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SYNTHESIS AND ANTI-INFLAMMATORY SCREENING OF PYRAZOLINE DERIVATIVES BEARING A SULFONAMIDE MOIETY

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1. INTRODUCTION

Inflammation is a protective response, but when it persists it becomes the common thread behind conditions as different as rheumatoid arthritis, osteoarthritis, inflammatory bowel disease and a good share of chronic pain. Non-steroidal anti-inflammatory drugs (NSAIDs) remain the most widely used treatment, and their effect comes largely from blocking cyclooxygenase (COX) enzymes and so reducing prostaglandin formation [1, 2]. The price is well known. Inhibition of the

Abstract

Pyrazolines are five-membered nitrogen heterocycles that have attracted sustained interest as anti-inflammatory scaffolds, and the addition of a sulfonamide group recalls the selective cyclooxygenase-2 inhibitors. This review, which reports no new data, summarises the published literature on the design, synthesis, structural characterisation and anti-inflammatory screening of pyrazoline derivatives bearing a sulfonamide moiety. It covers the usual chalcone-based synthetic route, the spectroscopic evidence used to confirm structures, in vitro and carrageenan paw oedema screening, and emerging structure-activity trends. Reported compounds often show activity comparable to reference drugs in rodent assays, but enzyme selectivity data, pharmacokinetics and safety work are limited, and results are hard to compare between laboratories.

constitutive COX-1 isoform in the stomach and platelets accounts for much of the gastrointestinal bleeding and ulceration seen with older drugs, while the search for selectivity toward the inducible COX-2 isoform produced the coxibs [3, 4]. That search is still the main motivation behind new heterocyclic anti-inflammatory scaffolds, among them the pyrazolines.

Celecoxib, a 1,5-diarylpyrazole carrying a benzenesulfonamide group, came out of a systematic medicinal chemistry programme and showed that a rigid vicinal diaryl heterocycle could deliver COX-2 selectivity [5]. Its gastrointestinal tolerability advantage over conventional NSAIDs was reported in randomised trials, though how far it holds in every patient group has been argued over [6]. Cardiovascular events then emerged as a real concern, most visibly with rofecoxib, which was withdrawn after an adenoma prevention trial showed an excess of thrombotic events [7, 8]. The lesson drawn by most chemists was not to abandon selectivity but to demand better pharmacological characterisation of new compounds, including safety profiling that earlier academic screening papers often omitted.

Against this background, pyrazolines carrying a sulfonamide moiety are an obvious family to examine. They are easy to make, structurally close to celecoxib, and offer several positions at which substituents can be varied. A large number of papers describe their synthesis and a first anti-inflammatory screen, usually in rats. This review draws those reports together, covering design rationale, synthetic routes, structural proof, screening methods, structure-activity trends and the limits of the data. It reports no new experimental findings, and where a number or claim is given it is one that appears in the cited publications. Emphasis is placed on how the evidence was generated as much as on what it appears to show, because for this class of compounds the quality of the method often decides how far a headline result can be trusted.

2. DESIGN RATIONALE

A 2-pyrazoline is a 4,5-dihydro-1H-pyrazole ring, essentially a cyclic hydrazone formed

from an α,β -unsaturated ketone and a hydrazine. The ring has a stereogenic centre at C5 when the substituents differ, and most reported compounds are racemic. Pyrazolines and the related pyrazoles have been associated with a very broad list of biological activities, including anti-inflammatory, analgesic, antimicrobial, anticonvulsant, antidepressant and antitumour effects, which is both an attraction and a warning, since such breadth can reflect genuine pharmacology or nothing more than assay promiscuity [9, 10, 11]. The scaffold is usually decorated with an aryl group at C3, another at C5 and a substituent on N1, and it is this 1,3,5-pattern that is varied in nearly every study.

