Chapter 18. Newer Agents for the Treatment of Arthritis

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Introduction — Many compounds are in use or under study for the control of the painful symptoms of arthritis and other inflammatory diseases of the musculoskeletal system. The literature on non-steroidal antiinflammatory (NSAI) drugs has increased dramatically since Wong[1] last surveyed the field for this series in 1975. In addition to the NSAI agents, several immunoregulatory drugs, last reviewed by Chang,[2] have been shown to control immune-mediated inflammation and, although still in the experimental phase of clinical trials, such agents offer the possibility of achieving more than palliative control of the symptoms of arthritis. Among the various anti-arthritic agents, the NSAI drugs are by far the largest and most important class. More than 120 such compounds have been assigned a generic name, suggesting that many have progressed beyond initial testing in animals. Several such agents have recently been marketed with claims for rheumatoid arthritis (RA), osteoarthritis (OA) and acute inflammatory conditions of connective tissue. The present review will focus on the literature of 1975-1977, with emphasis on the newer, more potent compounds of both the NSAI and immunoregulatory type. Several recent reviews and texts are available which discuss the drugs used in the treatment of arthritis[3-8] and their possible mechanisms of action.[9-14] Reviews of the inflammatory process,[15-16] the rheumatic diseases,[17-22] including the rheumatism literature[19] for the years 1973-1974, and a compilation of papers from an international meeting on inflammation,[23] have also appeared.

Mechanisms of Action — Some new insights have been gained concerning the mechanisms by which NSAI agents control inflammation. The ability of these agents to influence the biosynthesis of prostaglandins (PG), reviewed more recently by Vane and Lewis,[24] is viewed as a basic mode of action of these drugs.[25] Support was obtained for a role for PG in RA when elevated PG levels were found in articular tissue from arthritis patients,[26,27] and by the detection of a human lymphocyte factor which stimulates PG production in rheumatoid synovial cells.[28] Furthermore, NSAI drugs inhibit PG production by synovial cells in organ culture[29,30] and PG levels are reduced in synovial fluid of arthritic patients dosed orally with NSAI agents.[31] The PG inhibitory potency of NSAI agents *in vitro* is dependent on both the tissue source and the way the prostaglandin biosynthetase system is handled.[32] As a result, studies with NSAI agents have shown either good correlations[29,33,34] or poor correlations[35-39] between *in vitro* inhibition of PG synthesis and *in vivo* antiinflammatory activity. It is not unexpected that *in vitro* activity should fail to correlate with *in vivo* activity when one considers that complex metabolic and pharmacokinetic factors may be superimposed on the *in vivo* situation.

Whereas steroids block both PG and collagenase production by RA synovial cells, indomethacin inhibits PGE_2 production but stimulates collagenase production.[40] This finding may explain in part why NSAI drugs relieve inflammation but do not prevent tissue damage in arthritic patients. A further difference between steroids and NSAI agents is that the former inhibit the release of arachidonic acid from cell membranes[41] whereas the latter inhibit the cyclooxygenase step in PG production.

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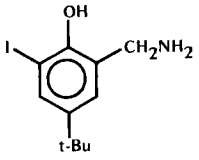
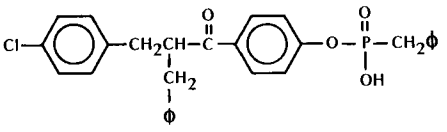
Evidence exists suggesting that inhibition of PG synthesis does not entirely explain the antiinflammatory activity of NSAI drugs.[42-45] Information on a possible role of the endoperoxide PGG_2 in inflammation has been obtained from studies with MK-447.[46] This compound has significant antiinflammatory activity in the rat but does not inhibit the PG cyclooxygenase. It does, however, suppress PGG_2 levels suggesting that PGG_2 or some substance derived from PGG_2, rather than PGE or PGF, may trigger the inflammatory response.[46] An understanding of the role of the thromboxanes in inflammation[47] may offer new therapeutic approaches for agents with more specific actions, especially in view of the compounds (e.g. dipyridamole, N-0164, L-8027) already reported[48-50] to preferentially inhibit thromboxane production. Other



MK-447



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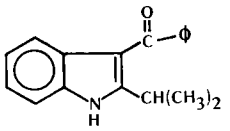


