Review Article

New Acetamide Derivatives of the COX-II Inhibitors-A Brief Review

Karam S. Atrushi[1], Dana M. Ameen[2], Faris T. Abachi[3]*

[1]Department of Pharmaceutical Chemistry, College of Pharmacy, University of Duhok, Duhok. [2]Department of Pharmaceutical Chemistry, College of Pharmacy, Hawler Medical University, Erbil. [3]Department of Pharmaceutical Chemistry, College of Pharmacy, Cihan University Erbil, Iraq.

Abstract

The most traditional and popular agents are non-steroidal anti-inflammatory drugs (NSAIDs). However, due to their side effects on different organs. In this review, several compounds created as acetamide derivatives to maintain their anti-inflammatory properties, selective COX-II inhibitors, are discussed. Numerous literature reviews have highlighted the significance of these anti-inflammatory heterocyclic compounds in treatments, taking into consideration the significance of this pharmacological class. Cyclooxygenase-II (COX-II) inhibitors can be used in a wide variety of applications thanks to the prodrug method. It plays a big part in drug development. Many researchers have created different prodrugs using acetamide molecules to adjust pharmacokinetic parameters, enhance organoleptic qualities, or increase chemical properties. A huge quantity of amide derivatives belonging to different classes of compounds exhibit cyclooxygenase-II inhibitors and mainly to treat arthritis, pain, menstrual camps, and colonic polyps, they used for relief of pain, fever, swelling, and tenderness. Finally, the nanoparticles of cyclooxygenase (II) inhibitors were used for improving the efficacy.

Keywords: NSAIDs, COX-II inhibitors, Prodrug, Acetamide derivatives

Introduction

Inflammation is a complicated process that has been related to rheumatoid arthritis, a dangerous condition. It has been challenging to find efficient anti-inflammatory medications that treat these degenerative effects of inflammation with few side effects. Inflammation has also been associated to numerous disorders, including cancer [1], diabetes [2], obesity [3], asthma [4], fatty liver [5], microbial infections [6], and Alzheimer's disease [7].

Arachidonic acid (C20AA), an intermediate produced during the complex chemistry of prostaglandins (PGs), is converted to prostaglandin H2 (PGH2) by cyclooxygenase enzymes (COXs) as depicted in **(Figure 1)**.

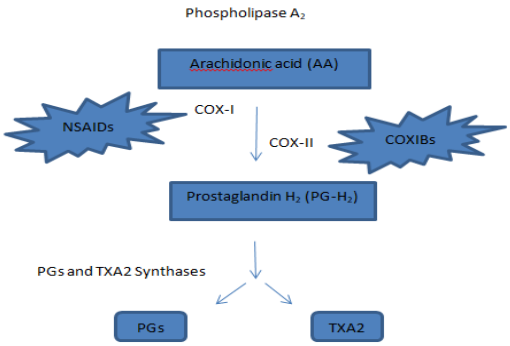


Figure 1. A diagram of the prostaglandin synthesis.

The most potent anti-inflammatory drugs including cyclooxygenase I & II (COX-I & COX-II) [8], nitric oxide donors (NOs), and inducible nitric oxide synthetase (iNOS) [9] are among the organic synthetic substances. Since COX-II is a pathologic enzyme that is primarily responsible for inflammation, it is always viewed as having powerful anti-inflammatory potency and being a promising and effective anti-inflammatory drug.

Acetamide derivatives are important scaffolds that are frequently found in nature and among legally available small-molecule drugs.

According to a brief review of the literature on the biological activities of acetamide derivatives, they have potent antimicrobial [10], anti-inflammatory [11], anti-

Address for correspondence: Faris T. Abachi, Department of Pharmaceutical Chemistry, College of Pharmacy, Cihan University Erbil, Iraq.
faris.hamid@cihanuniversity.edu.iq

This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-Share Alike 4.0 License, which allows others to remix, tweak, and build upon the work non commercially, as long as the author is credited and the new creations are licensed under the identical terms.

How to cite this article: Atrushi KS, Ameen DM, Abachi FT. New Acetamide Derivatives of the COX-II Inhibitors-A Brief Review. Arch Pharm Pract. 2023;14(2):59-65. https://doi.org/10.51847/oxEu4M59dg

tumor [12], anti-HIV [13], antiviral [14], anticonvulsant [15], analgesic [16], anti-cancer [17], anti-allergic [18], sedative-hypnotic [19], and antihypertensive [20]. The synthetic adaptability of quinazolinones, which enables the synthesis of a large number of structurally different derivatives, has further aided this wide range of biological functions [21]. The chemical structures of this group of COX-II inhibitors are significantly different from those of the classical NSAIDs, mainly due to the absence of the typical amide group.