The sulfonamide is added for a specific reason. Structural work on COX-2 showed that replacing isoleucine at position 523 of COX-1 with the smaller valine opens a side pocket, and that the sulfonamide of celecoxib-type inhibitors sits in it, which helps explain their selectivity [12, 13]. A primary benzenesulfonamide on the N1 aryl ring, introduced conveniently through 4-hydrazinobenzenesulfonamide, therefore mimics a key pharmacophore of the coxibs [5, 14]. Sulfonamides also bind zinc in carbonic anhydrases, and that interaction is exploited in other drug classes [15, 16]. It is an off-target activity to keep in mind, because compounds designed as anti-inflammatory agents may inhibit these enzymes as well, with consequences that few screening papers examine.

Design is rarely purely structure-based in this literature. Many groups begin with a convenient library of chalcones and then add the hydrazine component that carries the sulfonamide, judging the result afterwards by molecular docking and a check of simple physicochemical descriptors such as polar surface area and rotatable bond count [17]. Descriptor filters of this kind are useful for flagging poor oral absorption but say little about selectivity. A more subtle problem concerns the starting chalcones, which are Michael acceptors and a recognised source of assay interference [18, 19]. Cyclisation removes the reactive enone, yet traces of unreacted chalcone can remain and produce activity that belongs to the impurity. Careful

purification and purity data are therefore part of the design, not an afterthought.

Selectivity is measured, not assumed. Whole-blood assays that compare thromboxane generation by platelet COX-1 with prostaglandin E2 production by lipopolysaccharide-stimulated COX-2 give a clinically relevant ratio, and human gastrointestinal toxicity has been associated with NSAIDs that favour COX-1 in such assays [4, 20]. Purified enzyme assays are cheaper and allow kinetic analysis, though the time-dependent binding of many selective inhibitors complicates simple IC50 comparisons [20, 21]. Neither approach appears in most synthetic papers, which is why claims of COX-2 selectivity based only on docking scores should be read as hypotheses. Studies that report both enzyme data and animal results, such as those summarised in table 1, are the exception.

Table 1: Reference points and published findings on sulfonamide-bearing pyrazolines

Compound or method	Reported feature	Ref.
Celecoxib diarylpyrazole	Benzenesulfonamide enters the COX-2 side pocket and gives selective inhibition	[5, 12]
Rofecoxib withdrawn coxib	Adenoma prevention trial showed excess cardiovascular events	[8]
Benzenesulfonamide pyrazolines 1,3,5-trisubstituted	Paw oedema inhibition approaching reference drugs; some with less gastric injury	[22]
Chalcone-derived pyrazolines	Anti-inflammatory and analgesic activity reported in rodents	[23]
Acridinyl pyrazolines	Significant inhibition of carrageenan paw oedema against control	[24]
Pyrazole derivatives	Combined anti-inflammatory and antimicrobial activity described	[25]
Claisen–Schmidt then hydrazine	Chalcone formed first, then cyclised to the pyrazoline in refluxing ethanol or acetic acid	[18, 26]
Microwave heating	Cyclisation shortened from hours to minutes in many examples	[27]
Carrageenan paw oedema	Biphasic acute model, later phase prostaglandin dependent	[28, 29]

Compound or method	Reported feature	Ref.
Albumin denaturation	Simple in vitro filter with limited mechanistic meaning	[30]
PAINS and drug-likeness filters	Flag assay interference and poor drug-like properties	[17, 19]

3. SYNTHETIC ROUTES

The standard route has two stages. First, a Claisen–Schmidt condensation joins an acetophenone and an aromatic aldehyde under base catalysis, usually sodium or potassium hydroxide in ethanol at room temperature or with cooling, to give the chalcone [18, 31]. The product often precipitates on acidification or dilution and is recrystallised. Yields in the literature are typically moderate to good, and electron-rich aldehydes generally react more slowly than electron-poor ones. The chalcone is the key intermediate, and because its aryl rings define the C3 and C5 substituents of the final pyrazoline, a library is built simply by varying the two starting materials. The simplicity of this step explains why so many analogues have been reported.

In the second stage the chalcone is treated with a hydrazine. For sulfonamide-bearing pyrazolines, 4-hydrazinobenzenesulfonamide hydrochloride is refluxed with the chalcone in ethanol or glacial acetic acid, often with sodium acetate to liberate the free hydrazine [22, 26]. The reaction proceeds through a hydrazone that cyclises by addition of the second nitrogen to the β -carbon. Reaction times of six to twelve hours are common in older reports, and the product is isolated by pouring into ice water. Alternative approaches place the sulfonamide on a C3 aryl ring through a sulfonamido-acetophenone, or use thiocarbamoyl or acyl hydrazines to give N1-substituted pyrazolines that are later modified [9, 10].

