Bioorganic & Medicinal Chemistry 26 (2018) 4113–4126

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Synthesis and biological properties of aryl methyl sulfones

Lorena Navarro[a], Gloria Rosell[a], Silvia Sánchez[c], Núria Boixareu[d], Klaus Pors[d], Ramon Pouplana[b], Josep M. Campanera[b,*], M. Dolors Pujol[a,*]

[a] Laboratori de Química Farmacèutica (Unitat Associada al CSIC), Facultat de Farmàcia, Universitat de Barcelona, Av. Diagonal, 643, E-08028-Barcelona, Spain
[b] Departament de Farmàcia i Tecnologia Farmacèutica, i Fisicoquímica, Facultat de Farmàcia i Ciències de l'Alimentació, Universitat de Barcelona, Av. Diagonal 643, E-08028-Barcelona, Catalonia, Spain
[c] Unitat de Farmacologia, Departament Patologiai Terapèutica Experimental, Facultat de Medicina, Universitat de Barcelona, L'Hospitalet de Llobregat, E-08907-Barcelona, Spain
[d] Institute of Cancer Therapeutics, School of Pharmacy and Medical Sciences, Faculty of Life Sciences, University of Bradford, BD7 1DP West Yorkshire, UK

ARTICLE INFO

Keywords:
Anti-inflammatory
Analgesic
NSAIDs
Methyl sulfones
COX-inhibitors
Binding free energy estimation

ABSTRACT

A novel group of aryl methyl sulfones based on nonsteroidal anti-inflammatory compounds exhibiting a methyl sulfone instead of the acetic or propionic acid group was designed, synthesized and evaluated *in vitro* for inhibition against the human cyclooxygenase of COX-1 and COX-2 isoenzymes and *in vivo* for anti-inflammatory activity using the carrageenan induced rat paw edema model in rats. Also, *in vitro* chemosensitivity and *in vivo* analgesic and intestinal side effects were determined for defining the therapeutic and safety profile. Molecular modeling assisted the design of compounds and the interpretation of the experimental results. Biological assay results showed that methyl sulfone compounds **2** and **7** were the most potent COX inhibitors of this series and best than the corresponding carboxylic acids (methyl sulfone **2**: IC_{50} COX-1 = 0.04 and COX-2 = 0.10 μM, and naproxen: IC_{50} COX-1 = 11.3 and COX-2 = 3.36 μM). Interestingly, the inhibitory activity of compound **2** represents a significant improvement compared to that of the parent carboxylic compound, naproxen. Further support to the results were gained by the docking studies which suggested the ability of compound **2** and **7** to bind into COX enzyme with low binding free energies.

The improvement of the activity of some sulfones compared to the carboxylic analogues would be performed through a change of the binding mode or mechanism compared to the standard binding mode displayed by ibuprofen, as disclosed by molecular modeling studies. So, this study paves the way for further attention in investigating the participation of these new compounds in the pain inhibitory mechanisms. The most promising compounds **2** and **7** possess a therapeutical profile that enables their chemical scaffolds to be utilized for development of new NSAIDs.

1. Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are the most prescribed pharmaceutical compounds in the world to alleviate inflammation and pains associated with several pathological conditions and are often the initial treatment for common inflammation. NSAIDs are a heterogeneous group of various chemical structures with variable benefit/risk profile. Usually the use of NSAIDs is associated with several adverse effects, including gastrointestinal damage. The clinically used NSAIDs exert their therapeutical effects by inhibition of the biosynthesis of prostaglandins (PGs) and thromboxanes (TX). In general, the biosynthesis involves the conversion of arachidonic acid to prostaglandin G_2 (PGH_2), a reaction catalyzed by the sequential action of cyclooxygenase (COX) (Fig. 1). Most NSAIDs inhibit COX-1 and COX-2 isoforms.[1–3] The constitutive COX-1 is responsible for the synthesis of cytoprotective prostaglandins in the gastrointestinal tract, and for the pro-aggregator thromboxane in blood platelets.[4] In the inflammation process COX-2 is responsible for production of prostaglandins, considered mediators of inflammation (Fig. 1).