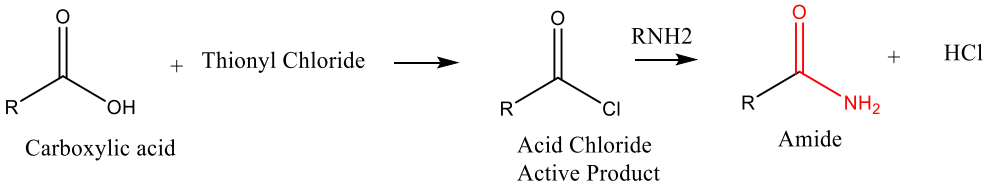
The aim of this review is to explain different structural modifications of different amides is extremely important in COX-II inhibitors, as well as in drugs and peptide synthesis. The acetamide compounds have great importance in medicinal chemistry. Different procedures are used in organic and synthetic medicinal chemistry, which highlights the significance of amide bond formation.

Synthesis of Amides

There are many routes of the synthesis of amides

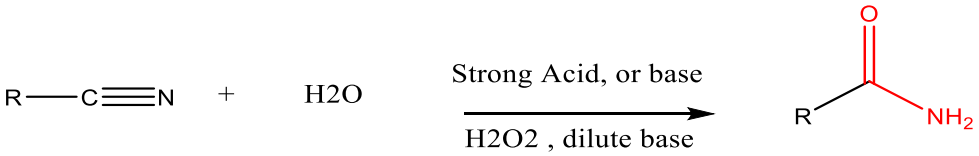
Via Acid Chloride

The reactivity of the carboxylic acids or esters is very low to form amide unless activation to form acid chlorides (halogen is a good leaving group) [22]:



Hydrolysis of Nitriles

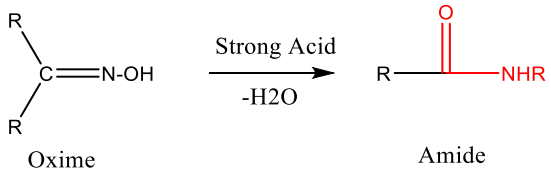
The nitrile group is a highly active group and easily hydrolysis in acid or basic media [23]:



This method was used for the hydrolysis of toxic drugs containing cyanides.

Beckmann Rearrangement of Oximes

In the reaction of ketone with hydroxyl amine to form Ketoxime (Oxime), the oxime is unstable and can undergo rearrangement in strong acid to form amide [24].



Today in the modern methodology used in the preparation of the amide using green chemistry, the synthetic procedure includes the reaction carried out in conditions water [25], microwave [26], ultrasound [27], electro synthesis [28].

Peptide Synthesis in the Liquid Phase

In the peptide synthesis, there are many coupling agents were used in the amide formations either liquid phase or solid phase, examples are shown in **(Figure 2)**, *N*,*N*′-dicyclohexylcarbodiimide (DCC), 1-ethyl-3-(3′-dimethylaminopropyl)-carbodiimide hydrochloride (EDC), 1,1′-carbonyldiimidazole (CDI). These reagents are mainly used for macromolecules in solution, and other methods are used in the solid phase in different techniques [29].

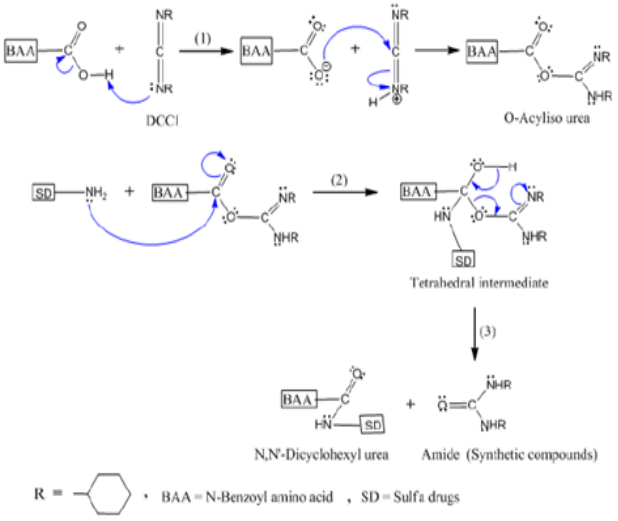


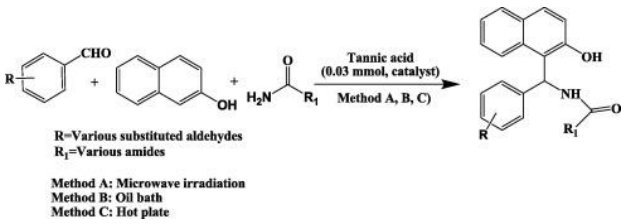
Figure 2. Mechanism preparation of amide derivatives using DCCI

Amide formation reactions make up around 16% of all reactions used in the synthesis of novel pharmaceuticals since they continue to be one of the most commonly conducted reactions.