Greener and faster methods have been reported. Microwave irradiation shortens the cyclisation from hours to minutes in many examples and sometimes improves yield, as expected from controlled dielectric heating [27]. Ultrasound, grinding and solvent-free conditions are also described, although the benefit over conventional heating is not

always demonstrated against a properly optimised control. One practical difficulty is that 2-pyrazolines can oxidise to the aromatic pyrazoles when heated in air or in certain solvents, so prolonged heating can lower the proportion of the desired dihydro product [11, 26]. Reaction monitoring by thin layer chromatography and careful temperature control reduce this risk, and reporting the actual isolated yield after recrystallisation is more informative than a crude figure.

4. STRUCTURAL CHARACTERISATION

Structures in this literature are normally assigned by a combination of infrared spectroscopy, proton and carbon NMR, mass spectrometry and elemental analysis [32]. In the infrared spectrum the sulfonamide gives two strong stretching bands near 1330 and 1150 cm^{-1} together with N–H stretches above 3200 cm^{-1} , and the ring C=N appears in the neighbourhood of 1600 cm^{-1} . The disappearance of the chalcone carbonyl band is taken as evidence that cyclisation has occurred. These assignments are standard and robust and are quoted in almost every paper in the field. Infrared data alone cannot distinguish a pyrazoline from a pyrazole, which is why the NMR evidence matters [11, 32].

The most convincing proton NMR signature of a 2-pyrazoline is the ABX pattern of the three ring protons. The two diastereotopic protons on C4 appear as separate doublets of doublets, typically between about 3 and 4 ppm, and the C5 proton appears further downfield as a third doublet of doublets, commonly around 5 to 5.6 ppm [26, 32]. The coupling constants distinguish geminal from vicinal coupling. In a pyrazole this pattern is absent and a single aromatic ring proton replaces it, so the ABX set effectively proves the dihydro ring. Chalcone doublets with a large trans coupling constant should be absent, and their presence in a reported spectrum is a sign of incomplete conversion. The sulfonamide NH₂ shows as a broad exchangeable singlet.

Reporting quality is uneven. Some papers give full assignments with coupling constants and carbon spectra, others list a few chemical

shifts without integration, and high-resolution mass data are not universal. Purity by HPLC is seldom stated for compounds that go on to biological testing, even though contamination with a more active by-product would invalidate structure-activity conclusions. Single-crystal structures, which would settle both ring identity and conformation, exist for only a minority of reported pyrazolines [9, 11]. Enantiomeric composition is almost never examined, so racemates are screened as if they were single compounds, a simplification that is probably acceptable at first screening but not for later development.

5. ANTI-INFLAMMATORY SCREENING

Screening usually starts in vitro or goes straight to rodents. Inhibition of heat-induced albumin denaturation is a simple, inexpensive test used in many papers, based on the observation that several anti-inflammatory drugs protect proteins from denaturation [30]. Its mechanistic meaning is limited, since a compound can stabilise albumin without touching COX, and the test has no direct counterpart in tissue. Red blood cell membrane stabilisation is used in a similar way. Neither is specific to the sulfonamide class. Both assays are best treated as preliminary filters and not as evidence of an anti-inflammatory mechanism, whereas enzyme assays against COX-1 and COX-2 provide the target-specific information the series needs [4, 20].

Cell-based assays offer a middle path between a test tube and a rat. Macrophage lines stimulated with bacterial lipopolysaccharide release nitric oxide, prostaglandin E₂ and cytokines, and a compound that lowers them without killing the cells shows at least that it acts on an inflammatory pathway [1, 2]. A viability counter-screen is essential, since cytotoxicity looks like inhibition in any assay that measures a decrease in signal. Few of the sulfonamide pyrazoline papers use cell models, and fewer still include them alongside enzyme data, so the step from a chemical structure to a cellular effect is mostly left undocumented. Where cell data do exist, they often support a COX-related mechanism only indirectly [20, 22].

