Nimesulide – Actions and Uses

Edited by K. D. Rainsford

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Preface

There can be few drugs used to treat pain and inflammation that have came from such modest and inauspicious beginnings to be so widely accepted in the world today as the title drug for this book, nimesulide. Originally it was developed in the mid-late 1960's by Riker Laboratories (USA) as part of a programme of drug discovery in new non-steroidal anti-inflammatory drugs (NSAID) and pesticides. Helsinn Healthcare SA (Lugano, Switzerland) obtained the world-wide rights for this drug in the 1980's and this company has been the prime mover responsible for its subsequent development. This has involved extensive clinical studies in various arthritic and pain states as well as investigations into the mode of action of nimesulide. From the latter studies it emerged that the drug has selectivity for inhibition of the cyclo-oxygenase-2 (COX-2) enzyme that is responsible for prostaglandins involved in the development of inflammation. This discovery made during the early 1990's led to the recognition that nimesulide was probably the first drug among those NSAIDs used clinically to have COX-2 selectivity. Recently, there has been considerable debate about the degree of COX-2 selectivity shown by the coxibs and other NSAIDs. Nimesulide is classified as a *preferential* COX-2 inhibitor, due to the small degree of inhibition of COX-1 observed in many studies.

It has become clear in recent years that inhibition of COX-2 while significant is not the sole basis for controlling pain and inflammatory conditions. Furthermore, it has also emerged since the discovery of its COX-2 effects that the actions of nimesulide have been found to be more extensive than were originally envisaged in its early stages of development (i.e. inhibition of prostaglandin production and anti-oxidant activities). In addition, it is a potent inhibition of histamine release, modulator of cytokines, steroid receptor mimicry and range of enzymatic activities that underlie degradation of cartilage and bone in osteoarthritis and other joint diseases. Some of the actions of nimesulide may be important in understanding why this drug has low gastrointestinal (GI) side effects along with its proven ability to spare production of GI-protective prostaglandins. Thus, the broad-based biochemical and cellular actions of nimesulide along with its pharmacokinetic properties (rapid absorption, short-lived plasma half life) appear to underlie its reputation for being a very effective drug in controlling a variety of painful and inflammatory states while having low GI and some of the common side effects in comparison with other NSAIDs.

This book represents the first comprehensive monograph on nimesulide covering all aspects relating to its chemical and biological developments, pharmacoki-

netics, pharmaceutical properties, basic and clinical pharmacodynamics, clinical uses in various pain and inflammatory conditions as well as the evaluation, assessment and mechanisms underlying adverse side-effects from nimesulide.

The book would not have been possible without the valuable contributions of the leading experts in the field who have made significant contributions to understanding of the actions, uses and safety of the drug. The invaluable help and advice provided by the medical and scientific staff at Helsinn Healthcare including access to their scientific databases is also most gratefully acknowledged.

This book represents the original work of the authors and editor who are totally responsible for its contents. The opinions and views of these contributors are theirs alone. Thus, this book is an independent assessment of the state of art of knowledge on the drug.

I should like to acknowledge the valuable secretarial and administrative help of Mrs Marguerite Lyons of the Biomedical Research Centre at Sheffield Hallam University as well that of Mrs Veronica Rainsford-Koechli, the assistance in preparing a computer-based literature retrieval system proposed by Mr Alexander Rainsford, and the ever-willing help and assistance of the Library Staff of the Adsetts Learning Centre at Sheffield Hallam University and the Royal Society of Medicine Library, London.

Finally, but not last, my sincere thanks to Dr Hans-Detlef Klüber, Mrs Karin Neidhart and staff at Birkhäuser Verlag, Basel, for their help in the preparation and production of this book.

April 2005

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The discovery, development and novel actions of nimesulide

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Introduction

The historical development of the non-steroidal anti-inflammatory drugs (NSAIDs) has had several different phases. The use in the pre-nineteenth century period of various plant extracts for the treatment of pain classically culminated in the isolation and later synthesis, by Kolbe and Lautermann in 1874, of salicylic acid, probably the first synthetic NSAID [1, 2]. From this came the acetylated salicylate, aspirin, supposedly safer and more effective than salicylic acid at the end of that century [2]. The pyrazolones, antipyrine and aminopyrine, acetanilide and phenacetin were developed in the latter part of the nineteenth century as fever-reducing and pain-relieving agents [1, 3]. Today, these are described as non-narcotic analgesics as they do not have the anti-inflammatory properties of NSAIDs such as aspirin. The development of the analgesics, like that of other drugs to control infections in the nineteenth and early part of the twentieth centuries grew out of expansion of the dyestuff and other chemical industries in Germany, Britain and Switzerland at that time. The success in Germany of the chemical industry in the latter part of the nineteenth century was achieved from close collaborations with scientists and physicians in universities and research institutes. The German chemical industry was conscientiously scientific and highly commercial [3]. The chemical science of compound development was often based on concepts, and little basic biological information was available to enable development of targets as we know them today. Moreover, formal preclinical safety and efficacy studies, along with controlled clinical trials, were not undertaken with the new chemical derivatives – many of them derived from aniline, phenols, naphthalene and other members of the coal tar family of compounds. Clinical studies consisted of simple trials on a few patients. Full-scale toxicity studies were unheard of, although there was appreciation of the need to recognise toxic effects. Indeed with some drugs, such as aspirin, simple studies were undertaken to show that this drug caused less epithelial injury to the skin of fish than that produced by salicylic acid [2]. This period has been described as the age of 'empiricism' [1].

The serendipitous discovery by Landé and Forrestier of the antirheumatic effects of parenteral gold salts (originally discovered by Robert Koch in the 1890s

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to have antitubercular activity) which led Landé in 1927 to observe that aurothioglucose in various non-tubercular conditions produced marked relief from joint symptoms [1]. Empiricism and serendipity also played a part in the applications of D-penicillamine, anti-malarials, corticosteroids, sulphasalazine and methotrexate in the pre- and post-World War II period for the treatment of rheumatoid and related arthritic conditions [1].

In 1948–1949, Brodie and Axelrod discovered that paracetamol was the main metabolite of phenacetin in humans, which was then coming under serious criticism because of methaemoglobinaemia, hepatic and renal problems. Hinsberg and Treupel had found, in 1894, that paracetamol had antipyretic activity like that of phenacetin and antipyrine, although the effects were evident at higher doses of the latter two drugs than with paracetamol [4]. Because of the advent of aspirin and other analgesics paracetamol was forgotten until the observations of Brodie and Axelrod, after which it was marketed in the 1950s in the US in combination with aspirin and caffeine and in the UK on its own in 1956 and thereafter had a slow introduction in other countries. Again serendipity played a considerable part in the discovery and development of paracetamol.