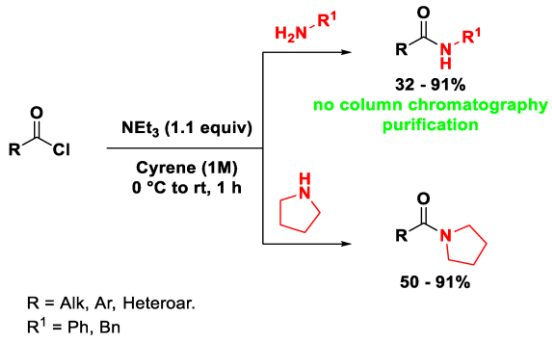
Greener Methods of Acetamide Synthesis

Training in green chemistry, in particular, at the fundamental level is intended to provide a solid foundation for the essential ideas of process excellence in design, biocatalysis, choice of solvents, reagents, equipment, and operational excellence [26].

It is reported that a new, simple, economical, and environmentally friendly technique for the synthesis of acetamide derivatives under thermal (hot plate and oil bath) and microwave irradiation procedures without the need for a solvent using tannic acid as a catalyst [30].



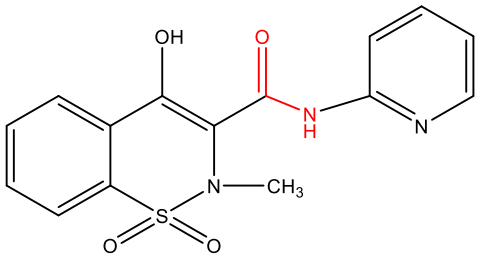
Cyrene was proposed as an alternative to the conventional coupling solvents, such as DMF and NMP, to carry out amide bond formation operations starting from acid chlorides [22] and carboxylic acids [31], and it generated surprising results. Bousfield *et al*. suggested a simple process for the synthesis of amides from acid chlorides in the bio-available solvent (**Scheme 1**) [31].



Scheme 1. Two approaches for amidation reactions using Cyrene as a catalyst.

Classification of Amides in Selective COX-II

Amides are classified into three types based on their names: primary amine, secondary amine, and tertiary amine (R may be aliphatic or aromatic). Usually, NSAIDs, peptides, and polymers are found as a secondary amide. The pharmacophore amide is existing in the Piroxicam as a secondary amide stabilized by hydrogen bond formation, and act as a linker and is known as a linker between the pyridine molecule and benzothiazine nucleus and known as cyclooxygenase-2 (COX-2) inhibitor, don't contain carboxylic acid moiety (modified NSAIDs to have highly COX-2 selectivity) [32].



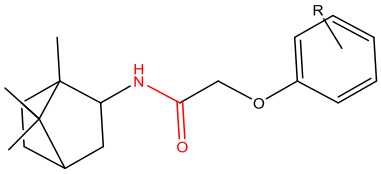
4-Hydroxy-2-methyl-N-(2-pyridinyl)-2*H*-1,2 benzothiazine-1,1-dioxide (Piroxicam)

These agents have utility in the treatment of Rheumatoid Arthritis (RA) and Osteoarthritis (OA).

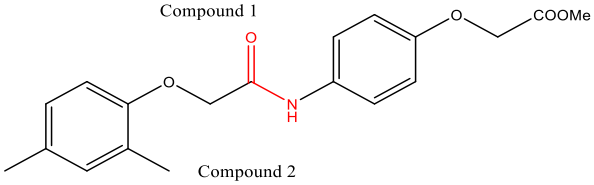
Chemistry and Pharmacology of New Acetamide Derivatives as COX-II Inhibitors

Compounds Having a Phenoxy Acetamide Group

Compounds 1 and 2 of substituted phenoxy acetamide were synthesized by Rani *et al*. (2015) [33]. The compounds' anti-inflammatory, analgesic, and antipyretic activities were evaluated using the carrageenan-induced rat paw edema method, the Eddy's hot plate method, and the brewer's yeast-induced pyrexia method, compounds I & IIrespectively [33].



Compound 1



Compound 2

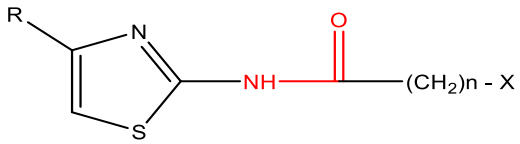
The chemical structures of methyl 2-(4-(2-(2,4-dimethylphenoxy)acetamido) phenoxy)acetate (I) 2-(substituted phenoxy)-N-(1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)acetamide (II) derivatives

Compounds Having a Phenol Acetamide Group

The anti-inflammatory activity IC_{50} values of 0.768 and 0.616 mol/L as compared to Celecoxib (reference) IC_{50} 0.041 mol/L in vitro were determined by Cheng's group after testing two phenol products as COX-II inhibitors [34].

Compounds Having a Thiazole Acetamide Group

Thiazole-based derivatives selective COX-II inhibitors



General structure of thiazolyl-N- substituted amide derivatives.