L-8027

effects observed with NSAI agents which may contribute to their mechanism of action include: inhibition of neutrophil chemotaxis,[51] reduced leukocyte migration,[52] effects on lysosomal enzyme release,[53-55] impairment of phagocytosis,[56] inhibition of superoxide anion production in macrophages,[57] stabilization of cell membranes[58] and inhibition of the production of vasodilator mediators.[59]

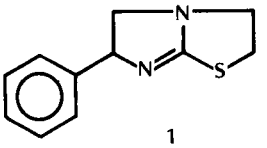
The mechanism of action of immunoregulatory agents of both the suppressive and stimulatory type, and the basis for their use in the treatment of RA, have been discussed by Chang[2] and Maini.[22]

Methodology — Various, now generally standard, animal models of inflammation have been reviewed.[60,61] The most commonly used test for the identification and characterization of antiinflammatory agents is the rat foot edema (RFE) test in which an edema is provoked in the paw of a rat by injection of carrageenan. This test has a PG mediated phase of the inflammatory response which is less intense in essential fatty acid deficient rats,[62] presumably due to deficient levels of arachidonic acid. Another widely used model, the rat adjuvant arthritis (RAA) test, produces a more chronic type of inflammation. In this model there is evidence for an immune-mediated inflammatory component involving a critical role for T-cells.[63,64] Modifications of this procedure permit the detection of immunological agents,[65,66] analgesics,[67] as well as NSAI drugs.[68] Morphological studies suggest a similarity between the lesions in the RAA model and human RA.[69,70] Considerable effort is being directed toward the development of other models of chronic inflammation.[71] In this regard, ovalbumin,[72] carrageenan,[73] bovine serum albumin,[74] Fab_2[75] or an extract of *Erysipelothrix rhusiopathiae*[76] have been utilized to provoke synovitis in rabbits. Although evaluation of compounds in the rabbit synovitis model is relatively time consuming, its similarity to human RA will likely encourage its use.

A detailed discussion of the immunologically-based models is beyond the scope of this review. *In vitro* methods for measuring cell-mediated immunity[77] and models of lymphokine production,[78] and of autoimmune diseases,[79] are available. Reviews on lymphocyte function[80] and the role of lymphocytes in clinical disorders[81] provide a useful background for models suitable for measuring drug effects on the immune response.

Compounds Under Investigation

Immunoregulatory Agents — There has been an explosive increase in the literature on the use of levamisole (LVS, **1**) in several inflammatory diseases. A valuable entry to the more than 400 publications on this drug is provided by a review of the literature through late 1976.[82] LVS has achieved particular attention for the treatment of RA (reviewed through 1976 by Trabert *et al.*[83]), with mostly positive effects observed but some negative results and often severe side effects also reported.[82-86] Double-blind clinical trials of LVS in RA confirm the results achieved in most open clinical trials — i.e. when LVS is administered against a background of NSAI drugs, clinical symptoms of RA improve in many patients after three months of therapy.[87] However, immunological parameters do not necessarily correlate with clinical improvement, and side-effects, in particular agranulocytosis, can be serious, occurring in up to 20% of patients.[88]



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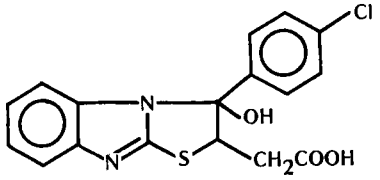
Several mechanisms of action, mainly involving T-cell function, have been proposed to explain the beneficial effect of LVS.[82] Enhanced phagocytosis[89,90] and chemotaxis[91,92] have been observed *in vitro*, but the clinical relevance of some of these *in vitro* effects, which have sometimes been observed with concentrations as high as 1 mM, is not certain. Variable results are obtained with levamisole in the RAA model,[93,94] and in the autoimmune disease model of NZB/W mice.[95,96] Delayed hypersensitivity in rats is enhanced by LVS.[97]

Other immunostimulatory compounds include Wy-13,876 (**2**), which increases T-lymphocytes and rosette formation in rats and inhibits tumor growth in mice.[98] The anthranilic acid derivative, **3**, promotes lymphocyte blastogenesis and antibody production in rats and suppresses both RAA and the autoimmune disease of NZB/W mice.[99]



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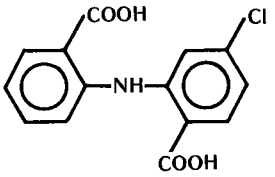

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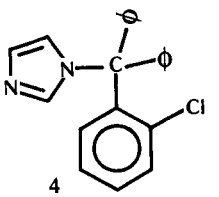

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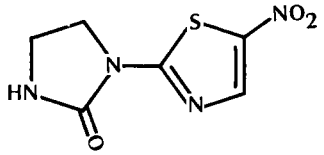
Among the immunosuppressive agents receiving attention are two imidazole derivatives, clotrimazole (**4**) and niridazole (**5**), the pyridine derivative oxisuran (**6**), and frentizole (**7**).