In the late 1940s phenylbutazone was discovered by Stenzel at J R Geigy Pharmaceuticals in Basel, Switzerland, looking for acidic compounds to solubilise the basic compound, aminopyrine, in attempts to use it as an injectable form and improve the latter's effectiveness for arthritic conditions [1]. Studies soon established that the combination was more effective and had a longer duration of effect than aminopyrine from which it emerged that phenylbutazone was the more active of the two components. The key to the discovery of phenylbutazone was undoubtedly the animal assays for anti-inflammatory activity pioneered by Gerhard Wilhelmi at J R Geigy Pharmaceuticals, notably the ultraviolet (UV) light-induced erythema in guinea pigs [1, 5].

Animal assays for anti-inflammatory activity (including the cotton pellet granuloma and carrageenan-induced paw oedema in rats) and the beginnings of structure-activity determinations in empirical screening played a major part in the discovery of indomethacin, an indole, which was based on an idea by T-Y Shen and Charlie Winter that 5-hydroxytryptamine (serotonin) was important in inflammation [1]. The UV erythema assay in guinea pigs was employed by Stewart Adams in the discovery of ibuprofen in the early 1960s but significantly he employed assays for analgesic activity (the Randall-Selitto test in rats) and gastrointestinal toxicity in dogs, as well as detailed investigations on the absorption and distribution of radiolabeled drugs to discriminate those which had low liver accumulation [5].

Knowledge of the mechanisms underlying the development of inflammation in the pre-prostaglandin era [6] and of the actions of aspirin, phenylbutazone, indomethacin and ibuprofen were rudimentary at the time of the discovery of the newer drugs in the 1950s–1960s. Histamine, kinins, possibly 5-hydroxytrypta-

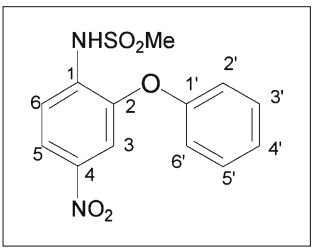

Figure 1
Chemical structure of nimesulide [CA Registry 51803-78-2] known systematically as: Methanesulfonamide, N-(4-nitro-2-phenoxyphenyl)-, or 2-phenoxy-4-nitromethanesulfonanilide, or 4-nitro-2-phenoxymethanesulfonanilide.

mine and a range of metabolic effects involving mitochondrial production of adenosine triphosphate (ATP) and the connective tissue components, as well as effects on leucocytes were considered possible targets for the action of these drugs [7–9] – later to be known as non-steroidal anti-inflammatory agents (NSAIDs) to distinguish them from anti-inflammatory corticosteroids. The pioneering studies of the late Professor Derek Willoughby, Professor Gerald Weissman, Dr Anthony Allison, Dr Philip Davies and many others in the period of the late 1950s to the 1970s saw recognition of a whole range of cellular inflammatory events that are regulated by leucocytes and various plasma – and tissue – derived factors, the interferons, lymphokines and other progenitors of the cytokines heralded the broader and more complex view of inflammation [10, 11]. It was only later after the discovery in 1971 by Professor Sir John Vane, FRS, Nobel Laureate, and his colleagues that the inhibition of the production of prostaglandins in inflammation and platelet functions represented a mechanism for the actions of aspirin and related drugs [1, 6].

In this historical setting the discovery of nimesulide (4-nitro-2-phenoxymethane sulphonanilide; Fig. 1) took place before the period when the prostaglandins were being first found to have roles in inflammation, pain, fever and thrombosis*. Since inevitably the state of the science underlying disease processes serves as the basis for drug discovery at any one period in time it is to the period of the 1960s that we look to understand the biochemical and cellular responses involved in the development of inflammation and pain. The concepts of inflammation and pain at

* *The US patent granted to Moore et al. [14] cites continuation-in-part or abandoned applications dating back to 13 April 1970. Thus, it can be assumed that the concept development of R-805 and others in this series took place in the period before the discovery by Vane (1971) and others of the effects of aspirin and other analgesics on inhibiting production of prostaglandins as a basis to their action in inflammation and other therapeutic actions.*

that time centred on the roles of (a) histamine, kinins and slow reacting substance in anaphylaxis and other systemic mediators of pain and acute inflammatory reactions, (b) the emerging involvement of polymorpho-neutrophil leucocytes (PMNs), monocytes/macrophages and lymphocytes in regulating the major inflammatory reactions, and (c) the changes in the cartilage, synovial and bone metabolism of collagen, glycosaminoglycans/proteoglycans, glucose, fatty acid and in mitochondria [7–9]. Pain was considered to be linked to inflammation [8]. Most of the anti-inflammatory drugs were discovered in this period by testing of compounds *in vivo* in animal models.

Discovery of R-805 – nimesulide

The development of nimesulide arose from investigations by Dr George (GGI) Moore (a medicinal–organic chemist; Fig. 2), Dr Karl F Swingle (a pharmacologist), Dr Bob (RA) Scherrer (a medicinal chemist) and their colleagues at Riker Laboratories Inc (Northridge, California, US, later part of the 3M Company at St Paul, Minnesota, US). They had the idea that since the evidence in the late 1960s suggested that free radicals were important in chronic inflammatory diseases then drugs which scavenge these radicals might have novel anti-inflammatory mechanisms to control chronic inflammation. They undertook a detailed structure-activity analysis and determined the pharmacological properties of the sulphonamides [12]. This class of agents had previously been considered in the 1940s to have antirheumatic activity as a consequence of their antibiotic effect by Svartz and her colleagues at Pharmacia in Sweden and this culminated in the development of the sulphonamide–salicylate conjugate, sulphasalazine [13].