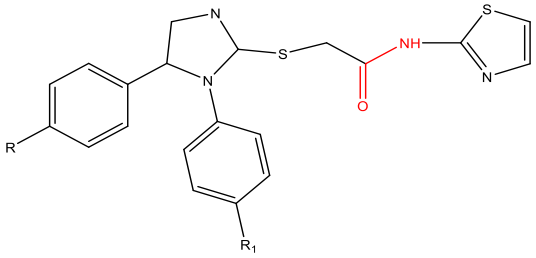
To determine whether there is any relationship between anti-inflammatory activity (CPE%, percentage inhibition of carrageenan mice paw edema in log-form) [10], regression analysis was carried out:

log CPE % = -0.001(0.036) clog D 7.6 + 0.0002(0.01)clog D7.42 + 1.672(0.032) (1)

n = 26, r = 0.067, r^2 = 0.005, s = 0.124, F = 0.052, p = 0.949

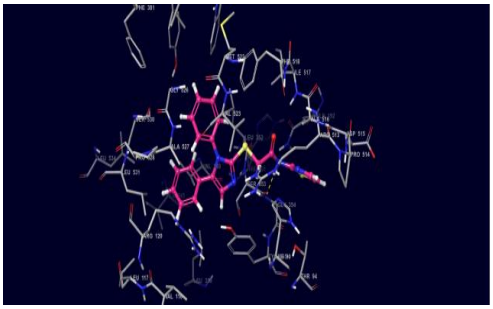
Several physicochemical parameters will affect, lipophilicity, polarizability, steric, and electronic variables [10].

Compounds Having an Imidazole Acetamide Group

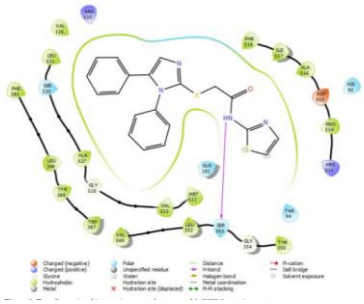


[(1,5-disubstituted phenyl-1H-imidazol-2-yl) thio] -N-thiazol-2-yl acetamide derivatives

Strong interactions between ring nitrogen, carbonyl, phenyl, secondary amine functional groups, and active site amino acids may be seen in the molecular docking of the compounds with COX-II enzyme [35]. With the amino acids Trp 387 and Ser 353, the nitrogen atom of the compound's acetamide moiety forms a hydrogen bond. This suggests a strong relationship between theoretical and practical anti-inflammatory drug effects **(Figure 3)** [35].



a)

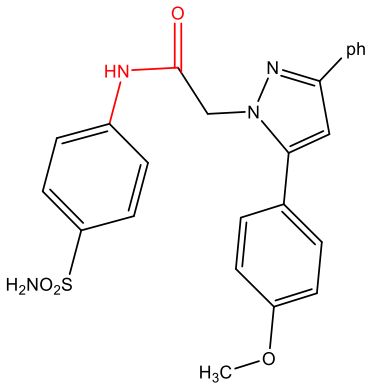


b)

Figure 3. The 3D and 2D docking of the thiazole acetamide derivatives with COX-II

Compounds Having a Pyrazole Acetamide Group

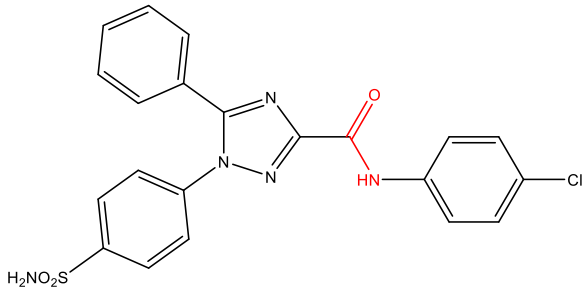
In medicinal chemistry, pyrazole is a favored pharmacophore with a great potential for anti-inflammatory drugs, particularly for novel COX-II inhibitors [36]. The COX-II inhibitor that contains an acylamino spacer, 2-(5-(4-methoxyphenyl)-3-phenyl-1H-pyrazol-1-yl)-N-(4-sulfamoylphenyl) acetamide, demonstrated potential anti-inflammatory efficacy.



2-(5-(4-methoxyphenyl)-3-phenyl-1H-pyrazol-1-yl)-N-(4-sulfamoylphenyl)acetamide.

Compounds Having a Triazole Acetamide Group

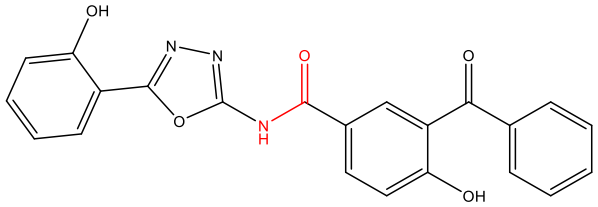
Triazole acetamide compounds COX-2 inhibitory potency and selectivity are mainly dependent on the size and the nature of substituents attached in C-3 and C-4. Recently, new compounds with high COX-2 selectivity were prepared, bearing 4-NH_2SO_2Ph and amide groups essential for the activity [37].