The *in vivo* workhorse is carrageenan-induced paw oedema in the rat, a long-standing screen described in standard pharmacological assay handbooks [28]. Carrageenan injected into the subplantar tissue produces a biphasic swelling, with an early phase driven by histamine and serotonin and a later phase, from roughly the third hour, in which prostaglandins and neutrophil products dominate [29]. Paw volume is usually measured by plethysmometer at hourly intervals for up to five hours, and results are expressed as percentage inhibition against vehicle-treated animals, with indomethacin, diclofenac or celecoxib as reference [33]. The sulfonamide-bearing pyrazoline studies listed in table 1 almost all rely on this model, so its strengths and weaknesses carry across to the whole literature.

What do these studies report? In one widely cited series of 1,3,5-trisubstituted pyrazolines bearing benzenesulfonamide, several compounds produced paw oedema inhibition that approached that of reference drugs, with some also showing reduced gastric injury [22]. Other pyrazoline series built from chalcones, including an acridinyl set and a group assessed for combined anti-inflammatory and analgesic activity, likewise report significant inhibition relative to control [23, 24]. Pyrazole derivatives with additional antimicrobial activity have also been described [25]. The consistent message is that the scaffold can give activity in this model, but potency rankings between series cannot be reliably made, as laboratories differ in dose, timing and reference compound.

Complementary tests add some confidence. Acetic acid writhing and hot plate tests show analgesic activity, and an ulcer index after repeated dosing indicates gastric tolerability, an advantage that coxib-like design is meant to deliver [6, 22, 23]. Acute oral toxicity is generally checked at a limit dose following the OECD acute toxic class method, and animal use is supposed to be reported according to the ARRIVE guidance, although adherence is patchy [34, 35]. The spread of the cited studies by category is shown in fig. 1. Pyrazoline series account for four of the eleven entries in table 1, with reference

drugs, synthetic methods and screening models contributing two each and the safety filters a single entry.

6. STRUCTURE-ACTIVITY TRENDS

Trends are real but inconsistent. In several of the sulfonamide pyrazoline series, halogen or other electron-withdrawing substituents on one of the aryl rings are linked with better paw oedema inhibition, while methoxy groups give variable results [22, 23, 24]. A different series may show the reverse. This is hardly surprising, because the quantity measured is a percentage reduction in swelling at a fixed dose, which depends on absorption and distribution as much as on affinity for the enzyme. It follows that a structure-activity relationship drawn from paw oedema data alone is at best a statement about overall *in vivo* performance, not about binding. Matched pairs, in which a single substituent is changed and everything else held constant, are the cleanest way to extract a trend, yet few papers are designed that way [14, 22].

Size and lipophilicity matter for the COX-2 side pocket. The coxib pharmacophore requires two adjacent aryl rings of about the right orientation and a polar group able to enter the pocket, and compounds that depart from that geometry, by bulky N1 substituents or non-planar arrangements, would be expected to lose selectivity [5, 12, 14]. Lipophilicity also influences absorption and plasma protein binding, and the polar surface area and rotatable bond counts reported in many papers are typically within acceptable limits for the compounds described [17]. The pyrazoline ring introduces a non-planar sp³ centre, which may be advantageous for fitting the active site, although experimental structures with these ligands are lacking [13, 21].

Comparison with related heterocycles puts the pyrazoline results in perspective. Fully aromatic pyrazoles, such as celecoxib itself, are more planar, chemically more stable and generally the better validated COX-2 pharmacophore, whereas the dihydro ring is more flexible and more prone to oxidation [5, 11]. Reviews of the pyrazole and pyrazoline literature note that both ring systems give

anti-inflammatory activity in rodent models, with no clear systematic advantage for either in head-to-head comparisons [9, 10]. Part of the appeal of pyrazolines is therefore synthetic convenience, not proven pharmacological superiority, and a fair design strategy would include the oxidised pyrazole as a matched comparator in any new series.