It has recently been reported that classical NSAIDs such as celecoxib possess preventive effects against colorectal cancer (CRC)[5] and Alzheimer's disease.[6] Moreover, these compounds continue to be used as

Abbreviations: COX-1, cyclooxigenase-1; COX-2, cyclooxigenase-2; NSAIDs, nonsteroidal antiinflammatory drugs; PG, prostaglandin; PGH_2, prostaglandin G_2; SAR, structure-activity relationships; QSAR, quantitative structure-activity relationships; ACHN, 1,1′-azobis(cyanocyclohexane); DMDS, dimethyl sulfide; IC_{50}, inhibitory concentration at 50% inhibition; BINAP, 2,2′-*bis*(diphenylphosphino)-1,1′-binaphthyl; DCM, dichloromethane; DMF, dimethylformamide; ESI, electrospray; HMRS, high resolution mass spectrometry; NMR, nuclear magnetic resonance; PDA, protein data bank; TLC, thin layer chromatography; TFA, trifluoroacetic acid; TFAA, trifluoroacetic anhydride

* Corresponding authors.
E-mail address: mdpujol@ub.edu (M.D. Pujol).

https://doi.org/10.1016/j.bmc.2018.06.038
Received 11 May 2018; Received in revised form 26 June 2018; Accepted 28 June 2018
Available online 30 June 2018

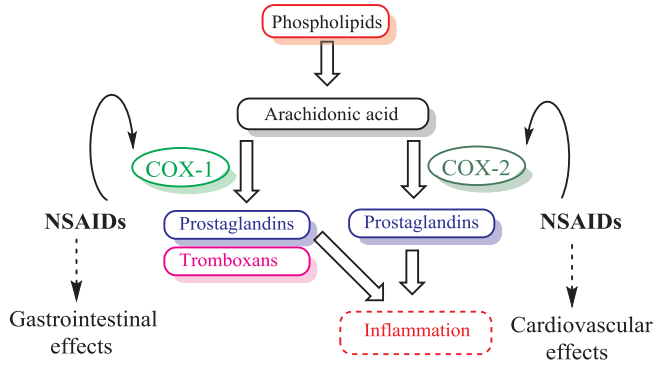


Fig. 1. Inflammation biochemical pathways.

remedies for rheumatic[7] and autoimmune anti-inflammatory diseases.[7c] In general, NSAIDs (Fig. 2) are potent anti-oxidants that exert both anti-inflammatory and antitumor activity.[8–10] In regard the latter, ibuprofen inhibits tumor growth and liver metastasis.[9a] While long-term use of acetaminophen enhances the development of leukemia regular treatment with NSAIDs correlates with a reduced risk of lymphoma and leukemia development.[11] The chronic use of NSAIDs inhibit the growth of adenomatous polyps of patients with familial adenomatous polyposis and reduce the risk of CRC.[12] Selective COX-2 inhibitors showed a safe profile in the gastrointestinal tract, but recent studies suggest that the long-term treatment by selective COX-2 inhibitors is limited because of cardiovascular thrombotic events related to the aggregatory properties of these drugs.[13] Moreover, COX-2 makes a significant contribution to the production of inflammatory PGs while the inhibition of COX-2 attenuates the expression of inflammatory mediators such as TNF-α, iNOS and IL-1β.[14] NSAID compounds are often associated with the presence of gastrointestinal side effects and new agents with diminished off-target effects are highly desirable.

In the present study based on the previous work[15] related to COX-1/COX-2 inhibitors and the properties of NSAIDs, we designed a series of seven new compounds derived from classic and commercial NSAIDs in order to study their potential therapeutic properties (Fig. 3). Specifically, the purpose of the study was to evaluate whether the replacement of the acetic or propionic acid group by a methyl sulfone group, a more lipophilic group with low acidic properties, could lead to high COX activity and reduced risk of side-effects, thereby result in better anti-inflammatory and safety profile than the parent classical NSAIDs scaffolds.