N-(4-chlorophenyl)-5-phenyl-1-(4-sulfamoylphenyl)-*1H*-1,2,4-triazole-3-carboxamide

Compounds Having an Oxadiazole Acetamide Group

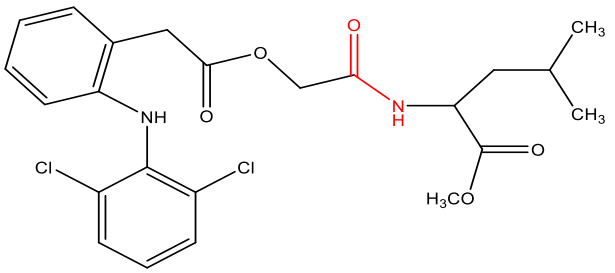
The bioisosteric replacement of the 1,3,4-oxadiazole moiety in medication manufacture and design has a history. Recently, three groups reported the synthesis of COX-II inhibitors with an oxadiazole derivative Here, the compound 3-benzoyl-N-(5-(2-hydroxyphenyl)-1,3,4-oxadiazol-2-yl)-4-(l1-oxidaneyl) benzamide as combined an amide linkage with benzophenone's oxadiazole moiety, which is said to have anti-inflammatory agents [38].



3-benzoyl-4-hydroxy-N-(5-(2-hydroxyphenyl)1,3,4-oxadiazole-2-yl)benzamide.

Prodrugs of COX-II Acetamide Inhibitors

Instead of having gastrointestinal side effects, the discovery of COX-2 selective inhibitors offered the same effectiveness, but came with a higher risk of increased serum potassium levels and possible liver damage. Drugs that are precursors of aceclofenac amino acid will improve solubility, stability at acidic pH, and hydrolysis at physiological pH 7.4. To get over some of the disadvantages, aceclofenac's amino acid acetamide linkage was synthesized utilizing DD [39].



methyl (2-(2-(2-((2,6-dichlorophenyl)amino)phenyl)acetoxy)acetyl)leucinate

Methyl(2-(2-(2-((2,6-dichlorophenyl)amino) phenyl)acetyl) leucinate.

Mutual Prodrugs

Mutual prodrugs can be defined as two pharmacologically active drugs linked together so that each drug acts as moiety for the other drug and vice versa. Acetamide functional group is amenable to prodrug design for COX-II inhibitors, the amidase is the hydrolyzing enzyme in vivo [33].

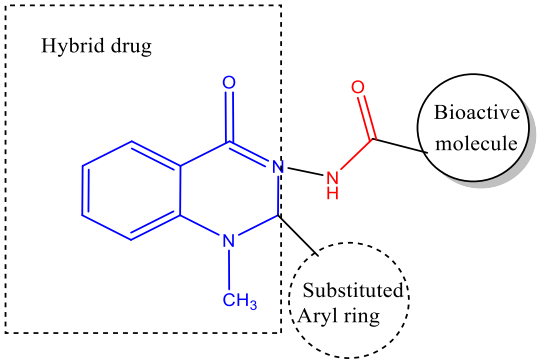


Figure 4. Molecular design for hybrid bioactive acetamide compounds selective for COX-II.

By possessing cyclooxygenase-2 antagonist activity, novel benzophenone attached oxadiazole compounds were created and found to be effective at treating inflammatory paw edema [38]. As a mutual prodrug, a new hybrid drug made of bioactive molecules and other substituted aryl compounds is also being developed **(Figure 4)** [40, 41].

Reactive oxygen species (ROS), which are produced by COX-2, are what prevent the production of pro-inflammatory cytokines like NO, PGE2, IL-6, and. TNF-α18. COX-II inhibition causes a sharp decrease in the amount of ROS in the upstream mechanism and keeps NF-κB in an inactive state of bondage to P-IκB in the downstream [42].

Nanoparticles of NSAIDs

Anti-inflammatory medicines have made use of medication delivery systems mediated by nanoparticles. The etiology of inflammation has had a significant impact on a variety of illnesses, including inflammatory bowel disease, rheumatoid arthritis, and osteoarthritis. Numerous hybrid NPs have recently been investigated for use in the treatment of inflammation [43]. Recent studies have noted that one or more materials are synthesized into nanostructures, and the properties of each material are completely utilized, for enhanced biocompatibility and targeting capabilities. Each structure has unique characteristics that enable NPs to be implanted in the proper tissues. To create an NP-based drug delivery system, manufactured NPs are used as carriers and filled with anti-inflammatory medications **(Figure 5**) [43].

