https://dx.doi.org/10.22161/ijaers.5.2.9 *ISSN: 2349-6495(P) | 2456-1908(O)*

Using of Naproxen drug for novel synthesis of 4-thiazolidinone derivatives and application of these drugs as no steroidal anti-inflammatory drug (NSAIDs) and as anti-epileptic agent

Maryam Seyfimoghaddam[1], Naser Foroughifar[1], Hoda Pasdar[1], Alireza Khajeh-Amiri[2]

[1]Department of Chemistry, Tehran North Branch, Islamic Azad University, Tehran, Iran
[2]Young Researchers and Elites Club, Yadegar-e Imam Khomeini (RAH) Share Rey Branch, Islamic Azad University, Tehran, Iran.

Abstract— *Non-steroidal anti-inflammatory drugs (NSAIDs) are now one of the most frequent drugs used in treatment of pain, inflammation and fever. In this study the aim is the synthesis of derivatives of 4-Tiazolidinon from naproxen with the possible anti-pain effects, and the main purpose of providing these derivatives is to achieve a compound with more anti-pain power and less side effects in comparison with applied drugs in clinics. Synthesis of these derivatives is done on chloride in presence of a group of new liquids like recyclable ionic liquids choline chloride, which the main advantages of these ionic liquids are the cheapness, availability, being non-toxic, and easy recyclability. This reaction was done in four stages. All the structures were verified by using data of spectrum testing, [1]H-NMR, FT-IR.*

Keywords— naproxen, non-steroid, 4-tiazolidinon.

I. INTRODUCTION

To date, Nonsteroidal anti-inflammatory drugs (NSAIDs) are known as one of the most commonly used drugs for treatment of pain, inflammation, and fever [1]. Despite the abundant clinical usage of these types of drugs, some drawbacks including digestive and renal complications encourage scientists to design and synthesize new pain-relievers [2, 3]. In this study, we aimed the synthesize of 4-thiazolidinone derivatives from naproxen with probable analgesic and anti-inflammatory effects. The main goal is the development of new compounds with more therapeutic effects and less side-effects respect to common medications in clinics. Generally, one of the biggest problems for using of NSAIDs is their side-effects, which is mainly due to rising leukotriene levels at inhibition of cyclooxygenase enzyme and leading arachidonic acid to the lipoxygenase pathway.[4] On the other hand, generation of free oxygen derivatives such as superoxide anions through reduction of oxygen provokes producing other activate molecules like hydrogen peroxide (H_2O_2) and hydroxyl radicals. Interference with arachidonic acid causes chemotactic materials production which continues inflammation.[5,6] To diminish the side-effects of anti-inflammatory drugs, synthesis of 4-thiazolidinone heterocyclic compounds was investigated based on various reports about their anti-inflammatory effects. 4-thiazolidinone derivatives compounds show higher anti-inflammatory effects but lower side-effects than conventional drugs.[7] Implying analgesic and anti-inflammatory effects of N-aryl hydrazone naproxen in previous researches, hybrid compounds from 4-thiazolidinone and N-aryl hydrazone naproxen were developed to investigate their pharmacological studies for anti-inflammatory and pain-relieving effects as well as their digestive complications related to commonly used drugs.[9,10] These compounds were synthesized via previously reported methods and general procedures. Chemical structures of the intermediates and final products were confirmed using ^{1}HNMR, ^{13}CNMR, and IR spectroscopy.

II. EXPERIMENTAL SECTION

2.1. General Methods:

All reaction were monitored by "TLC" on pre-coated silica gel plates (60 F 254:Merck) column chromatography was performed on 100-200 mesh silica gel (SRL,India) using 10-20 fold execess (by weight) of the crude product.