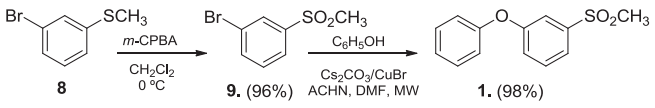
Here we report on the synthesis of a series of sulfones as a new class of NSAIDs and report on their biological properties by comparing them with the respective carboxylic acids chosen as models.

Compounds **1–5** derive from the direct substitution of alkylcarboxylic group by methyl sulfone of the classical NSAIDs fenoprofen, naproxen, ibuprofen, metiazinic acid and indomethacin respectively, and were chosen due to their structural variability and anti-inflammatory profile. Two additional methyl sulfones were also studied, compounds **6** and **7**, which were derived from not only a direct substitution of the alkyl carboxylic acid of ketoprofen but also changes at other positions of the scaffold.

2. Results and discussion

2.1. Synthesis and biological evaluation of methyl sulfones

The methods used for the synthesis of aryl sulfones from different starting materials were readily available and enabled the synthesis of target compounds in a conventional and safe manner. The general synthetic routes are illustrated in Schemes 1–7.



Scheme 1. Synthesis of compound **1**.

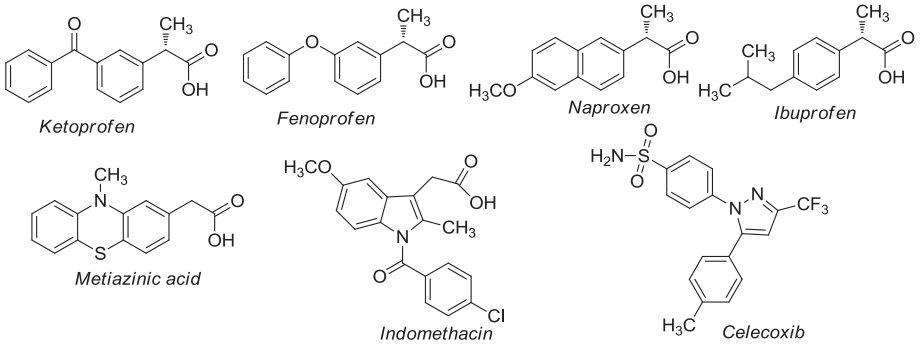
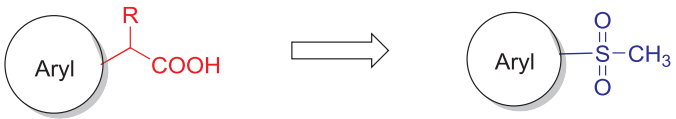


Fig. 2. Classical NSAIDs.



Fenoprofen (arylpropionic acid, R = CH_3)
Naproxen (arylpropionic acid, R = CH_3)
Ibuprofen (arylpropionic aci, R = CH_3)
Metiazinic acid (arylacetic acid, R = H)
Indomethacin (arylacetic acid, R = H)

Ketoprofen (arylpropionic acid, R = CH_3)
Ketoprofen (arylpropionic acid, R = CH_3)

1. Aryl = 3-(phenoxy)phenyl
2. Aryl = 2-(6-methoxynaphthalenyl)
3. Aryl = 4-(isobutylphenyl)
4. Aryl = 10-methyl-phenothiazyn-2-yl
5. Aryl = 3-(2-methyl-5-methoxy-1-(4-chlorophenylcarbonyl)indolyl)
6. Aryl = 4-(4-chlorophenylcarbonyl)phenyl
7. Aryl = 4-(3-furanylcarbonyl)phenyl

Fig. 3. Design strategy of methyl sulfones.