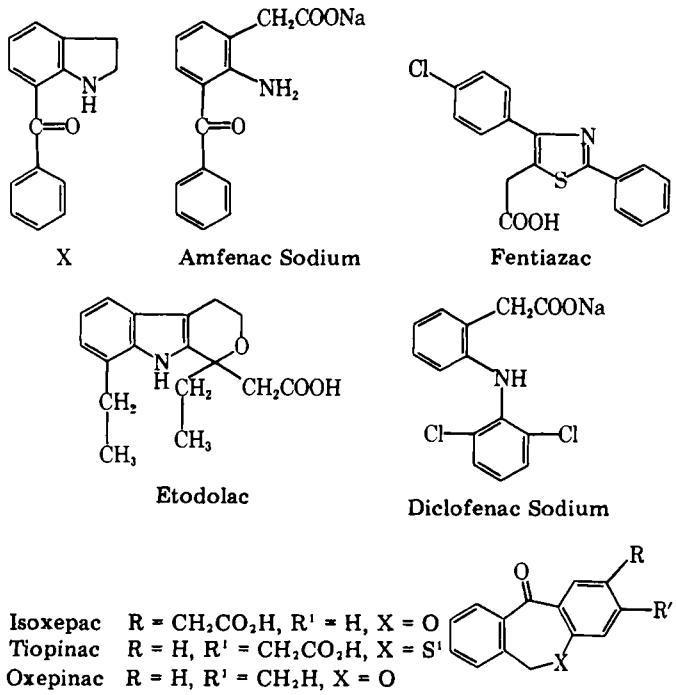


Figure 8.

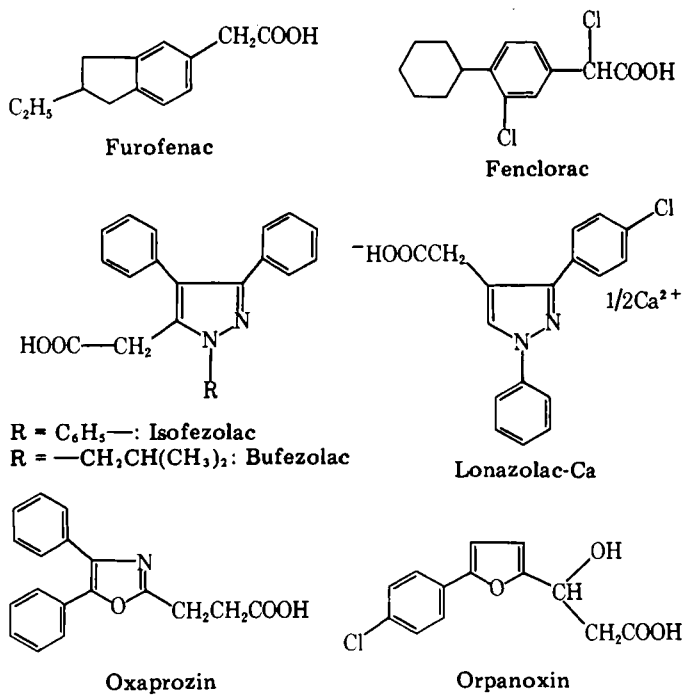


Figure 9.

Diflunisal, a follow-up of flunisal recalled from the clinic (65), was chosen out of more than 500 salicylates. The product is more potent, longer acting, and less toxic than aspirin. Its analgesic potency is about 4 times greater than aspirin. It does not affect platelet aggregation and bleeding time at therapeutic doses in humans. In animal models it was shown to have 7–9 times greater potency than aspirin both in acute and chronic assays (66). Already introduced in 17 countries, diflunisal has recently been approved for marketing in the United States under the analgesic indication (67, 68).

Sulfasalazine was introduced in Great Britain around 1940. Subsequently, on the basis of an unfavorable report, it was abandoned. Later (1965) it was proven effective against ulcerative colitis. Lately this product has been reexamined for the treatment of RA and the results were found particularly encouraging (51, 52). As mentioned earlier, sulfasalazine might have immunological activity.