Dr Moore has kindly provided a statement about the thinking and important aspects concerning the concepts that underlay the development of the methane sulphonanilides leading to the identification of nimesulide:

> My name is George G. I. Moore, and I am the inventor of nimesulide, originally R-805. I am currently a Corporate Scientist at 3M Co., working at the St Paul (MN) main campus. Following a BA (Honors in Chemistry) from Cornell University in 1962 and a PhD in Organofluorine Chemistry from University of Colorado in 1965, I joined 3M's fledgling pharmaceuticals project. Our synthetic group included several noteworthy chemists, such as John Gerster, who was to invent the first fluoroquinolone antibacterial and later the immune response modifier imiquimod, and Bob Scherrer, inventor of Parke-Davis' meclofenamic and mefenamic anti-inflammatory agents. At that time, our main approach was application of 3M fluorochemistry to pharmaceutical and agrochemical syntheses. In the antiinflammatory area, two fluoroalkanesulfonanilides (triflumidate and diflumidone) had been identified for clinical

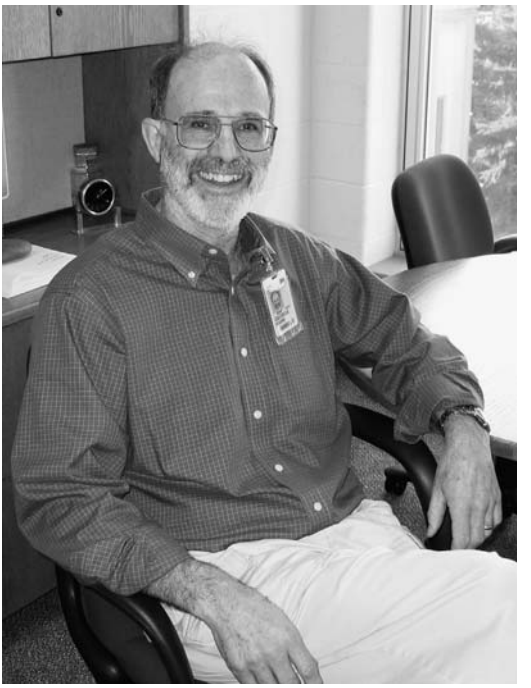

Figure 2
Dr George Moore, the chemist who discovered nimesulide (originally coded R-805). He was born in Boston (USA) in 1941, graduated BA (Honors) in chemistry at Cornell University in 1962, then PhD in organofluorine chemistry at University of Colorado in 1965. He then joined the 3M Company (St Paul, MN), which was subsequently incorporated into Riker Laboratories and then moved from Northridge, CA, to St Paul, MN. He is now a Corporate Scientist in the Industrial Business Laboratory at the 3M Company. Thanks to Dr Moore for providing this photo and biographical details.

trials. My role was synthetic expansion of this series, but by late 1969, it seemed that no improvement in the acute therapeutic ratio was forthcoming, and management decided to curtail syntheses. My young assistant, Larry Lappi, and I had just made a 'final' series which included 4-nitro-2-phenoxy trifluoromethanesulfonanilide, the CF_3-analog of what would become R-805. Karl Swingle, our chief anti-inflammatory pharmacologist, found this exceptionally potent in rat paw carrageenan and other models. With renewed management support, we developed a selective nitration process which allowed us to rapidly make a series of analogs. R-805 was synthesised in early 1971, and it unexpectedly had, by far, the best acute therapeutic ratio. (In both anti-inflammatory and herbicidal activities until this point, the order of activity for

RSO_2NH-Ar had been CF_3>CF_2H>CFH_2>CH_3; in R-805, the 4-NO_2 offset the usual decrease in acidity.) Scherrer, who had been mentoring this synthetic program, used his study of R-805 partitioning into octanol–water to develop his concept of physiological distribution of ionisable drugs. Following secondary evaluations, the material was designated as R-805 for clinical trials in our newly-acquired subsidiary, Riker Laboratories.

This work led to a broader discovery. I focused on the special role of the 4-NO_2 group in this material and several related sulphonanilides. Screening of a variety of materials and use of the emerging science of QSAR showed no correlation with acidity or lipophilicity. There was a weak correlation with the radical stabilisation parameter, 'E_R', (weak in that E_R values were available for only four substituents), with nitro by far the best. This, and the recently-published involvement of PGs in inflammation, led me to hypothesise in late 1971 that free radical scavenging might be involved. I made many types of modified antioxidants, primarily phenolic but including N- and C-based radicals. Swingle found an exceptionally high percentage of these series was effective in his models, strengthening an antioxidant–anti-inflammatory association. We went on to identify one of these for topical trials.

At about this time, Riker reassessed its business plan and decided to discontinue the anti-inflammatory area. R-805 was made available for license, and we all went on to other things, but we still take pride in the fact that nimesulide is used today.

Moore and co-workers recognised from their structure-activity analyses that the anti-inflammatory properties of trifluoro-alkane-sulphonamides are related to the powerful lipophilic properties of the CF_3SO_2 group which serves as a powerful electron attractor (Hammet coefficient, s = 1.3) and their acidic properties [12]. The development of nimesulide (R-805) was to some extent an extension of the recognition of the acidic properties of the nitro-group which is located at the *para*-position of the methyl-sulphonamido-moiety [14] (Fig. 1).

In the structure-activity analysis of this series the anti-inflammatory activities were determined using the UV erythema assay in guinea pigs and the rat paw carrageenan assay, while the analgesic activity was determined in the Randall-Selitto in rats and the phenylquinone writhing test in mice [12, 14–17]. Assays of prostaglandin synthesis inhibition were later performed using the bovine seminal vesicle microsomal preparation *in vitro* [15], which was a standard preparation employed at that stage (containing what is now known to be COX-1). Studies by Rufer and colleagues [18] discovered the basis of the oxy-radical scavenging effects of nimesulide during prostaglandin endoperoxide metabolism were similar to those of the phenolic compound, MK-886, which had been previously shown by Kuehl and co-workers [19] to stimulate prostaglandin production *in vitro* as a result of scavenging the peroxy-radical formed during the oxygenation of the 15-carbon moiety

of arachidonic acid. This formed one basis in support of the free radical concept being a basis for the therapeutic target set by Moore and his colleagues in their development of the methane sulphonanilides. Later studies [16] (also reviewed in Chapter 4) have subsequently shown that there are other antioxidant mechanisms involved in the anti-inflammatory activity of nimesulide.

Chemical synthesis

The synthesis mentioned in the original patent [14] (Fig. 3) involved dissolving 2-phenoxymethanesulphonanilide (initially prepared by treating 2-phenoxyaniline with methyl-sulphonyl chloride) in glacial acetic acid with warming, then mixing in 70% nitric acid (Fig. 4). After heating, the mixture is poured onto water and the precipitate collected by filtration. Following recrystallisation from ethanol, a light tan solid is recovered with MPt 143–144.5 °C which is 4-nitro-2-phenoxymethanesulphonanilide. Several other synthetic procedures for the synthesis of nimesulide, its intermediates and analogues have been subsequently reported [20–26] (Fig 5).