IR spectra were recorded on a shimadzu FTIR 300 spectrometer in KBr pellets. Melting points were all determind by open glass capillary method on a melting point apparatus and are uncorrected. All used chemical or solvents were purchased from standard commercial suppliers (sigma Alderich and merck) and used as received without further purification. ^{1}H and ^{13}C NMR spectra were recorded on a bruker ACF-300 machine or a varian 300 or 400 MHZ spectrometer using either DMSO-d6 as a solvent with tetramethylsilane as internal refrence [11].

https://dx.doi.org/10.22161/ijaers.5.2.9 *ISSN: 2349-6495(P) | 2456-1908(O)*

2.2. Preparation of Intermediates (I)-(IV)

2.2.1. Synthesis of 2-(6-metoxy-naphthalene-2-yl) ethyl propanionate:

To a solution of 2-(6-methoxy-naphtalen-2-yl) propionic acid methyl ester (500 mg, 0.01 mol) in ethanol (20 ml) was added a few drops of conc.H_2SO_4 dropwise and the mixture was stirred at 85-90 ^oC for 12 h. After the completion of the reaction (indicated by TLC) ethanol was treated with water [12], The separated solid was filtered and dried to give the desired product as a colorless salid (yield .96%) mp 104-106 ^oC- ^{1}H-NMR (400 MHz, DMSO-d_6): δ, 7.78-7.69 (m, 3H, ArH), 7.45 (dd, J = 8.3 and 1.6 Hz, 1H), 7.25-7.24 (m. 1H), 7.13(dd, J=8.8 and 2.5 Hz,1H), 4.21(q, 2H, J=6.4 Hz), 3.86(s. 3H, OMe), 3.66 (q, 1H, J=6.4 Hz), 1.59 (d, 3H, J=5.7), 1.21 (t, 3H, J=5.9); FT-IR (KBr, cm^{-1}) 3310,3250, 2979, 2939, 1656, 1623.

2.2.2. Synthesis of 2-(2- metoxy naphtalen-6-yl)propan hydrazide:

To a solution of 2-(6-metoxy naphtalen-2-yl) propanionate (1mmol-0.23g) in ethanol (5ml) was added hydrazine hydrate (3.0 ml) with vigorous stirring at room temperature. The mixture was then stirred at 85-90 ^oC for 12h [12]. After completion of the reaction (indicated by TLC) ethanol was treated with water [12], The separated solid was filtered and dried to give the desired product as a colorless salid (yield .78%) mp 110-1112 ^oC-FT-IR (KBr) νmax (cm^{-1}): 3284 (NH), and 3093 (CH-aromatic),2998, 2971, 1672 (C=O, keton), 1489 (C=C), 1091(C-C). ^{1}HNMR (DMSO-300MHz) δ ppm: 9.99 (s, 1H, NH, D_2O exchangeable); 9.20 (s, 1H, NH, D_2O exchangeable); 7.23-7.93(m,4H, Ar-H), 7.24 (s, 1H, Ar- H), 383 (3H, s, OCH_3), 3.63(1H, q, J=5.4), 1.59 (3H, d, J= 5.85), 2.11 (s, 3H, CH_3).

2.2.3. General method for synthesis of 1-arylidene-2-(3-(6-methoxynaphthalen-2-yl) but-1-en-2-yl)hydrazine:

To a solution of 2-(2- metoxy naphtalen-6-yl)propan hydrazide (500 mg, 0.01 mol) in dichloromethan (20 ml) was added zinc chloride (0.1 g) and derivatives of aldehyde (1 mmol) and the mixture was stirred at 85-90 ^oC for 12 h. After the completion of the reaction (indicated by TLC) ethanol was treated with water [12], The separated solid was filtered and dried to give the desired product as a white solid; Yield 91%, m.p: 150-160˚C; FT-IR (KBr, cm^{-1}); 3329 (N-H), 3214 (C-H), 1680 (C=O), 1605 (C=N); 1524 (C=C);; 1242 (C-N). ^{1}HNMR (DMSO, 300MHz) δ ppm: 12.18(s, 1H, NH, brs), 7.82-8.16 (m, 4H, $H_{aromatic}$), 7.69 (s, 1H, C=CH), 6.51-7.39 (m, 4H, $H_{aromatic}$), 3.71(s, 3H, OCH_3). (Scheme 1)