Tromaril, an anthranilic acid derivative, is reported to be an effective agent in the treatment of rheumatoid disorders. Like the fenamates its side effects were skin rashes, itching, and diarrhea. The product inhibits platelet aggregation without affecting coagulation (69, 70).

Enolic Acids—The enolic acid type of AI drugs, of which butazolidine (PB) is the prototype, has been revived lately by the success story of piroxicam (Pfizer) (Fig. 7). This drug [already approved in 21 countries (71) and recently launched in the United States (68)] has a remarkably long plasma half-life, allowing a once-a-day (20 mg recommended) dose. The compound has high potency and its side effects are confined to the GI tract (72). An analogue, isoxicam, is undergoing Phase III evaluation in the United States (73), while quite a few more are currently in preclinical studies (74).

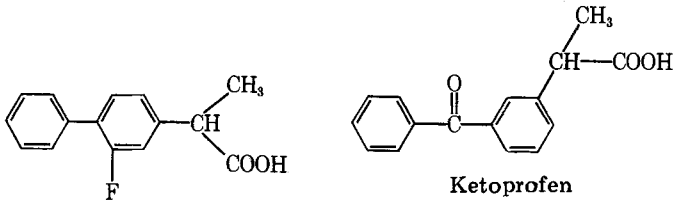
A new group in this class of products comprise the 1-benzothiepin analogues, some of which showed activity in rats at doses as low as 1 mg/kg/d (75). A representative of this group, enolicam sodium, is currently being evaluated in animals (76).

Replacing the *n*-butyl moiety of phenylbutazone (PB) by a prenyl group gave a compound comparable, in animal models, to PB in efficacy, but with fewer side effects on the hematopoietic system and the GI tract. Clinical evaluation, on the whole, indicated the same trend. At present this drug, feprazone, has been introduced in five countries abroad (77). Another congener of PB, apazone, was recalled recently from Phase III clinical trials (78).

Aryl and Heteroaryl Alkanoic Acids—Amphenac sodium (Fig. 8), originally discovered as the metabolite of 7-benzoylindoline (X), has potent AI activity against acute inflammation and comparable or superior activity to PB in suppressing chronic inflammation in rats (79). The product possesses strong analgesic and antipyretic activity. In pyloric-ligated rats or Heidenhain pouch dogs, the compound did not produce gastric mucosal damage; in chronic administration to rats, intestinal lesions were produced at 10 times the rate of PB (80). Relative to aspirin, the inhibition of CO enzymes by this product is about 600 times more efficient (81). Amphenac sodium is currently in Phase II of clinical trials (82).

Contrary to myalex which turned out to be hepatotoxic in humans (83), fentiazac, a close analogue, seems to undergo a metabolic detoxification process (84). In AA tests the product is 5 times more effective than PB (85). It has analgesic and antipyretic activity and the ability to decrease macrophage migration (86). The drug is already marketed in more than 15 countries; in the United States, it is undergoing Phase II evaluation (87).

Isoxepac (Hoechst) which is in late clinical trials (88) was reported to have high levels of gastric intestinal tolerance, its therapeutic index in dogs being 10–12 times that of indomethacin (89). According to the same source, the effective dose in AA rats is 39–78 times lower than the ulcerogenic dose. The Japanese firm Diichi Seiyaku is currently investigating oxepinac, the corresponding analogue with the acetic acid chain at position 3 of the dibenz[*b*,*e*]oxepin system. In animal models this product exhibits potency similar to that of indomethacin both in the acute and chronic assays (90). Syntex has been developing tiopinac, the sulfur analogue of oxepinac, for which



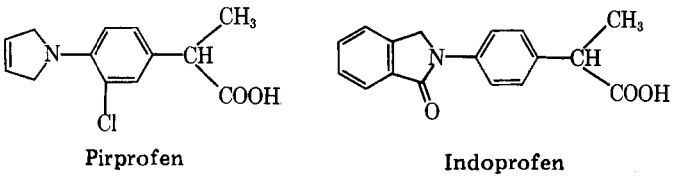


Figure 10.

activity equal to or greater than PB and/or indomethacin was reported. As an analgesic the product is said to be particularly effective against the pain of inflammed joints (91).