Of the efforts to produce other methane sulphonanilides only diflumidone [15] appears to have proven to be a clinical candidate, but is no longer under development.

Development of nimesulide

Following the initial discovery, and the pharmacological and toxicological studies of R-805 it was investigated for clinical efficacy and safety in patients with rheumatoid arthritis [27]. These studies showed that the drug was effective in controlling pain and inflammation. Some of these studies were performed at what is now regarded as very high doses (up to 800 mg/d) and it was not surprising that some liver enzymes were elevated in these patients.

In 1980, Helsinn Healthcare SA of Lugano, Switzerland, acquired the worldwide licensing rights for nimesulide and proceeded to invest in extensive clinical and basic studies on the actions of the drug. The production by Helsinn of nimesulide was first commenced in 1985. The first certificate of analysis released is reported in Figure 6. It was first introduced in Italy in 1985. Nimesulide is now marketed in over 50 countries worldwide [27, 28], through partnerships with leading pharmaceutical companies in most of these countries [27]. The countries where it is marketed by Helsinn and its partners include many in continental Europe, Central and South America, and the Far East. For commercial reasons the drug has not been marketed by Helsinn or others in the US, UK or Australia [27]. The various trade mark names for nimesulide registered worldwide and originated by Helsinn are shown in Appendix A. Nimesulide is produced and sold

United States Patent Office

3,840,597

Patented Oct. 8, 1974

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3,840,597

SUBSTITUTED 2-PHENOXY ALKANE-SULFONANILIDES

George G. I. Moore, Birchwood, and Joseph Kenneth Harrington, Edina, Minn., assignors to Riker Laboratories, Inc., Northridge, Calif.

No Drawing. Continuation-in-part of application Ser. No. 118,476, Feb. 24, 1971, which is a continuation-in-part of abandoned application Ser. No. 28,148, Apr. 13, 1970. This application July 3, 1972, Ser. No. 268,606

Int. Cl. C07c *143/74*

U.S. Cl. 260—556 F 31 Claims

ABSTRACT OF THE DISCLOSURE

Diphenyl ethers wherein an alkyl- or haloalkylsulfonamido substituent group is oriented ortho to the ether linkage and a nitro or amino substituent is oriented in the 4 or 5 positions with respect to the sulfonamido group are active anti-inflammatory agents.

This is a continuation-in-part of the copending application, Ser. No. 118,476 filed Feb. 24, 1971, and now abandoned, which is a continuation-in-part of application Ser. No. 28,148 filed Apr. 13, 1970, now abandoned.

This invention relates to diphenyl ethers substituted by an alkyl- or haloalkylsulfonamido group and a nitro or amino group (as defined herein) wherein the orientation of the groups is critical. In particular the invention relates to such compounds wherein the alkyl- or haloalkylsulfonamido group is oriented in the 2 position (ortho) with respect to the ether linkage and the nitro or amino group is oriented in the 4 or 5 position with respect to the alkyl- or haloalkylsulfonamido group, and to salts thereof. The rings and the sulfonamido nitrogen are optionally substituted. The compounds are anti-inflammatory agents. Methods for the preparation and use of the compounds are also described.

Alkysulfonamido and haloalkylsulfonamido substituted diphenyl ethers have ben alluded to heretofore. Thus, see British patents 738,758, 854,956 and 856,452, French patent 1,188,591 and U.S. Pat. 3,223,582. However, none of these patents disclose or suggest the compounds of the present invention wherein a nitro and amino group must be present, nor do they suggest the critical nature of the orientation of the substituent groups to obtain high activity. Furthermore, the pharmacological activity of the compounds of the invention is not suggested by the prior art.

Many non-steroidal anti-inflammatory agents have been discovered in recent years, and some are currently marketed for the treatment of various conditions treated by anti-inflammatory, analgetic and antipyretic agents. However, these agents have significant side-effects which prevent their use in many patients. The search for anti-inflammatory agents with reduced side effects and improved therapeutic ratio is continuing. The compounds of the present invention are effective anti-inflammatory agents with excellent therapeutic ratios.

It is therefore an object of the present invention to provide compounds which are anti-inflammatory agents.

It is another object of the invention to provide anti-inflammatory compositions containing one or more haloalkyl- or alkylsulfonamidoaryl compounds as active ingredients therein.

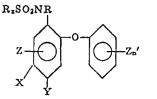
It is a further object of the invention to provide a method for controlling inflammation in mammalian tissue.

Still other objects will be made apparent by the following specification.

2

DETAILED DESCRIPTION OF THE INVENTION

According to the present invention there is provided a class of compounds of the formula



I

wherein R_x is an optionally halogenated lower alkyl radical, R is hydrogen, cyano, alkyl, alkylsulfonyl, haloalkylsulfonyl, a cation or

where R^1 is alkyl and A is oxygen or a carbon-carbon bond, X is alkoxy, alkyl, halogen, acetamido, nitro, hydrogen, amino, alkoxycarbamoyl or dialkylamino, Y is nitro, amino, alkoxycarbamoyl, dialkylamino or hydrogen, provided that one of X and Y is nitro, amino, alkoxycarbamoyl, or dialkylamino, Z is halogen, nitro or hydrogen, Z′ is halogen, alkyl, alkoxy, nitro, amino alkanamido, haloalkyl, hydroxy, dialkylamino, alkoxycarbamoyl, alkylthio, alkylsulfonyl, alkanoyl, or alkylsulfinyl and *n* is 0–2 (zero, one or two), provided that the individual aliphatic groups appearing in the R_x, R, X, Y and Z moieties, including those characterized as lower alkyl, contain from one to four carbon atoms each. By alkanamido herein is meant the group

and by alkoxycarbamoyl is meant

Compounds of the invention wherein R is hydrogen or a cation are presently most preferred. The compounds in which R is alkyl or alkylsulfonyl are preferred to those in which R is haloalkylsulfonyl, cyano or

When R is alkyl, alkylsulfonyl or haloalkylsulfonyl it preferably contains one carbon atom. The preferred halogens in the haloalkylsulfonyl R moieties are fluorine and chlorine. When R is

A is preferably oxygen, and R′ preferably contains one or two carbon atoms.

