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Design and Synthesis of new Naproxen Analogues as Potential Anti-inflammatory Agents

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Abstract:

4-aminobenzenesulfonamide derivatives were linked to α-carbon of naproxen a non-selective non-steroidal anti-inflammatory drug (NSAID) to increase its size, so; increase its selectivity toward COX-2 enzyme, rather than COX-1 enzyme, that lead to reduce gastrointestinal side effects of this drug.

The chemical structures of the synthesized compounds and their intermediates were confirmed and characterized using elemental microanalysis (CHN), FTIR, and other physicochemical properties like melting points, Rf values.

Key words: amine derivatives, anti-inflammatory Agents, derivatives of naproxen

تصميم و تصنيع مشتقات جديدة لعقار النابروكسين كأدوية محتملة مضادة للالتهاب

.الخلاصة:

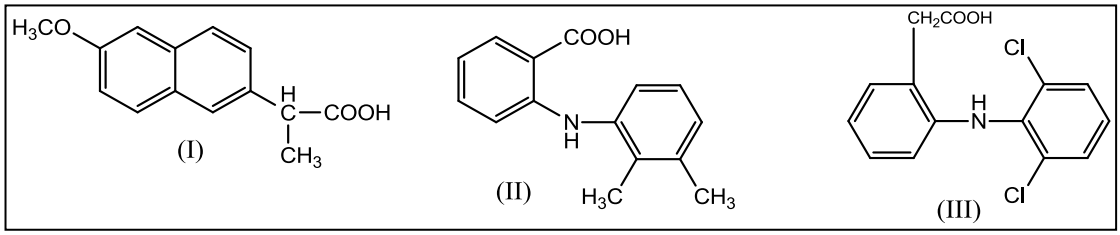
لقد تم تصنيع مشتقات لعقار النابروكسين (دواء مضاد للالتهاب غير ستيرويدي) بواسطة اقترانه مع المشتقات الأمينية [4 aminobenzenesulfonamide]-لذرة الكاربون ألفا لعقار النابروكسين لزيادة ضخامته لغرض تقيمها كأدوية ممكنة مضادة للالتهابات تستهدف الإنزيم سيكلوأوكسيجيناز-2 بانتقائية عالية للحد من الآثار الجانبية المعدية والمعوية لهذا العقار. وقد تم اثبات هوية التراكيب الكيميائية لهذه المركبات باستخدام التحليل الدقيق للعناصر ,(CHN) طيف الاشعة تحت الحمراء وبعض الخواص الفزيوكيمياوية مثل درجة الانصهار و معامل التاخير(Rf).

الكلمـــــات المفتاحيـــــة: مشـــــتقات الأمـــــين، الادويـــــة المضـــــادة للالتهابـــــات، مشـــــتقات نابروكســـــين.

Introduction:

Due to their analgesic, and anti-inflammatory properties, non-steroidal anti-inflammatory drugs (NSAIDs) are the most used therapeutic agents in the world [1, 2]. However, the use of non-selective NSAIDs as naproxen (I), mefenamic acid (II), and diclofenac (III) [3], result in different gastrointestinal (GI) adverse events, ranging from minor bleeding to sever gastric ulceration [4]. The mechanism of action of NSAIDs is produced through their inhibitory activity of the cyclooxygenases enzymes (COXs) involved in the biosynthesis of prostaglandin H2 (PGH2) [5]. Two isoforms of COX enzymes (COX-1 and COX-2) has been detected, COX-1 is considered as "housekeeping", which is constitutively expressed in stomach and provides cytoprotection for the GIT [6], while COX-2 is inducible and formed at site of inflammation, and exhibits a major role in prostaglandin biosynthesis in inflammatory cells [7]. The isolation of the second isoform of cyclooxygenase enzyme, led to an enormous burst in activity in the field of pharmaceutical chemistry, and industrial pharmacy aimed for the synthesis of selective COX inhibitors, to avoid serious side effects associated with non-selective agents [8]. Several therapeutic indications of selective COX-2 inhibitors have been found [9], which include the treatment of Alzheimer disease [10] and Parkinson disease [11, 12]. Other searches show that the COX-2 enzyme can considered as a novel target in the controlling of some malignant

tissues [13], infectious diseases [14], and endometriosis [15].