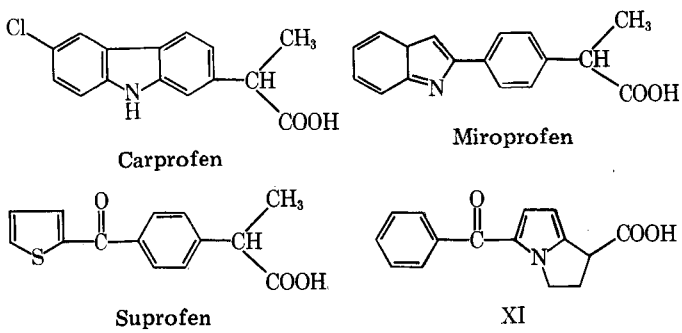
Etodolac is structurally related to prodolic acid, and like this compound, which for a while was considered for clinical trials (92), it is more active against the chronic than against the acute model of inflammation (93). The product is a good analgesic and its therapeutic index is 3 and 4 times higher than that of PB and indomethacin (94). It is now in Phase III of clinical assay (95).

Diclofenac sodium[7] is currently undergoing Phase II evaluation in this country (96). Structurally it is close to meclofenamic acid, the first fenamate approved for distribution in the United States. The drug was shown to be equipotent to indomethacin in the CPE, the rat AA, and the mouse writhing phenyl-*p*-benzoquinone assays. Moreover it possesses, as compared with indomethacin, a favorable therapeutic index and the ability to normalize the erythrocyte sedimentation rate (ESR) (97).

Furofenac (Fig. 9) was reported to have marked AI and antiplatelet aggregation activity, low toxicity, and weak ulcerogenicity. It is a PG and thromboxane synthetase inhibitor. In anticipation of clinical trials a metabolic study in animals and in humans has been conducted (98).

Fenclorac presents the singularity of having a chlorine atom α to the carboxy function. The product is in Phase II of clinical evaluation in the United States (99). In animal models its potency lies between aspirin and indomethacin. Its therapeutic ratio, however, is 3–9 times higher than indomethacin. It is also nonulcerogenic in rats at doses less than the LD_{50} (100).

In terms of the AI activity profile, bufezolac is about half as active as indomethacin, while isofezolac is equipotent. The



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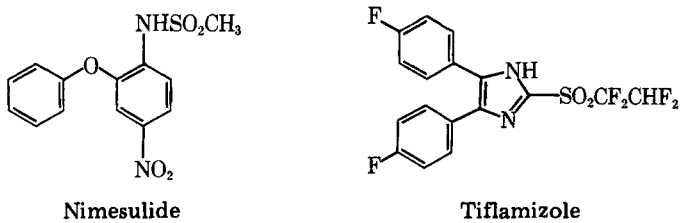


Figure 12.

latter is also more potent in inhibiting the biosynthesis of PG's than indomethacin while the former is much weaker, thus explaining the greater gastric tolerance of bufezolac as compared with isofezolac and/or indomethacin. Results of the analgesic assays as well as the acute toxicity determinations are quite different depending on the animal species tested, thus showing for these two pyrazole derivatives different species sensitivities or a difference in pharmacokinetics between species. These two substances have been considered for clinical trials (101). Structurally they are related to lonazolac calcium[8], which is sold in Germany as an AI drug (102, 103).

Both oxaprozin and orpanoxin have potent analgesic, antipyretic, and AI activity in animal screens (104, 105). The former compared favorably in terms of efficacy with aspirin in clinical studies. It was found to cause significantly less tinnitus and no significant toxic effects (106). The drug is highly protein bound (107) and has a long half-life allowing a once-a-day dosing regimen (108). Regarding orpanoxin, it was speculated that its nonulcerogenicity in rats ($\leq$2 g/kg) was due to its selective lack of effect on stomach PG biosynthesis (105). Clinical work on this substance has recently been deemphasized (109).