2.2.4. Synthesis of 2-(6- metoxy naphtalen-2-yl)propanoil)-propamido-N-(2-hydroxy phenyl)-6-mercapto-thiazolidine-4-one:

To a solution of 1-arylidene-2-(3-(6-methoxynaphthalen-2-yl)but-1-en-2-yl)hydrazine (1mmol) in dichloromethan (5ml) and zinc chloride (0.1 g) was added 2,2-dithiopropanoic acid (1mmol) with vigorous stirring at room temperature. The mixture was then stirred at 85-90 ^oC for 6h. Yield 78%, m.p 110-120 °C. FT-IR (KBr) νmax (cm^{-1}): 3233 (NH), and 3093 (CH), 1672(C=O), 1489 (C=C), 1091(C-C), ^{1}HNMR (DMSO-300MHz) δ ppm: 9.99 (s, 1H, NH); 7.23-7.93 (m,4H, Ar-H); 7.24(s, 1H,Ar-H); 2.11-2.27(s, 3H, CH_3).

2.3. Antibacterial Activity:

To examine the antibacterial activity of some synthesized compounds, one gram negative bacteria: Escherichia Coli (ATCC, 6538). One gram positive bacteria: Staphylococcus Aureus (ATCC, 25922), were selected and tested by the disc diffusion method [15] using Mueller–Hinton Agar against. Tetracycline was used as standard. Normal saline was used for preparation of inoculants having turbidity equal to 0.5 McFarland standards. Tested compounds were dissolved in dimethyl sulfoxide (DMSO) for the preparation of stock solution. The solvent control was included, although no antibacterial activity has been noted. Culture was carried out with sterile swab and microtube suspension was cultured for 24 h and then inoculated onto Mueller Hinton agar. Blank discs with a diameter of 6 mm and containing 30 µg of the concentration of these compounds (D_3) were placed on Muller Hinton agar medium.

After 24 h incubation at 37 °C, area of growth inhibition was measured. Disks containing 10 µg of 5 dimethyl sulfoxide were used as the negative control. Each concentration was repeated 4 times for each of the bacteria and the average results of inhibitory effects are show in Table 1.

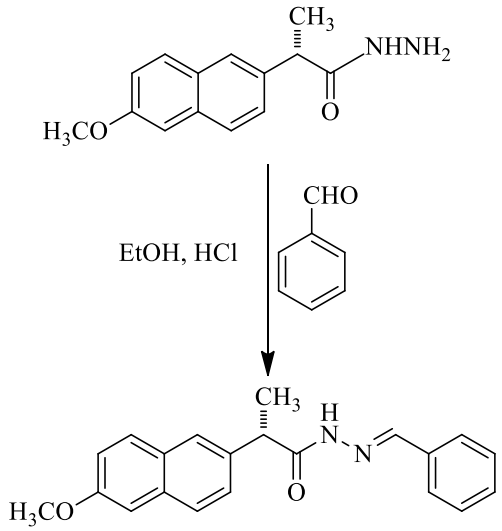
Determination of the minimum inhibitory concentration (MIC) values for some synthesized compounds against six microorganisms was carried out using disc diffusion method. In this method, concentration of 10, 20, 30, 50, 150 µg /mL were used for all bacteria per disc and there were incubated at 37 °C for 24 h. MIC value was defined as lowest concentration of compound for inhibition growth of the tested bacteria.

3. Results & discussion:

In this study in the presence of deep eutectic solvent as environmentally friendly catalyst and reaction medium, synthesize of some thiazolidine-4-one derivatives from naproxen has been discussed (scheme2). This reaction was more efficient in good yield in short time duration. Finally, after completion the reaction, that's possible to separate the

https://dx.doi.org/10.22161/ijaers.5.2.9 *ISSN: 2349-6495(P) | 2456-1908(O)*

catalyst. The results led to the synthesis of 3-(2-(2- metoxy naphtalen-6-yl)propanoil)-1,3,4 tiadiazolidin-2-ones substances with possibly particular biological and medicinal properties. The structure of synthesized compounds (f-g) was confirmed by FT-IR, ^{1}H-NMR, ^{13}C-NMR spectroscopic methods. All the physical, chemical properties, IR, NMR of the compounds are reported in experimental parts. All the compounds display antibacterial effect against Gram positive bacterias, S. aureus, and E. coli Gram negative bacteria. Specifically, the synthesized compounds screened for their biological study which displayed moderate to good activity.