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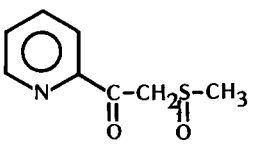

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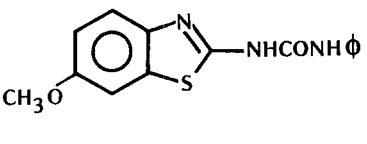

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Clotrimazole (**4**), an antifungal agent, was reported to produce rapid improvement in 10 RA patients.[100] Data from animal studies[101] and another clinical trial in RA patients[102] suggest that stimulation of the adrenal glands, with an ensuing elevation of serum cortisol levels, is responsible for the activity of clotrimazole. Niridazole (**5**), a human anthelmintic drug, has modest antiinflammatory properties[103] and is a suppressor of cellular hypersensitivity,[104,105] perhaps due to an active metabolite formed *in vivo*.[106] The drug suppresses experimental allergic encephalomyelitis in rats[107] and mice[108] but is carcinogenic in rodents.[109,110] In man, niridazole inhibits the mixed lymphocyte reaction.[111]

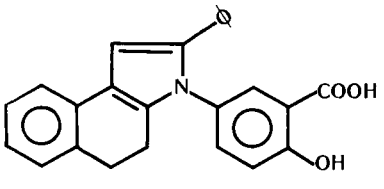
Oxisuran (**6**) has been reported to be a differential inhibitor of cell-mediated hypersensitivity.[112] Recent data suggest that this compound acts by stimulating the pituitary adrenal system, producing elevated levels of circulating steroids.[113] Indeed, the effects of oxisuran have been duplicated in mice by administration of corticosterone.[113]

The immunosuppressive urea derivative frentizole (**7**) inhibits murine lymph node cells and suppresses macrophage phagocytosis.[114] The compound was found to either increase or decrease survival time of mice infected with various bacterial, viral or fungal organisms,[115] suggesting a differential drug effect on the immune response to these organisms.

NSAI Agents — These agents are conveniently grouped into acidic compounds of the arylcarboxylic or enolic type and non-acidic compounds.

A. *Arylcarboxylic Acids* — Carboxylic acids form the largest structural class of NSAI drugs. Indomethacin and the more recently marketed drugs, naproxen, ibuprofen, fenoprofen and tolmetin, have been thoroughly reviewed elsewhere[3-9,116] and will not be discussed here. Approximately 70 other carboxylic acids have been reported to have significant antiinflammatory activity in animal models and some in man. Some of these compounds, such as ketoprofen, alclofenac and flurbiprofen have been discussed in earlier reviews in this series (e.g. Wong[1]). This review will focus on a discussion of the newer agents. The relative antiinflammatory potencies of several NSAI drugs have been published.[117-120] All of the NSAI agents have a similar profile of activity which includes anti-edema, antipyretic and analgesic effects. None of the NSAI agents are clinically clearly superior to high doses of aspirin but some are less toxic and are used in patients who are not controlled by aspirin. All of these agents, like aspirin, have gastrointestinal side-effects but the search for a more potent and safer drug continues.

Among benzoic acid derivatives reported to exhibit antiinflammatory activity, fendosal (HP-129, **8**), possesses prolonged analgesic effects.[121] Tolfenamic acid (**9**), 600 mg/d, controls the symptoms of RA[122,123] and is reported to cause only minor gastrointestinal effects.[124] Diflunisal (**10**), an aspirin derivative, differs from the latter drug principally by a longer half-life and greater potency.[125,126]



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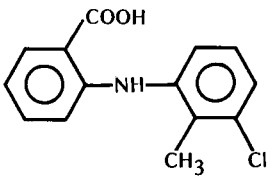

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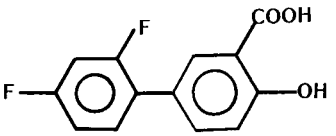