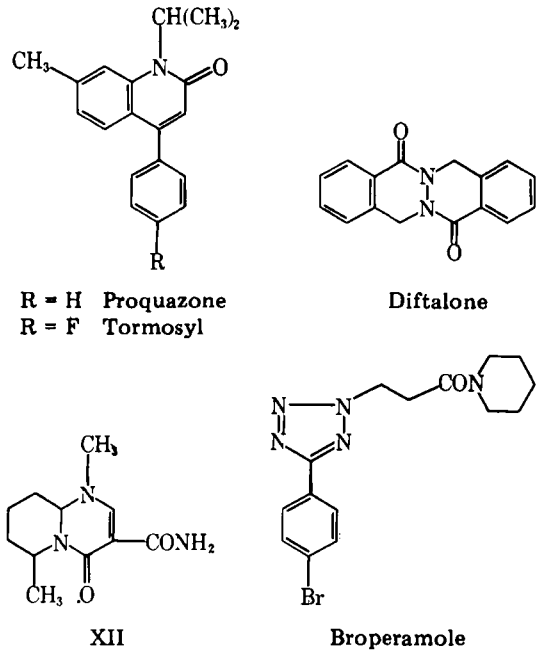
Chemically, oxaprozin and orpanoxin are unusual in that they are β-substituted propionic acids. This breaks the unwritten rule that AI activity is restricted to an acetic, α-methylacetic, or again, butyric acid residue which can be transformed to an acetic acid function by β-oxidation.

Flurbiprofen, ketoprofen, pirprofen, and indoprofen (Fig. 10) are either currently in advanced stages of clinical testing or awaiting FDA approval for marketing (110–113). Except for pirprofen, these drugs have already been introduced in several countries abroad for treatment of rheumatoid arthritis and other related diseases. In the classical AI screen, potencies equal to or greater than indomethacin and/or PB have been demonstrated for these compounds (114–117).

Flurbiprofen is well tolerated in humans. In the treatment of RA disease, 100–300 mg was reported to be equivalent to 75–100 mg of indomethacin (110). The product is also being evaluated as an ophthalmic AI agent (118). Ketoprofen was shown in a double-blind crossover study to be equipotent to indomethacin (119). Compared with aspirin, 240 mg of the compound, given daily, had the same effectiveness as 4 g of aspirin, with less side effects (111). Several clinical trials have determined the potency of pirprofen to be the same as aspirin in RA and higher in osteoarthritis (116). It was also found to be a good analgesic agent in the treatment of postoperative pain. Likewise indoprofen (100 and 200 mg) was evaluated in oral and other surgical procedures and found to have superior analgesic activity when compared with aspirin (600 mg) (120). In another clinical study involving RA patients, no difference was seen between indoprofen and indomethacin (121).

[7] Used extensively in Europe, Voltaren.

[8] Active ingredient of Irritren.



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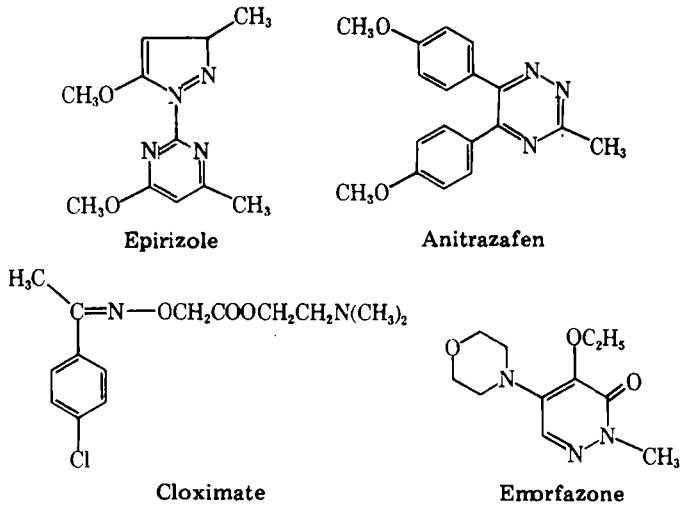


Figure 14.

Double-blind studies comparing carprofen (Fig. 11), indomethacin, ibuprofen, and oxyphenbutazone have been reported. The compound proved highly effective, but it induced GI irritation more often than indomethacin (122). Animal studies, in parallel with indomethacin, had indicated equipotent AI activity, lower potency (10–25 times) in inhibiting PG synthesis, and lower ulcerogenic activity (123, 124).