R_x may be straight or branched chain when it contains three or four carbon atoms. R_x preferably contains one carbon atom. R_x is preferably methyl, chloromethyl, fluoromethyl, difluoromethyl or trifluoromethyl, and most preferred is methyl.

It is preferred that *n* is zero or one. Most preferred is *n* equal to zero. When *n* is one, Z′ is preferably oriented para or ortho, and most preferably Z′ is halogen oriented para. Orientation is relative to the diphenyl ether oxygen.

It is presently preferred that Z is hydrogen. When Z is halogen it is preferably chlorine.

Most preferably X is hydrogen and Y is nitro. Other preferred combinations are those in which X is amino and Y is hydrogen; X is ethoxycarbamoyl and Y is hydrogen; X is dimethylamino and Y is hydrogen; and X is acetamido and Y is nitro.

Figure 3

US Patent number 3,840,597 issued to George GI Moore and JK Harrington from earlier applications [continuation in part] of February 24 1971 and April 13 1970 and assigned to Riker Laboratories Inc., Northridge, CA, USA [14]. The initial date of the application (1970) clearly antedates the first report of Vane and colleagues of the discovery of action of NSAIDs in controlling prostaglandin production.

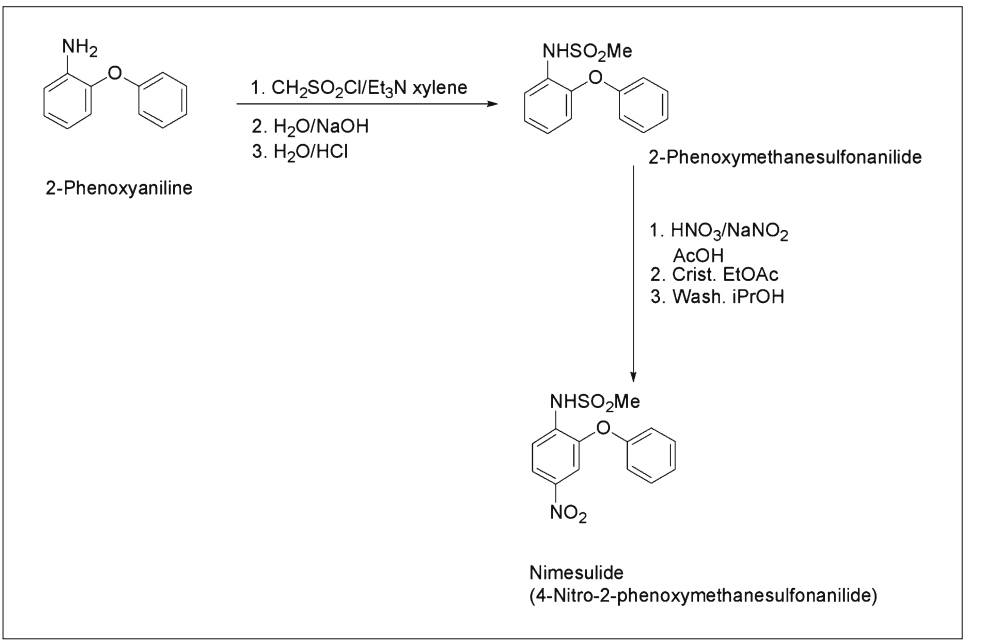


Figure 4
Scheme for the synthesis of nimesulide [14].

by a considerable number of generics manufacturers in Italy, India, China and South America, which is a reflection on its widespread acceptance as an effective pain-relieving and anti-inflammatory agent.

The principal indications for the drug in most countries are for the relief of pain, symptomatic treatment of painful osteoarthritis, extra-articular disorders including tendinitis, bursitis, post-surgical pain including that from dental surgery, ear, nose and throat conditions, dysmenorrhoea and other acute pain states [28]. The most recent Summary of Product Characteristics in force in the EU countries and showing the endorsed indications of the drug as approved in 2003 by the European Medicines Evaluation Agency (EMEA) is shown in Appendix B. This has been prepared and approved from the most up-to-date information on the safety and efficacy of nimesulide and must be regarded as an international standard for recommendations for the use of this drug.

Clinical studies supporting therapeutic claims have been undertaken by Helsinn worldwide in over 90,000 patients [28]. To date over 346 million treatment courses have been employed using the product from Helsinn [28].

After acquiring the licence worldwide, Helsinn then licensed the product for veterinary indications to the French pharmaceutical company, Virbac S.A. [27].