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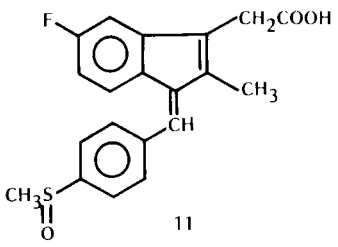
Acetic acid derivatives are well represented among the NSAI agents. Sulindac (**11**), an indene derivative of indomethacin, is effective in OA[127,128] and in RA[129] at daily doses of 300-400 mg. In several models of inflammation the sulfide metabolite derived from **11** is more potent than sulindac itself,[130] indicating the sulfide to be the active species *in vivo*. Mucosal injury[131] and intestinal blood loss[132] are reported to be less severe with sulindac than with aspirin.



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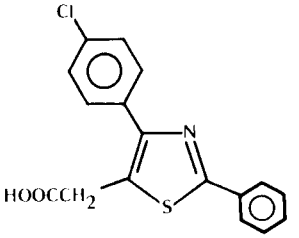

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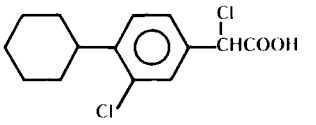

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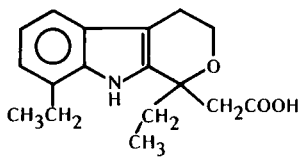
Fentiazac (BR-700, **12**) is more potent than ibuprofen in the RFE test,[134] is an effective analgesic in rodents, suppresses RAA,[133] and reduces mononuclear cell migration into granulomas *in vivo*.[135] Fenclorac (WHR-539, **13**) is one-third as potent as indomethacin as an inhibitor of the RFE test (ED_{50} 7.9 mg/kg),[137] but is more potent than indomethacin as an inhibitor of PG synthesis.[136] The half-life of this compound in man is 3 hr.[138]

Etodolic acid (AY-24,236, **14**) is equipotent with phenylbutazone in the RFE test,[140] and is a potent inhibitor of RAA.[139] Similarly, tianafac (**15**) is as active as phenylbutazone in the RFE test, but is less ulcerogenic.[141,142] A series of abstracts report the pharmacology and antiarthritic efficacy (300 mg/d) of clopirac (BRL-13,856, **16**).[143]



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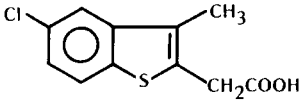

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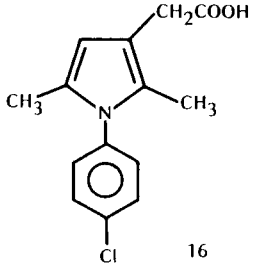

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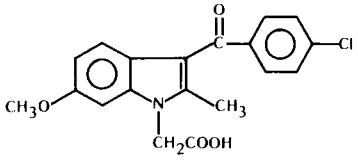
Clometacine (RU-3959, **17**), a positional isomer of indomethacin, is much less potent than indomethacin.[144] DD-3314 (**18**) is more than twice as active as indomethacin in the RFE test.[145] A basic derivative of fentiazac, the thiazole acetic acid **19**, was reported to be more potent than phenylbutazone in the RFE test.[146]



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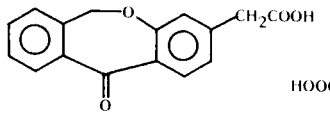

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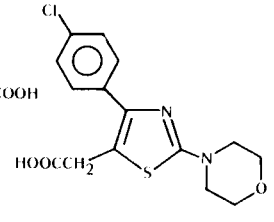

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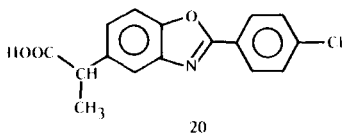
Many propionic acid derivatives related to ibuprofen have been shown to control inflammation. Benoxaprofen (**20**) is 5 times more potent than phenylbutazone in the RFE test.[147] The compound exhibits only weak PG synthetase inhibiting properties[148] and has a long half-life (37 hr) in man.[149] The isoindole derivative indoprofen (K-4277, **21**) is 19 times more potent than phenylbutazone[150] and has a half-life of 3 hr in man.[151,152] The drug causes less fecal blood loss than aspirin.[153] In the treatment of OA[154] it is comparable (600 mg/d) to ibuprofen (900 mg/d).