Miroprofen, a strong analgesic, specifically inhibits pain responses and acute inflammation associated with increased vascular permeability. The substance also has AI activity, being as potent as PB in inhibiting rat AA. Its ulcerogenic potential also compares well with that of PB. Its efficacy in relieving gingivitis was demonstrated in a clinical study (125).

In the rat D-AA screen, suprofen was found to have the highest safety margin when compared with PB, tolmetin, indomethacin, and aspirin: 48:20:16:8:2, respectively. Also observed in the rats undergoing that test was a reduction of bone erosion at 10–40 mg/kg (126). Moreover it was shown that suprofen is a potent antagonist of acetic acid-induced writhing in rats (127) of ultraviolet erythema in guinea pigs (128), and of sodium urate crystal-induced arthritis in dogs (129). In the clinic, drowsiness was observed as one of its side effects (130).

(±)-5-Benzoyl -3*H*- 1,2-dihydropyrrolo[1,2-*a*]pyrrole-1-carboxylic acid (XI) has in lieu of an α-methyl substituent to the carboxylic acid rest, an α-methylene group fixed in a pentacyclic ring (131). This product, which is undergoing phase I clinical trial, is a potent platelet inhibitor with strong analgesic and AI activities (132).

Miscellaneous Acidic Compounds—Nimesulide (Fig. 12), an acidic compound by virtue of its sulfonamide functional group, was reported to respond quite effectively in acute and chronic animal AI assays and to present a marked superiority in the therapeutic index to most reference NSAI drugs (133). Compared with indomethacin, its AI potency was of the same order; however, the product was 10 times less effective in suppressing PG *in vitro* (134). In clinical studies, nimesulide was evaluated in 70 patients with rheumatic disorders for a mean duration of 26 d. A complete cure or significant improvement in 86% of patients was reported. Side effects were mainly GI disturbances (135).

Another nonalkanoic acidic drug is the hexafluoroimidazole derivative tiflamizole. In animal studies, the product was about 10 times as potent as indomethacin in D-AA and E-AA screens (ED_{50} 0.03 mg/kg/d). An unusual feature was the duration of the therapeutic effect following daily oral doses of 0.09 mg/kg for 7 d. The inhibition persisted for more than 70 d when, in the case of indomethacin, there was a flare up after 2–3 days. The drug had a long half-life, was rapidly absorbed, and slowly excreted in various animal species. There was apparently no evidence of metabolites. Tiflamizole strongly suppressed bovine seminal vesicle PG synthetase (IC_{50} $4 \cdot 10^{-7}$ mol/L); nevertheless, its ulcerogenic activity in rats, was found to be weaker than that of the regular AI drugs in use (136–138). This compound is currently in Phase II of clinical evaluation (139).

Nonacidic NSAI Drugs—There are not many nonacidic NSAI drugs available for the treatment of RA. Benzydamine (mostly an analgesic agent) and tiaramide (sold in Japan) are two examples of this class of product. Also, relatively few novel compounds of this type have been developed to the point of clinical trial. Proquazone (Fig. 13), which is sold in Germany and in Switzerland, is actually in Phase II of clinical trials in the United States (140). Like the acidic NSAI drugs, the compound blocks the CO pathway of the arachidonic cascade. It is particularly effective in inhibiting collagen-induced platelet aggregation (141). In clinical tests, proquazone was found to be comparable with indomethacin in terms of efficacy and tolerance (142). Evaluated in postoperative dental pain, it was found to have 5–6 times the potency of aspirin (143). Some lower intestinal intolerance appears to be the main problem. Recent reports would attribute disease-modifying capability to this drug (53–55). Tormosyl, the corresponding fluoro analogue of proquazone, has been evaluated as an analgesic in humans (144).

The phthalazine derivative, diftalone, had AI potency in animal models approximately equal to that of PB, while gastro-ulcerogenic activity (in rats) and manifestations of acute toxic effects were practically absent (145). In the clinic it was found effective for the treatment of RA and comparable with indomethacin. Suppression of the ESR was also reported (56).