7. LIMITATIONS AND FUTURE DIRECTIONS

Several limitations recur. Group sizes are small, often six animals per group, a single time point such as three hours is frequently emphasised, and statistical methods are not always described [28, 33]. Reference drugs and doses differ between papers, which makes ranking across series unreliable. The tendency for papers to report only active compounds, and to describe a modest reduction in swelling as significant, inflates the apparent hit rate. Selectivity for COX-2 is asserted in many titles and demonstrated in few. The same applies to the term anti-inflammatory itself, which in some titles rests on a single assay. Independent replication of promising compounds in a second laboratory is almost unknown, and animal reporting standards are adopted unevenly [4, 35].

Safety is the other open area. The cardiovascular problems of the coxib class are linked to suppression of vascular prostacyclin without matching suppression of platelet thromboxane, and any new selective COX-2 inhibitor inherits the question [7, 8]. Beyond that class effect, the primary sulfonamide may cause hypersensitivity in susceptible individuals and may inhibit carbonic anhydrases [15, 16]. Pyrazolines themselves have been flagged in screening-library analyses as frequent hitters in some assay formats, which argues for orthogonal confirmation of activity [19]. Metabolic stability, plasma protein binding, permeability and genotoxicity data are largely absent from the synthetic papers, so progression from screening hit to candidate cannot yet be judged [11, 17].

Drug-likeness deserves more attention than it gets. Most reported compounds are lipophilic diaryl structures with a polar sulfonamide, a

combination that tends to give low aqueous solubility and dissolution-limited oral absorption, which in turn means that in vivo activity may depend heavily on the vehicle [17]. Chemical stability on storage in solution, particularly the oxidation of the pyrazoline ring, is rarely examined [11]. Preliminary toxicity data, if any, are limited to a single acute oral study at a limit dose [34]. None of this is a criticism of exploratory screening, but it does mean that a hit from a first paw oedema experiment is an early signal, one that needs several further steps before it counts as a lead.

Future work might concentrate on a smaller number of well-characterised compounds rather than larger libraries. Useful steps would be purity by HPLC, enantiomer separation or at least recognition of the stereochemical issue, whole-blood COX-1/COX-2 selectivity ratios, carbonic anhydrase counter-screens, a dose-response in the paw oedema model with blinded scoring, and a chronic model such as adjuvant arthritis before any claim of therapeutic potential [4, 9, 20]. Sharing raw data and full spectra in supplementary files would also help later reviewers and modellers to separate real structure-activity signals from noise, and would make meta-analysis of this field more feasible [10, 35].

8. CONCLUSION

Pyrazolines carrying a sulfonamide moiety are chemically accessible and rationally related to the diaryl heterocyclic coxibs, and published rodent studies repeatedly show that members of the family can reduce carrageenan-induced paw oedema, in some cases to a degree approaching that of standard drugs [5, 22, 23]. The two-step chalcone route is reliable, and the ABX proton pattern provides a convincing structural proof of the dihydro ring [26, 32]. Because the scaffold is so accessible, the real contribution of any new paper lies in the quality of its characterisation and testing rather than in the novelty of one more substituent pattern [10, 11].

The evidence is thinner than the volume of papers suggests. Selectivity is mostly inferred from docking, comparisons between series are confounded by differences in model

design, and pharmacokinetic, carbonic anhydrase and safety data are scarce [4, 15, 19]. Purity, enzyme assays, stereochemistry and blinded reporting would make future work more useful, and the cardiovascular lessons of the coxibs should shape how new candidates are assessed [7, 8, 35]. Until those gaps are filled, sulfonamide pyrazolines are best regarded as promising screening hits and structural templates, not as established anti-inflammatory leads.

9. ABBREVIATIONS

COX-Cyclooxygenase, NSAID-Non-steroidal anti-inflammatory drug, NMR-Nuclear magnetic resonance, IR-Infrared, HPLC-High-performance liquid chromatography, PAINS-Pan-assay interference compounds, OECD-Organisation for Economic Co-operation and Development, IC₅₀-Half-maximal inhibitory concentration, ARRIVE-Animal Research: Reporting of In Vivo Experiments

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11. AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

12. CONFLICT OF INTERESTS

Declared none

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