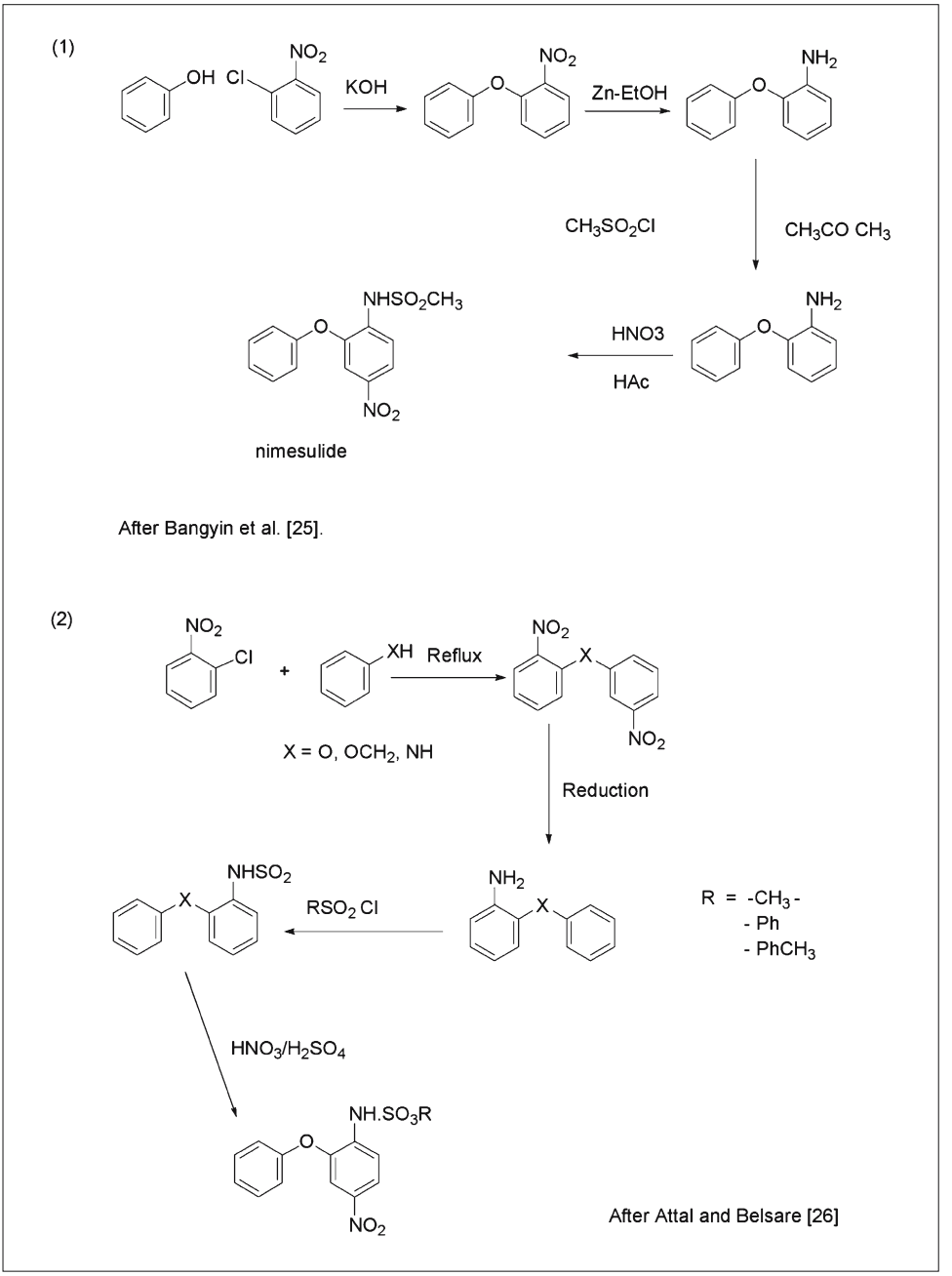
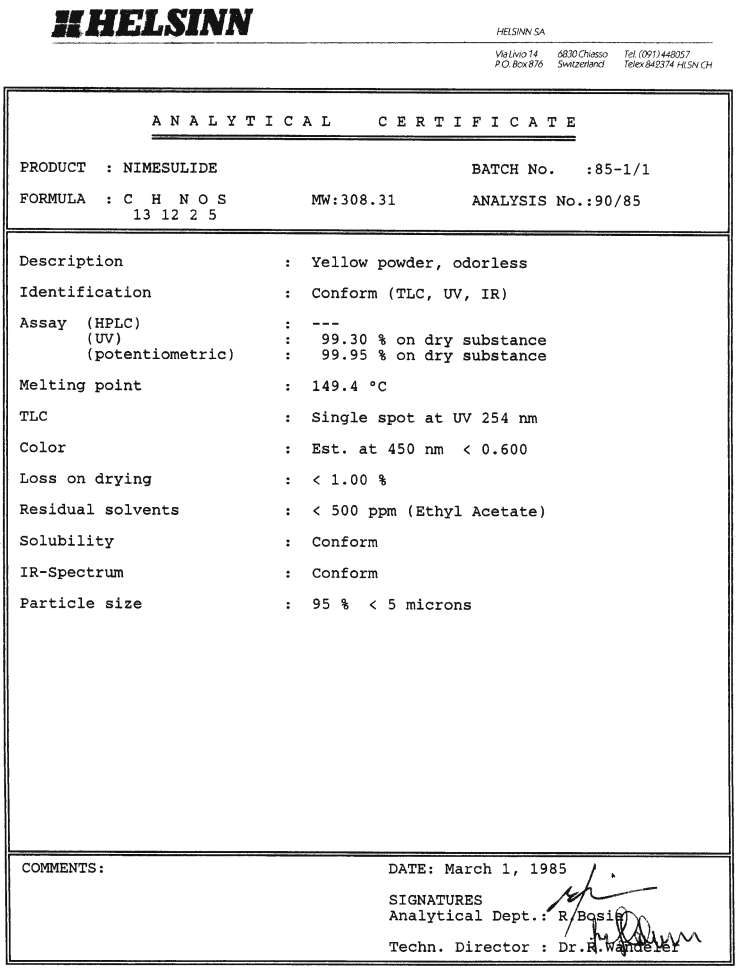


Figure 5
Some schemes for the synthesis of nimesulide, intermediates and analogues.



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A N A L Y T I C A L C E R T I F I C A T E

PRODUCT : NIMESULIDE — BATCH No. :85-1/1

FORMULA : C H N O S 13 12 2 5 — MW:308.31 — ANALYSIS No.:90/85

Description	:	Yellow powder, odorless
Identification	:	Conform (TLC, UV, IR)
Assay (HPLC)	:	---
(UV)	:	99.30 % on dry substance
(potentiometric)	:	99.95 % on dry substance
Melting point	:	149.4 °C
TLC	:	Single spot at UV 254 nm
Color	:	Est. at 450 nm < 0.600
Loss on drying	:	< 1.00 %
Residual solvents	:	< 500 ppm (Ethyl Acetate)
Solubility	:	Conform
IR-Spectrum	:	Conform
Particle size	:	95 % < 5 microns

COMMENTS:

DATE: March 1, 1985

SIGNATURES
Analytical Dept.: R. Bosia

Techn. Director : Dr. R. Wandeler

Figure 6
The first analytical certificate for production of nimesulide (of Helsinn's origin). The drug was first marketed in Italy in 1985.

Physical and chemical properties

Recently, a monograph for nimesulide was included in the European Pharmacopoeia (Ph. Eur mon. 01/2002:1548).