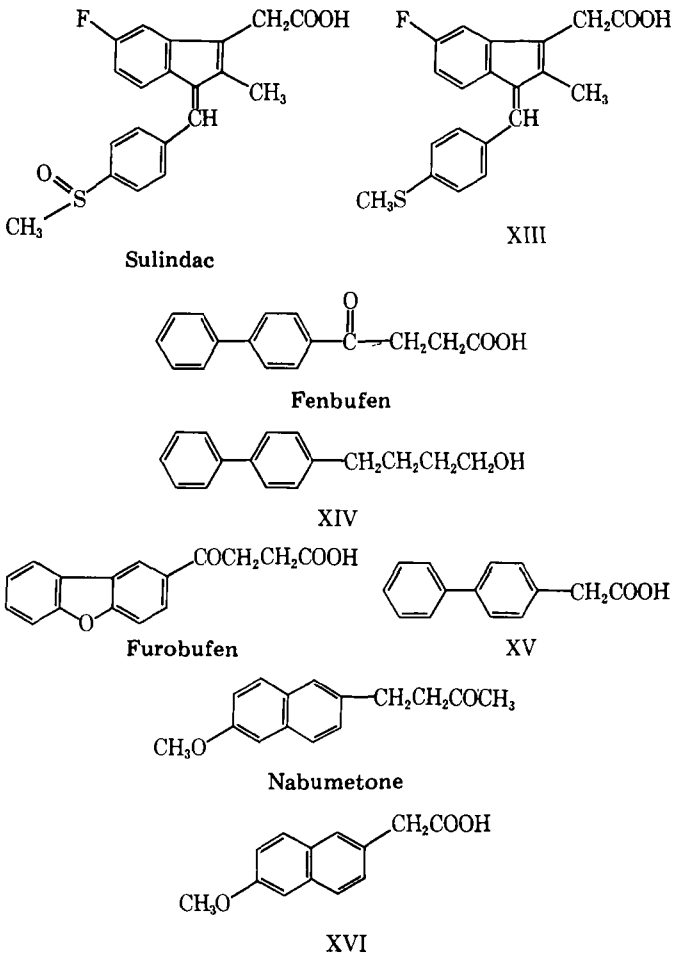


Figure 15.

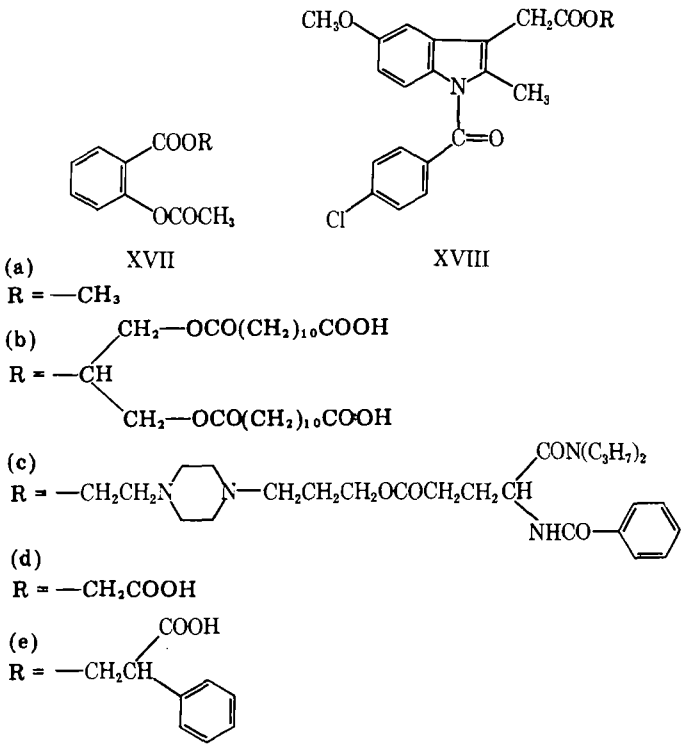


Figure 16.

Antipyretic, analgesic, and AI activity combined with a high therapeutic index as compared with indomethacin have been reported for 1,6-dimethyl-4-oxo-1,6,8,9,9a-hexahydro-4H-pyrido[1,2-*a*]pyrimidine-3-carboxamide (XII)[9]. A marked synergistic effect was observed in the reduction of rat CPE when a low dose of XII was coadministered with indomethacin. It is assumed that the product will be examined clinically and this synergistic effect evaluated (146).