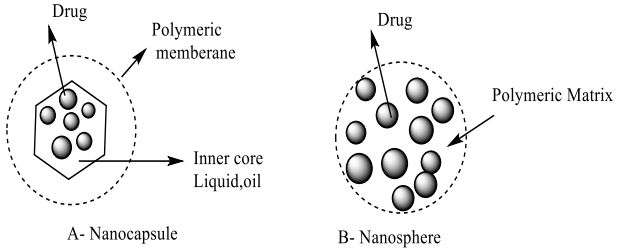


Figure 5. Two polymeric nano structures of drugs. A-nanocapsule, B- Nanosphere.

Nanospheres and nanocapsules, two different forms of polymeric nanoparticles, are effective drug delivery systems. The majority of the links between the polymer and the medicines are acetamide linkages, just like in liposomes and micelles. For the administration of targeted medications, compact lipid nanostructures and phospholipids are especially useful. The relatively new but rapidly developing fields of nanomedicine and nano delivery systems utilise COX-II inhibitors in the nano scale range as diagnostic tools or to administer therapeutic compounds to particular targeted regions in a controlled manner [44].

Conclusion

Medicinal chemists have been focusing their efforts on the design of new agents. In this brief review the spacer acetamide linkage especially of the powerful COX-II inhibitory compounds in various structure compounds, aromatic, heterocyclic agents as well as nano-NSAIDs to lessen their adverse effects.

ACKNOWLEDGMENTS: The author would like to thank the College of Pharmacy, the University of Dohuk for their assessments.
CONFLICT OF INTEREST: None
FINANCIAL SUPPORT: None
ETHICS STATEMENT: None

References

1. Saund D, Kotecha S, Rout J, Dietrich T. Non-resolving periapical inflammation: a malignant deception. Int Endod J. 2010;43(1):84-90. doi:10.1111/j.1365-2591.2009.01644.x
2. Lin MH, Wu WT, Chen YC, Lu CH, Su SC, Kuo FC, et al. Association between Non-Steroidal Anti-Inflammatory Drugs Use and the Risk of Type 2 Diabetes Mellitus: A Nationwide Retrospective Cohort Study. J Clin Med. 2022;11(11):3186. doi:10.3390/jcm11113186
3. Araújo JR, Tomas J, Brenner C, Sansonetti PJ. Impact of high-fat diet on the intestinal microbiota and small intestinal physiology before and after the onset of obesity. Biochimie. 2017;141:97-106. doi:10.1016/j.biochi.2017.05.019
4. Jakiela B, Soja J, Sladek K, Przybyszowski M, Plutecka H, Gielicz A, et al. Heterogeneity of lower airway inflammation in patients with NSAID-exacerbated respiratory disease. J Allergy Clin Immunol. 2021;147(4):1269-80. doi:10.1016/j.jaci.2020.08.007
5. Simon TG, Henson J, Osganian S, Masia R, Chan AT, Chung RT, et al. Daily aspirin use associated with reduced risk for fibrosis progression in patients with nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol. 2019;17(13):2776-84. doi:10.1016/j.cgh.2019.04.061
6. Oliveira IM, Borges A, Borges F, Simões M. Repurposing ibuprofen to control Staphylococcus aureus biofilms. Eur J Med Chem. 2019;166:197-205. doi:10.1016/j.ejmech.2019.01.046
7. Fu WY, Wang X, Ip NY. Targeting neuroinflammation as a therapeutic strategy for Alzheimer's disease: mechanisms, drug candidates, and new opportunities. ACS Chem Neurosci. 2019;10(2):872-9. doi:10.1021/acschemneuro.8b00402
8. Savjani JK, Mulamkattil S, Variya B, Patel S. Molecular docking, synthesis and biological screening of mefenamic acid derivatives as anti-inflammatory agents. Eur J Pharmacol. 2017;801:28-34. doi:10.1016/j.ejphar.2017.02.051
9. RA Abdellatif K, KA Abdelall E, B Bakr R. Nitric oxide-NASIDS donor prodrugs as hybrid safe anti-inflammatory agents. Curr Top Med Chem. 2017;17(8):941-55. doi:10.2174/1568026616666160927153435
10. Asirvatham S, Dhokchawle BV, Tauro SJ. Quantitative structure activity relationships studies of non-steroidal anti-inflammatory drugs: A review. Arab J Chem. 2019;12(8):3948-62.
11. Kartsev V, Geronikaki A, Zubenko A, Petrou A, Ivanov M, Glamočlija J, et al. Synthesis and Antimicrobial Activity of New Heteroaryl (aryl) Thiazole Derivatives Molecular Docking Studies. Antibiotics. 2022;11(10):1337. doi:10.3390/antibiotics11101337
12. Mahmood S, Khan SG, Rasul A, Christensen JB, Abourehab MA. Ultrasound Assisted Synthesis and In Silico Modelling of 1, 2, 4-Triazole Coupled Acetamide Derivatives of 2-(4-Isobutyl phenyl) propanoic acid as Potential Anticancer Agents. Molecules. 2022;27(22):7984. doi:10.3390/molecules27227984
13. Mallakuntla MK, Togre NS, Santos DB, Tiwari S. Implications of Fragment-Based Drug Discovery in Tuberculosis and HIV. Pharmaceuticals. 2022;15(11):1415. doi:10.3390/ph15111415
14. Zhang G, Wang M, Zhao J, Wang Y, Zhu M, Wang J, et al. Design, synthesis and in vitro anti-influenza A virus evaluation of novel quinazoline derivatives containing S-acetamide and NH-acetamide moieties at C-4. Eur J Med Chem. 2020;206:112706. doi:10.1016/j.ejmech.2020.112706