Nimesulide is a pale white-yellowish crystalline powder with a melting point of 147–149 °C and a molecular weight of 308.31 [29, 30]. It is a weak acid having a pKa of 6.4–6.8 [18, 30–32]. It has poor aqueous solubility but is soluble in

Table 1 – Solubility of nimesulide in various solvents

Solvent(s)			Solubility mg/ml	Dielectric Constant (ε) of Solvent(s)
Water			0.014	78.36
Glycerol			0.218	42.5
Methanol			8.812	32.63
Ethanol			3.320	24.3
Butanol			2.120	17.1
n-Octanol			0.970	9.72
Ethylene Glycol			0.510	37.7
Propylene Glycol			1.760	32.0
Polyethylene Glycol (PEG) 400			63.120	12.4
Glycerol	80% + Ethanol	20%	0.691	38.86
	60%	40%	1.693	35.22
	10%	90%	4.040	26.12
PEG 400	80%	20%	9.900	21.92
	60%	40%	24.640	19.54
	90%	10%	65.600	13.59
Water	80%	20%	0.101	67.55
	60%	40%	0.125	56.74
	90%	10%	3.320	24.30
Glycine-NaOH buffer	pH	7	0.034	–
		7.9	0.081	–
		8.84	0.807	–
		9.42	3.886	–
		9.52	6.914	–
		10.17	34.639	–

Partition coefficient in n-octanol/water = 1.788, pKa = 6.4–6.8 [18, 30–32]. The pKa varies according to different solvents/system. From: Seedher & Bhatia (2003) [34].

acetone, chloroform and ethyl acetate and is slightly soluble in ethanol [29, 30]. Details of the solubility in various solvents and solvent mixtures are shown in Table 1 [34]. Of the alcohols the drug is most soluble in methanol with progressive decrease in solubility with increase in carbon length of the respective alcohol and decrease in dielectric constant of the solvent (Tab. 1). The drug is most soluble in polyethylene glycol (PEG) 400 and this is a potentially useful solvent system for oral dosing of laboratory animals. The amount of PEG employed in oral dosing can be reduced by adding ethanol (Tab. 1). No doubt the addition

Table 2 – Crystal and Molecular Properties of Nimesulide

$C_{13}H_{12}N_2O_5S$ $M_r = 308.31$

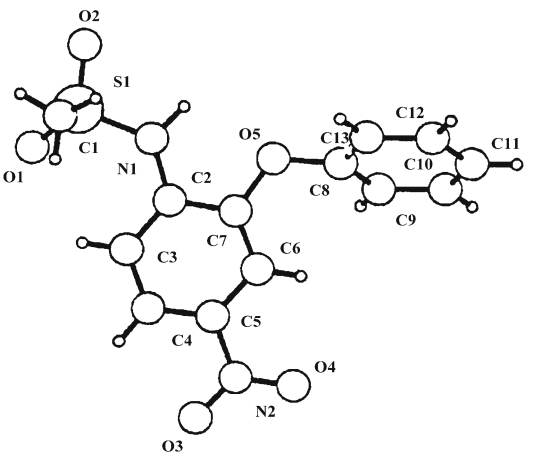
Crystal form Monoclinic $C2/_c$

Dimensions

a = 33.657 Å (3)
b = 5.1305 Å (3)
c = 16.0816 Å (10)
β = 92.368° (8)
V = 2774.5 Å (3)
Z = 8
$D_x = 1.476$ mg m^{-3}

θ = 28.31–32.35°
μ = 2.310 mm^{-1}
T = 293 K (2)
Prism 0.30 × 0.30 × 0.27

Molecular structure with atom-labelling scheme.



From: Dupont et al. [35].

of water to PEG-ethanol systems would ensure relatively high solubility so reducing the mass of the organic solvents added to an oral dosage form. Of particular utility are the observations that the poor water solubility of nimesulide is overcome when the drug is dissolved in relatively small amounts (10%) of added ethanol (Tab. 1) and this may be an advantage when preparing mixtures of the drug for tissue culture. There is a pronounced increase in aqueous solubility when the drug is dissolved in glycine-NaOH buffer at pH >7.2 (Tab. 1). Some COX-2 selective inhibitors (meloxicam, celecoxib, rofecoxib) also show similar

trends in solvent and solution properties to nimesulide although there are quantitative differences [33].

The liposolubility of nimesulide as determined by its partition coefficient, Log P, in *n*-octanol/water is 1.788 [34].

The crystal structure of nimesulide has been reported by Dupont et al. [35] and the details of this are shown in Table 2. The stereochemical structure (Tab. 2) reveals that the O^5 phenyl moiety is out of plane by about 75° with respect to the nitro-sulphonanilide [34]. The molecular conformation is stabilised by intramolecular NH···O hydrogen bond [35]. The cohesion of the nimesulide crystal is the result of the NH···O and van der Waal's interactions [35].

Acid-base hydrolysis of *N*-amido-methyl-sulphonamides at high temperatures (50°C) has been reported by Iley et al. [36]. The acid-catalysed pathway involves protonation of the amide followed by expulsion of a neutral amide and formation of a sulphonyliminium ion. The base-catalysed hydrolysis by nucleophilic attack of the hydroxide ion at the amide carbonyl carbon atom forms benzamide and sulphonamide by an Elcbrev mechanism involving ionisation of the sulphonamide.

Chemical analysis

Analysis in plasma and other biological fluids as well as in solids of nimesulide and its metabolites can be performed by high performance liquid chromatography (HPLC) using reverse phase columns and UV detection [29, 30, 37] (see also Chapter 2; Bernareggi and Rainsford), and HPLC combined with mass spectrometry [38–41]. The HPLC methods mostly employ either aqueous (with or without buffers such as phosphate) acetonitrile or methanol mixtures. In water based systems there will be two ionised states of nimesulide (with and without protonation of the amino group) present whereas the use of acidic phosphate buffers will control this and enable the non-ionised form to be determined [41].

A comprehensive determination of all the major metabolites of nimesulide present in urine and faeces, including phenolic glucuronides and sulphates, has recently been reported [40]. Determination of nimesulide in solid dosage forms has been undertaken by reverse-phase HPLC using electrochemical detection [41], or by fluorimetry using diazotisation of the drug with *N*-(1-naphthyl) ethylene [42], or by second order derivative UV spectrophotometry [43].

UV spectrophotometric analyses of pure and solid dosage forms have been applied using 50% v/v and 100% acetonitrile as solvents [44]. The limits of detection in these solvent systems were 0.46 µg/ml and 1.04 µg/ml respectively, and high precision and accuracy was claimed for these methods. The advantage of employing acetonitrile as the solvent is that this can be used to extract the drug from various matrices. Also subsequent HPLC can be performed following initial UV spectrophotometry of the samples by directly injecting the acetonitrile extract

onto the HPLC column without further purification, or if necessary using reverse-phase mini-columns.