Broperamole showed systemic AI activity 5–6 times that of PB in acute assays, and 10 times in the case of chronic assays. The product caused gastric irritation only at very high doses (147). It had topical AI activity, but less than that of hydrocortisone. The product is undergoing preclinical testings (148).

Epirizole (Fig. 14), a Japanese drug having higher analgesic activity than aminopyrine with less toxicity, is being evaluated for clinical trials in this country (149). Apparently this product can inhibit gastric lesions induced by acidic NSAI drugs (150).

The triazine anitrazafen is 50–100 times more potent than indomethacin in inhibiting fatty acid CO. It was found inactive in rat CPE and AA when given orally, but topically, it inhibited or reversed the formation of erythema induced by ultraviolet light (151). The development of this product, under evaluation for some time, may have been deemphasized (152).

In addition to showing good inhibiting activity in the usual assays of experimental inflammation, cloximate, an oxime ether derivative, showed marked activity in traumatic edema and in the Arthus antigen-antibody assay. Tested in acute and chronic experiments in rats and dogs, it had practically no harmful effect in the gastrointestinal mucosa. It is reported to be as potent as aspirin in blocking the biosynthesis of PGE_2. The product has been submitted to a first clinical trial (153).

Emorfazone, evaluated in acute models of inflammation showed analgesic and AI activity similar to PB (154). It was found to inhibit compound 48/80[10]- induced histamine release from mast cells and from rat skin, to have no effect on the immune system, and not to suppress PG synthesis. The main site of its anti-nociceptive activity was suggested to be in the periphery (155). Treatment of a group of patients with acute cystitis resulted in good to excellent remission of micturition pain in 14 of the 15 cases (156).

Prodrugs—Sulindac (Fig. 15), an indene isostere of indomethacin, was recently introduced in the United States. It is a prodrug for the active corresponding sulfide metabolite XIII. It has longer duration of action, fewer side effects than indomethacin, and it is claimed to be free of GI problems (157).

Fenbufen is characterized by its high analgesic activity, the sustained duration of its analgesic and AI action relative to the other known drugs, and the fact that it does not directly inhibit fatty acid CO. Its activity is due mainly to its main metabolite, biphenylacetic acid (BAA) (XV) which, in this case, must be obtained by quite an unusual transformation. This acid is a potent inhibitor of PG biosynthesis. The low potency of fenbufen to induce gastric irritation can be explained by the fact that BAA is not directly in contact with the GI tract (158, 159). Fenbufen is currently sold in more than 14 countries. Its introduction in the United States is expected in the near future (160).

The fluorene analogue, furobufen, has recently been recalled

[9] Code name: Chinoin-127.

[10] Mixture of polymeric amines; see W. D. M. Paton, *Br. J. Pharmacol.*, **6**, 499 (1951).

from clinical testing (161). In AA assays furobufen elicited similar activity to PB. The product has analgesic but no antipyretic activity (162). Thomae's butyryl alcohol derivative, 4-(4-biphenyl)butanol (XIV)[11], is also metabolized to XV and it presents, not unexpectedly, an activity profile similar to fenbufen[12].

Biotransformation of nabumetone to the active metabolite, 6-methoxynaphthalene acetic acid (XVI), is also responsible for the much reduced ability of this compound to induce gastric lesions as compared with standard drugs such as naproxen and/or indomethacin. The product is now being evaluated clinically (163, 164).

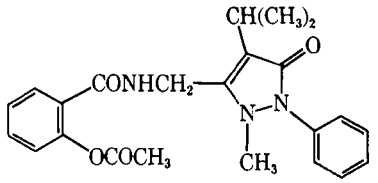
Most attempts to prepare AI prodrugs have revolved around modification of the acidic function, through esterification and/or amide formation, of known inflammation inhibitors. One of the most expedient ways would be esterification with methanol. Indeed, according to a recent report (165), the methyl esters of acidic NSAI drugs were found far less ulcerogenic than the acids, yet their AI activities were not changed appreciably. In the case of the methyl ester of aspirin (XVIIa) (Fig. 16) it was established that the toxicity after long-term oral administration to rats and guinea pigs was less than aspirin. Another study with radiolabeled salicylate derivatives showed that the methyl ester group did not quantitatively change the biodistribution of the active form generated *in vivo* (166).