Scheme1: General method for the synthesis of 1-benzylidene-2-(3-(6-methoxynaphthalen-2-yl)but-1-en-2-yl)hydrazine

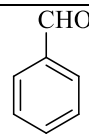
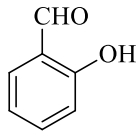
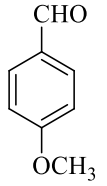
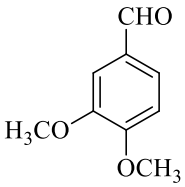
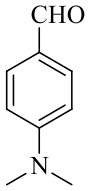
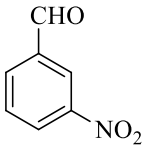
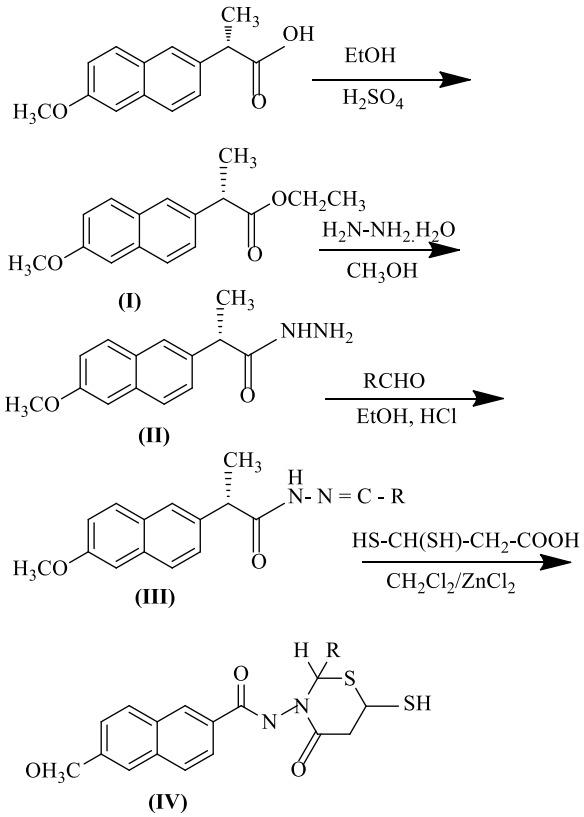
Entry	R= aldehyde	Time(hr)	*Yield (%)*	m.p(^{O}C)
1		6	95	157-159
2		3	90	182-185
3		3	70	160-162
4		4	80	170-172
5		3	40	190-193
6		3	50	200-202

Table 1. Synthesis of some 2-(6- metoxy naphtalen-2-yl)propanoil)-propamido-N-(2-hydroxy phenyl)-6-mercapto-thiazolidine-4-one with some aldehydes



R: C_6H_5, 2-OH-C_6H_4, 4-OCH_3-C_6H_4, 3,4-di-OCH_3-C_6H_3, 4-$(CH_3)_2N$-C_6H_4, 3-NO_2-C_6H_4

Scheme 2: Synthesis of some 2-(6- metoxy naphtalen-2-yl)propanoil)-propamido-N-(2-hydroxy phenyl)-6-mercapto-thiazolidine-4-one in the presence of some aldehydes

https://dx.doi.org/10.22161/ijaers.5.2.9 *ISSN: 2349-6495(P) | 2456-1908(O)*

REFERENCES

[1] Foroughifar, N,; Kalhor, M,; Mirabolfathy, M,; Synthesis and antifungal activity of novel 2-benzimidazolylimino-5-arylidene-4-thiazolidinones. J. Heterocyclic Chem., **2010**, 47, 77-80.