15. Abram M, Zagaja M, Mogilski S, Andres-Mach M, Latacz G, Baś S, et al. Multifunctional hybrid compounds derived from 2-(2, 5-dioxopyrrolidin-1-yl)-3-methoxypropanamides with anticonvulsant and antinociceptive properties. J Med Chem. 2017;60(20):8565-79. doi:10.1021/acs.jmedchem.7b01114
16. Verma V, Yogi B, Gupta SK. Synthesis of Novel N-(substituted phenyl)-N-(substituted) acetamide Derivatives as a potent Analgesic agent. Res J Pharm Technol. 2020;13(11):5158-64.
17. Omar AM, AboulWafa OM, El-Shoukrofy MS, Amr ME. Benzoxazole derivatives as new generation of anti-breast cancer agents. Bioorg Chem. 2020;96:103593. doi:10.1016/j.bioorg.2020.103593
18. Al Kury LT, Zeb A, Abidin ZU, Irshad N, Malik I, Alvi AM, et al. Neuroprotective effects of melatonin and celecoxib against ethanol-induced neurodegeneration: a computational and pharmacological approach. Drug Des Devel Ther. 2019:2715-27. doi:10.2147/DDDT.S207310
19. Zhu HY, Zhang D, Zhang Q, Zhao Y, He ZM, Gao YG, et al. 4-Hydroxybenzyl alcohol derivatives and their sedative–hypnotic activities. RSC Adv. 2018;8(35):19539-50. doi:10.1039/c8ra01972j
20. Albelwi FF, Abdu Mansour HM, Elshatanofy MM, El Kilany Y, Kandeel K, Elwakil BH, et al. Design, Synthesis and Molecular Docking of Novel Acetophenone-1, 2, 3-Triazoles Containing Compounds as Potent Enoyl-Acyl Carrier Protein Reductase (InhA) Inhibitors. Pharmaceuticals. 2022;15(7):799. doi:10.3390/ph15070799
21. Nasr T, Aboshanab AM, Mpekoulis G, Drakopoulos A, Vassilaki N, Zoidis G, et al. Novel 6-Aminoquinazolinone Derivatives as Potential Cross GT1-4 HCV NS5B Inhibitors. Viruses. 2022;14(12):2767. doi:10.3390/v14122767
22. John R. Handbook of Chemistry and Physics (99th ed.). CRC Press; 2018. pp. 3-5.
23. Xia Y, Jiang H, Wu W. Recent Advances in Chemical Modifications of Nitriles. Eur J Organ Chem. 2021;2021(48):6658-69.
24. Kaur K, Srivastava S. Beckmann rearrangement catalysis: A review of recent advances. N J Chem. 2020;44(43):18530-72. doi:10.1039/D0NJ02034F
25. Ke F, Xu Y, Zhu S, Lin X, Lin C, Zhou S, et al. Electrochemical N-acylation synthesis of amides under aqueous conditions. Green Chem. 2019;21(16):4329-33. doi:10.1039/C9GC01391A
26. Zarecki AP, Kolanowski JL, Markiewicz WT. Microwave-assisted catalytic method for a green synthesis of amides directly from amines and carboxylic acids. Molecules. 2020;25(8):1761. doi:10.3390/molecules25081761
27. Mahmoudi AE, Tachallait H, Moutaoukil Z, Arshad S, Karrouchi K, Benhida R, et al. Ultrasound-Assisted Green Synthesis of 3, 5-Disubstituted Isoxazole Secondary Sulfonamides via One-Pot Five-Component Reaction using CaCl2/K2CO3 as Pre-Catalyst in Water. ChemistrySelect. 2022;7(45):e202203072. doi:10.1002/slct.202203072.
28. Crocker MS, Deng Z, Johnston JN. Preparation of N-Aryl Amides by Epimerization-Free Umpolung Amide Synthesis. J Am Chem Soc. 2022;144(37):16708-14. doi:10.1021/jacs.2c05986
29. Cooper TW, Campbell IB, Macdonald SJ. Factors determining the selection of organic reactions by medicinal chemists and the use of these reactions in arrays (small focused libraries). Angew Chem Int Ed. 2010;49(44):8082-91. doi:10.1002/anie.201002238
30. Singh RK, Duvedi R. Environment-friendly green chemistry approaches for an efficient synthesis of 1-amidoalkyl-2-naphthols catalyzed by tannic acid. Arab J Chem. 2018;11(1):91-8. doi:10.1016/j.arabjc.2014.08.022