A rapid, sensitive and specific method has been reported by Patravale et al. [45] for the quantitative analysis of nimesulide and degradation products in solid dosage forms using high performance thin layer chromatography (HPTLC). Quantification was achieved using UV scanning densitometry. Using methanolic extraction recovery of nimesulide was found to be 99.5% with the limits of detection and quantitation being 60 and 100 ng respectively. This technique, while requiring some fastidiousness, offers considerable potential for routine laboratory analysis of solid nimesulide.

The extraction of nimesulide, like that of some other NSAIDs, from solid matrix forms may be achieved using supercritical CO_2 fluid extraction [46]. The reported method [46] applied to solubilisation of nimesulide achieved dynamic saturation at pressures between 100–220 bar at temperatures of 312.5 K and 331.5 K. Nimesulide and some other NSAIDs had relatively high solubilities with nimesulide having solubility of 0.85–9.85 $\times$ 10^5 mole fraction [46]. With automation and method development supercritical fluid extraction could be applied to extraction of the drug from complex biological matrices or fluids (e.g., frozen and crushed brain, bone marrow and bone, urine) where conventional solvent extraction methods may be more difficult.

Electrochemical detection applied to HPLC analysis of drugs, including the NSAIDs, often proves difficult because of the problem of poisoning occurring frequently of the electrode. Catarino et al. [47] developed a technique to overcome this problem by employing a twin channel system with passage of a regenerating solvent over the surface of the electrode. The method was applied to the amperometric determination of nimesulide in pharmaceutical preparations.

Chemical reactions of nimesulide

A key chemical property of nimesulide is its antioxidant potential and this has been investigated using a number of different chemical and biochemical procedures [48–52].

Direct evidence of oxy-radical scavenging activity of nimesulide and its 4-hydroxy-metabolite was shown by Maffei Facino and co-workers using electron spin resonance spectroscopy (ESR) [48]. Using 5,5-dimethyl-1-pyrroline-*N*-oxide (DMPO) in chloroform as a spin trapping agent and ultrasonic irradiation of water (sonolysis) to generate hydroxyl-radicals ($OH^{\bullet}$) these authors observed that 1–50 µmol/L nimesulide caused a concentration-dependent reduction in the DMPO-OH adduct observed by ESR; at the highest concentration the signal was almost completely inhibited (Fig. 7). 4-Hydroxy-nimesulide was appreciably less active in trapping the $OH^{\bullet}$ radicals since the concentration required for 50%

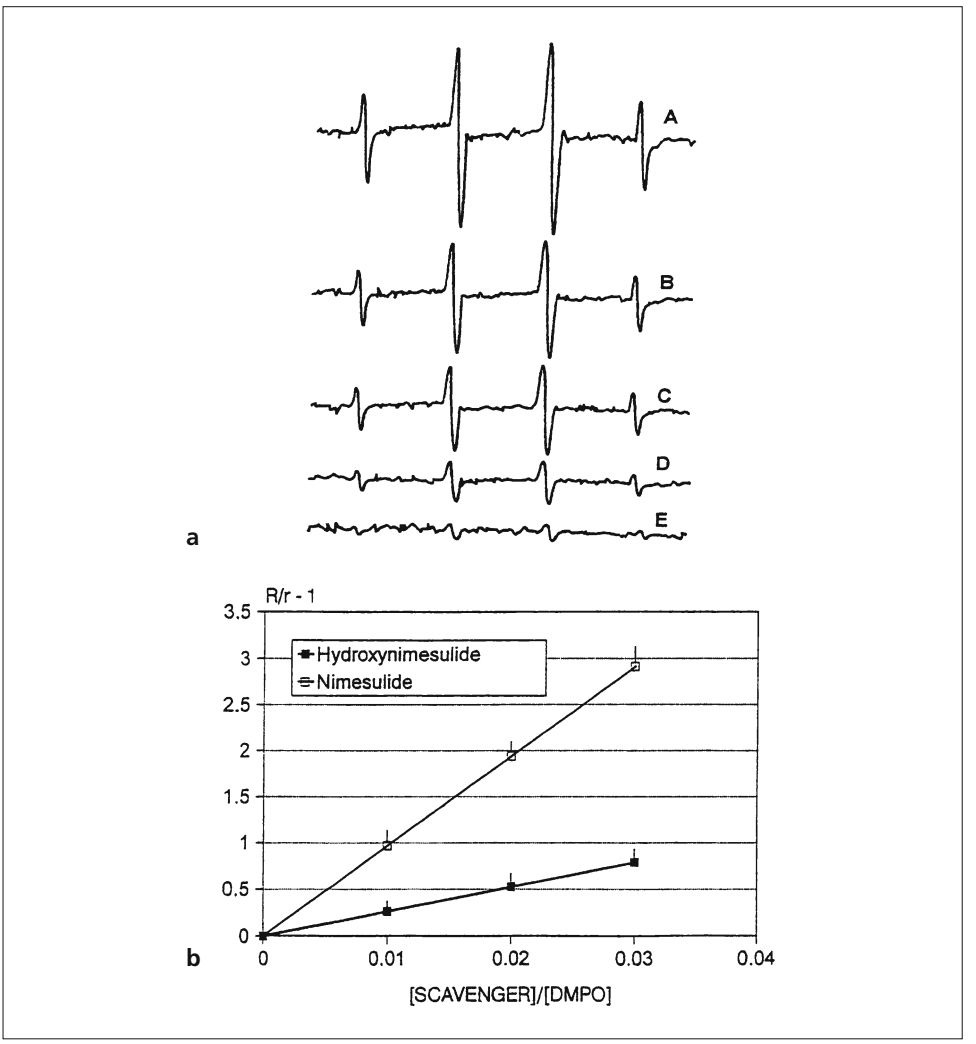


Figure 7

The ESR Spectra (upper panel; Figure 7a) and graph of the kinetic reactions (lower panel; Figure 7b) showing the hydroxyl scavenging activity of nimesulide and 4-hydroxynimesulide. (a) The ESR spectra were of the DMPO-OH spin adduct in the absence (A) and in the presence of increasing concentrations of nimesulide (B = 1 µmol/L; C = 10 µmol/L; D = 50 µmol/L; E = 100 µmol/L). These were recorded after 15 mins of ultrasound radiation. (b) Kinetic reactions of hydroxyl radicals with DMPO and nimesulide or 4-hydroxy-nimeslude. R and r are the initial rates of formation of DMPO-OH in the absence and presence of the two compounds. Data are means ± standard deviation of 5 determinations. From: Maffei Facino et al. [48]; reproduced with permission of the publishers of Arzneimittelforschung.