[2] B. Nahri-Niknafs, Org. Chem. J., 3(1), 17 **(2012).**

[3] "Thiourea". Merriam-Webster Dictionary. Retrieved **2016**-01-21.

[4] Bernd Mertschenk, Ferdinand Beck, Wolfgang Bauer "Thiourea and Thiourea Derivatives" in Ullmann's Encyclopedia of Industrial Chemistry **2002** by Wiley-VCH Verlag GmbH & Co. KGaA. All rights reserved. doi:10.1002/14356007.a26_803

[5] Agrawal, V.K.; Sachan, S.; Khadikar, P.V. QSAR studies on antihistaminic activity of some thiazolidine-4-ones. Acta Pharm., 2000, 50, 281–290. (b) Diurno, M.V.; Mazzoni, O.; Correale, G.; Monterrey, I.G.; Calignano, A.; La Rana, G.; Bolognese, A. Synthesis and structure–activity relationships of 2-(substituted phenyl)-3-[3-(N,Ndimethylamino)-propyl]-1,3-thiazolidin-4-ones acting as H1-histamine antagonists. II Farmaco**.,** **1999**, 54, 579–583.

[6] Bhati, S. K.; Kumar, A. Bhati, S. K.; Kumar, A. Synthesis of new substituted azetidinoyl and thiazolidinoyl-1,3,4-thiadiazino (6,5-b) indoles as promising anti-inflammatory agents. Eur. J. Med. Chem**.,** **2008**, 43, 2323-2338.

[7] Vigorita, M.G.; Ottanà, R.; Monforte, F.; Maccari, R.; Monforte, M.T.; Trovato, A.; Taviano, M.F.; Miceli, N.; De Luca, G.; Alcaro, S.; Ortuso, F. Chiral 3,3'-(1,2-ethanediyl)-bis[2-(3,4-dimethoxyphenyl)-4-thiazolidinones] with anti-inflammatory activity. Part 11: Evaluation of COX-2 selectivity and modeling. Bioorg. Med. Chem**.,** **2003**, 11, 999–1006.

[8] Chawla, P,; Singh, R,; Saraf SK,; Effect of chloro and fluoro groups on the antimicrobial activity of 2,5-disubstituted 4-thiazolidinones: a comparative study. Med Chem Res**,** **2011**, 21, 3263–3271

[9] Rawal, R. K.; Srivastava, T.; Haq, W.; Katti, S. B. J. An expeditious synthesis of thiazolidinones and tetathiazanones Chem. Res., 2004, 5, 368. (b) Rawal, R. K.; Tripathi, R. K.; Katti, S. B.; Pannecouque, C.; De Clercq, E. Synthesis and Biological Evaluation of 2, 3-Diaryl substituted-1, 3-thiazolidin-4-ones as Anti-HIV Agents. Med. Chem**.,** **2007**, 3, 355-367.

[10] Havrylyuk, D,; Mosula, L,; Zimenkovsky, B,; Vasylenko, O,; Gzella, A,; Lesyk R. Synthesis and anticancer activity evaluation of 4-thiazolidinones containing benzothiazole moiety. Eur J Med Chem., **2010**, 45, 5012–5021.

[11] Öcal, N,; Aydoğan, F,; Yolaçan, C,; Turgut, Z. Synthesis of some furo-thiazolidine derivatives starting from aldimines . J. Heterocyclic Chem**.,** **2003**, 40, 721-724

[12] Mamatha Nakka, a Murtuja Seikh Begum, a B. F. Mathews Varaprasad, a Lingam Venkata Reddy, a Abir Bhattacharya, b Madeleine Helliwell, c Alok Kumar Mukherjee, b Syed Sultan Beevi, a Lakshmi Narasu Mangamoori, a Khagga Mukkanti a and Sarbani Pal **J. Chem. Pharm. Res. **2010**, 2(6):393-409*