31. Bousfield TW, Pearce KP, Nyamini SB, Angelis-Dimakis A, Camp JE. Synthesis of amides from acid chlorides and amines in the bio-based solvent Cyrene™. Green Chem. 2019;21(13):3675-81. doi:10.1039/C9GC01180C, 3675-81.
32. Szczęśniak-Sięga B, Maniewska J, Poła A, Środa-Pomianek K, Malinka W, Michalak K. Synthesis of new piroxicam derivatives and their influence on lipid bilayers. Acta Pol Pharm. 2014;71(6):1045-50.
33. Rani P, Pal DK, Hegde RR, Hashim SR. Synthesis, characterization and pharmacological evaluation of substituted phenoxy acetamide derivatives. Hem Ind. 2015;69(4):405-15. doi:10.2298/HEMIND140330057R
34. Ju Z, Li M, Xu J, Howell DC, Li Z, Chen FE. Recent development on COX-2 inhibitors as promising anti-inflammatory agents: The past 10 years. Acta Pharm Sin B. 2022,12(6):2790-807. doi:10.1016/j.apsb.2022.01.002
35. Şahin Z, Kalkan M, Berk B, Yurttaş L, Bender C, Kaleli SN, et al. Synthesis, characterization, COX1/2 inhibition and molecular modeling studies on novel 2-thio-diarylimidazoles. Turk J Chem. 2021;45(6):1841-53. doi:10.3906/kim-2104-54
36. Mohammed KO, Nissan YM. Synthesis, molecular docking, and biological evaluation of some novel hydrazones and pyrazole derivatives as anti-inflammatory agents. Chem Biol Drug Des. 2014;84(4):473-88. doi:10.1111/cbdd.12336
37. Li SM, Tsai SE, Chiang CY, Chung CY, Chuang TJ, Tseng CC, et al. New methyl 5-(halomethyl)-1-aryl-1H-1, 2, 4-triazole-3-carboxylates as selective COX-2 inhibitors and anti-inflammatory agents: design, synthesis, biological evaluation, and docking study. Bioorg Chem. 2020;104:104333. doi:10.1016/j.bioorg.2020.104333
38. El-Sayed NA, Nour MS, Salem MA, Arafa RK. New oxadiazoles with selective-COX-2 and EGFR dual inhibitory activity: Design, synthesis, cytotoxicity evaluation and in silico studies. Eur J Med Chem. 2019;183:111693. doi:10.1016/j.ejmech.2019.111693
39. Dunetz JR, Magano J, Weisenburger GA. Large-scale applications of amide coupling reagents for the synthesis of pharmaceuticals. Org Process Res Dev. 2016;20(2):140-77. doi:10.1021/op500305s
40. Puttaswamy N, Malojiao VH, Mohammed YH, Sherapura A, Prabhakar BT, Khanum SA. Synthesis and amelioration of inflammatory paw edema by novel benzophenone appended oxadiazole derivatives by exhibiting cyclooxygenase-2 antagonist activity. Biomed Pharmacother. 2018;103:1446-55. doi:10.1016/j.biopha.2018.04.167
41. Sakr A, Rezq S, Ibrahim SM, Soliman E, Baraka MM, Romero DG, et al. Design and synthesis of novel quinazolinones conjugated ibuprofen, indole acetamide, or thioacetohydrazide as selective COX-2 inhibitors: anti-inflammatory, analgesic and anticancer activities. J Enzyme Inhib Med Chem. 2021;36(1):1810-28. doi:10.1080/14756366.2021.1956912
42. Popko K, Gorska E, Stelmaszczyk-Emmel A, Plywaczewski R, Stoklosa A, Gorecka D, et al. Proinflammatory cytokines Il-6 and TNF-α and the development of inflammation in obese subjects. Eur J Med Res. 2010;15 Suppl 2(Suppl 2):120-2. doi:10.1186/2047-783x-15-s2-120
43. Mabrouk AA, Tadros MI, El-Refaie WM. Improving the efficacy of Cyclooxegenase-2 inhibitors in the management of oral cancer: Insights into the implementation of nanotechnology and mucoadhesion. J Drug Deliv Sci Technol. 2021;61:102240. doi:10.1016/j.jddst.2020.102240.
44. Al-Lawati H, Binkhathlan Z, Lavasanifar A. Nanomedicine for the effective and safe delivery of non-steroidal anti-inflammatory drugs: A review of preclinical research. Eur J Pharm Biopharm. 2019;142:179-94. doi:10.1016/j.ejpb.2019.06.025