On the basis that triglycerides are able to pass through the stomach without undergoing hydrolysis and then to be absorbed in the intestines, it was assumed that NSAI drugs incorporated in the triglyceride structure would bypass the stomach and then be metabolized to provide free drug delivery.

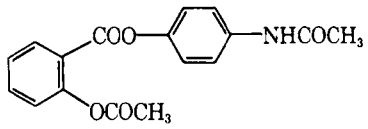
In the case of the triglycerides of aspirin (XVIIIb) it was found that the therapeutic ratio was improved 80-fold over aspirin. However, with indomethacin (XVIIb) only a threefold improvement was experienced. It was concluded that GI damage due to indomethacin is mainly produced systematically by the circulating drug, whereas in the case of aspirin the irritation is primarily the result of local action on the gastric mucosa (167–170). It was shown with the use of radiolabeled compounds that effective therapeutic concentration of the free active salicylate was easily obtained after ingestion of the triglycerides of aspirin (171).

The isoglutaminyl moiety of proglumetacin (XVIIIc) is said to procure protective activity to the gastric mucosa, while the presence of the piperazine nucleus seems important for providing a favorable therapeutic ratio (172). The product caused GI tract damage (in rats) only at dose levels close to the LD_{50} (173).

Acemetacin (XVIIId) was chosen from a series of more than 100 compounds, mostly esters and amides of indomethacin. In animal tests it was found to be more active than indomethacin (in acute and chronic assays), and to be equipotent with corticosteroid in the granuloma pouch test (cotton pellet). It is a weaker inhibitor of PG synthesis than indomethacin and, apparently in connection with that, it causes less damage to the mucous membrane of the gastrointestinal tract (174, 175). In a multicenter long-term study with 200 outpatients, the efficacy of acemetacin was assessed as good to very good in 75% of the cases. Only 3% of the patients gave preference to



XIX



Benorylate

Figure 17.

indomethacin in this study. Damage to the GI tract was observed but in general it was much reduced (176, 177).

Among a large series of esters of indomethacin, tropesin (XVIIIe) had the slowest rate of cleavage by action of serum esterases *in vitro*. Compared with indomethacin, the product exhibited the same AI efficacy, in acute and chronic models of inflammation, and a much lower tendency to induce gastric damage (UD_{50} 50 mg/kg *versus* 1 mg/kg for indomethacin). In a first clinical trial, symptoms of intolerance were not observed with daily doses of tropesin up to 210 mg (178).

The antiarthritic and analgesic activity of the double prodrug of aspirin and isopropylantipyrine (AIA)—*N*-(4-propyphenazon-5-yl)-2-acetoxybenzamide (XIX)—(Fig. 17), was found to have about the same potency as that of each moiety taken separately, but with the difference that the gastric ulcerogenic activity was much less pronounced. This product also showed practically no acute toxicity as shown by the LD_{50} values: 5 g/kg orally and subcutaneously, and 3.68 g/kg intraperitoneally in mice (179).

Benorylate, another example of a double prodrug (aspirin and paracetamol), is now marketed in Europe (180). It is believed that paracetamol, by stimulating stomach PG synthetase, inhibits the erosive action of aspirin (181).

CONCLUSION

Most of the compounds currently under investigation are CO inhibitors and as such are analogues of aspirin and/or indomethacin. Yet these may be justified as useful alternatives in view of individual diversity in response to treatment, if not as offering greater tolerance and, in some cases, the convenience of a once-a-day medication. More importantly, however, is the fact that a few of these may influence some of the more fundamental mechanisms of the disease, overlapping, it would seem, with the newer types of compounds whose mode of action is related either to their capacity to inhibit the chemotaxis of cells perpetuating the disease at the site of inflammation and/or to their selective control of the body's immune system.

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[11] Code name: CO-893.

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