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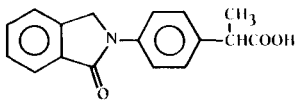

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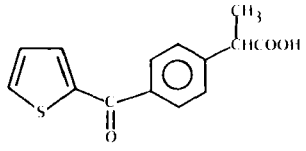

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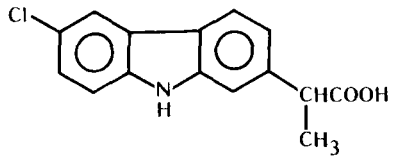
Several publications summarize the pharmacological and toxicological properties of suprofen (R-25,061, **22**), a potent antiinflammatory acid (e.g. in RAA, ED_{50} = 6 mg/kg).[155,156]

Other heterocyclic propionic acids include carprofen (Ro-5720, **23**), tiaprofenic acid (RU-15,060, **24**) and R-803 (**25**). Carprofen (**23**) is as potent as indomethacin in the RFE test but less potent in the RAA test.[157] In rodents, relatively low doses of carprofen have been reported to produce gastric ulcers.[157,158] Co-administration with aspirin results in lower peak plasma levels of carprofen.[159] The d-isomer of carprofen is more potent than the l-isomer both in the RAA test and as a PG synthetase inhibitor.[160] Early clinical evidence suggests that carprofen (300 mg/d) is effective in RA.[161] The pharmacokinetics of tiaprofenic acid (**24**) in man and animals have been reported and two metabolites identified.[162] The compound appears to be as potent as indomethacin in RA.[163,164] The benzofuran propionic acid R-803 (**25**) has an ED_{50} of 10 mg/kg in the RFE test and inhibits ultraviolet-induced erythema in guinea pigs and granuloma formation in rats.[165] Gastrointestinal bleeding in man following administration of 1200 mg of R-803 is reported to be less than with 3600 mg of aspirin.[166]



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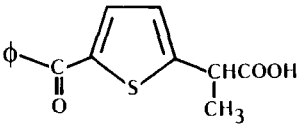

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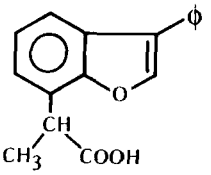

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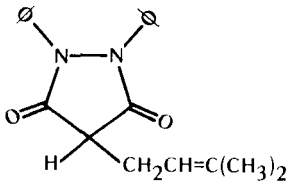
B. *Enolic Acids* — Several antiinflammatory agents are acidic but are not carboxylic acids. Phenylbutazone has been known for some time to be an effective NSAI agent and this has encouraged further research around this structure. A series of 26 publications has appeared on feprazone (DA-2370, **26**)[167] discussing the pharmacology, toxicology and clinical results with this compound. Clinical trials indicate 300-800 mg/d of feprazone to be effective in controlling the symptoms of inflammation in RA[168-170] and OA.[171] Gastrointestinal effects were milder, but other side-effects (rash, headache, etc.) resembled those seen with phenylbutazone.[172] The half-life in man is shorter (39 hr) than that of phenylbutazone (72 hr).[173] Trimethazone (**27**), 1000 mg/d, was as effective as phenylbutazone, 600 mg/d, in a trial in RA and was better tolerated.[174]



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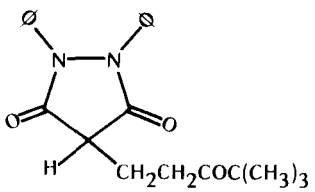

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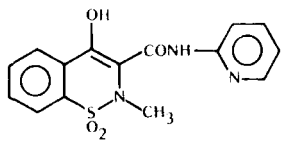
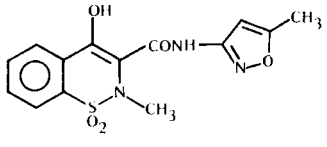
The potent antiinflammatory properties and long biological half-life of piroxicam (CP-16,171, **28**) have been reviewed.[175] Oral ED_{50} values in the RFE test (2 mg/kg) and in RAA (0.5 mg/kg),[176] and a long half-life in several species, including man (48 hr), are reflected clinically where the compound dosed at 20 mg once-a-day is found effective in RA and OA.[177,178,180] In contrast to other NSAI agents, concomitant salicylate administration does not affect the plasma kinetics of piroxicam.[180] Piroxicam is a potent (IC_{50} 0.2 μM) inhibitor of prostaglandin synthesis in cultures of MC5-5 cells.[179] The related compound isoxicam (W 8495, **29**), which is less potent in the RFE test (ED_{50} 50 mg/kg),[181] is reported to exhibit reduced gastric irritating effects in rodents.[181-183] Structure-activity relationships determined for a number of analogs indicate a crucial role of the 5-substituent of bucolome (**30**) for antiinflammatory activity.[184,185]



28



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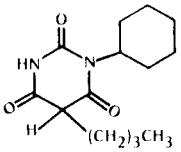
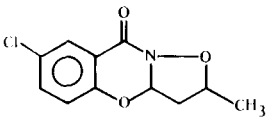


30

C. *Non-Acidic Compounds* — Non-acidic NSAI drugs, reviewed recently by Shen,[186] comprise a much smaller class of drugs, especially when one considers that several such compounds are merely pro-drugs (esters, hydroxamic acids, etc.) of the corresponding carboxylic acids. Meseclazone (W-2395, **31**) is active in the RFE test (ED_{50} 41 mg/kg) and the RAA model[187,188] and is less ulcerogenic than phenylbutazone in rats. The active species, however, is the hydrolysis product 5-chlorosalicylic acid.[189,190] The hydroxamic acids ibuproxam[191] (**32**) and indoxamic acid[192] (**33**) are related to ibuprofen and indomethacin, respectively. Rapid conversion of **32** to ibuprofen has been demonstrated in man.[193]



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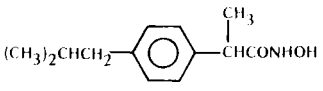

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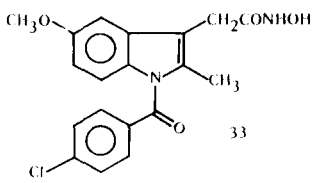
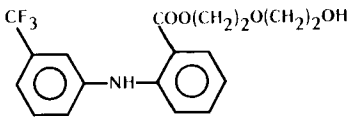


33

Etofenamate (**34**) is an ester pro-drug of flufenamic acid that rapidly penetrates skin after topical application. The pharmacology and toxicology of etofenamate are reported in a series of publications.[194] Clinical trials indicate that topically applied etofenamate produces beneficial effects in a variety of rheumatic diseases.[194] A longer half-life is observed for the parent drug after topical administration (3.3 hr) than after oral administration (1.6 hr). The activity of diphenpyramide (Z-876, **35**) (ED_{50} in the RFE test is 13 mg/kg) is reported to be mediated by its major metabolite, biphenylacetic acid.[195]



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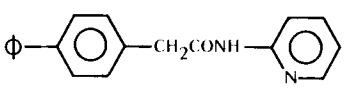

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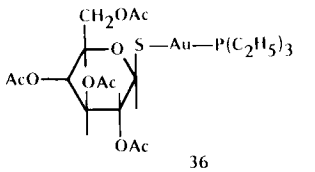

36

Auranofin (SKF D-39162, **36**), a gold derivative, has demonstrated activity following oral administration to either animals (RAA model)[196] or man (RA),[197] and serum IgG levels were observed to fall during therapy in man.

A series of publications review the present place of penicillamine in therapeutics.[199] In a recent double-blind multicenter trial, improvement was seen in a majority of RA patients but the drug caused adverse reactions in nearly 50% of patients.[198]

Conclusion — NSAI agents are of definite benefit to arthritic patients in aiding them to maintain a reasonably normal life by controlling the symptoms of inflammation. Although aspirin at high doses is often an effective antiinflammatory drug, toxic side-effects can limit its use. Individual variability in absorption and excretion leads to wide differences in serum concentrations after administration of a fixed dose of aspirin. Several of the newer NSAI drugs are more potent than aspirin on a dose basis and offer needed improved toleration. A longer half-life of some of the newer agents offers the convenience of less frequent dosing and provides more constant plasma drug levels with more uniform control of the symptoms of inflammation.

The immunoregulatory agents are at an earlier stage of development and those in clinical trials generally exhibit limiting side-effects. However, this class of compounds, rather than primarily alleviating symptoms, as the NSAI drugs do, offer the possibility of arresting the arthritic disease process and thereby halting progressive joint destruction. The trend in current drug research is toward the development of well-tolerated and safe drugs which will arrest or reverse the arthritic disease process.

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