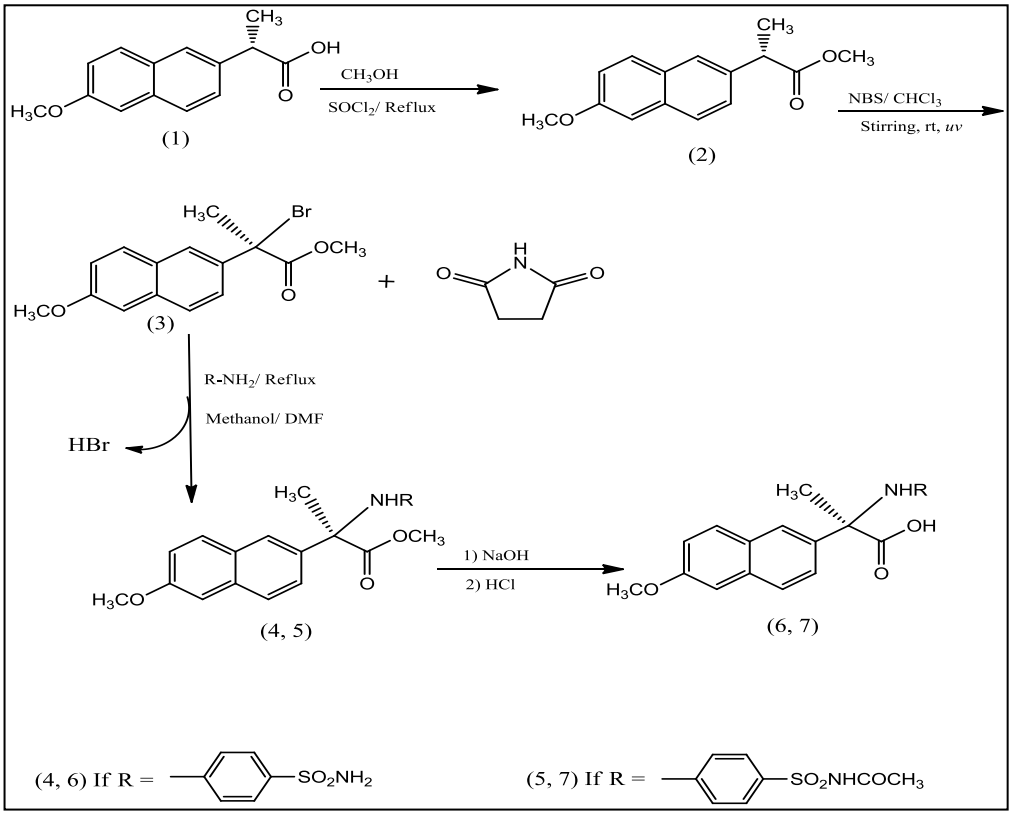


Materials and methods:

Experimental

All chemicals and solvents were of analytical grade and supplied from (Reidal Dehean Germany; Sigma-Aldrich Germany; BDH England). Naproxen was supplied from China. Melting points (uncorrected) were determined by capillary tube method by Thomas hover apparatus (England). Rf values were determined by using thin layer chromatography, on DC-Kartan SI Alumina 0.2 mm to evaluate the purity and completion of the reaction, using (n-hexane, acetic acid, ethyl acetate), (7: 0.5: 2.5:) [16] as mobile phase, and the detection of compounds spots was done usingUVspectrophotometer.Determination of FT-IR spectra has been done by using FT-IR spectrophotometer, at college of pharmacy, University of Kufa, by utilizing KBr discs. CHN analysis has been done in university of science in Jordan, by using Carlo Erba elemental analyzer.

Scheme 1 represent the chemical synthetic steps of all compounds, where the carboxyl group of naproxen was protected in the form of methyl ester, then, undergo nucleophilic substitution reaction with N-bromosuccinamide in presence of sunlight to give compound 3, which undergo nucleophilic substitution reaction with amine derivatives to give compounds 4, and 5, which are finally deprotected to liberate the free carboxyl groups in compounds 6, and 7.



Scheme 1: Synthesis of the compounds 4, 5, 6, and 7.

Chemistry:

Synthesis of methyl 2-(6-methoxy-naphthalen-2-yl)propanoate (compound 2): Naproxen solution (1g, 4.34mmol) in absolute ethanol was kept in low temperature {-15oC, using Chiller Julabo VC (F30)}, then added thionyl chloride (0.32ml, 4.34mmol) drop wise with stirring. Then the solution was stirred for additional 3 hours at 40oC, and then refluxed for 3 hours and keep at room temperature overnight. The solvent was evaporated by rotary evaporator, dissolved in alcohol and dried. The solid that obtained after evaporation was crystallized from acetone-ether [17]. The physicochemical properties in addition to percent yield and Rf values were given in table [1], and FT-IR spectral data was given in table 2, and Figure 1 represents these spectrums.

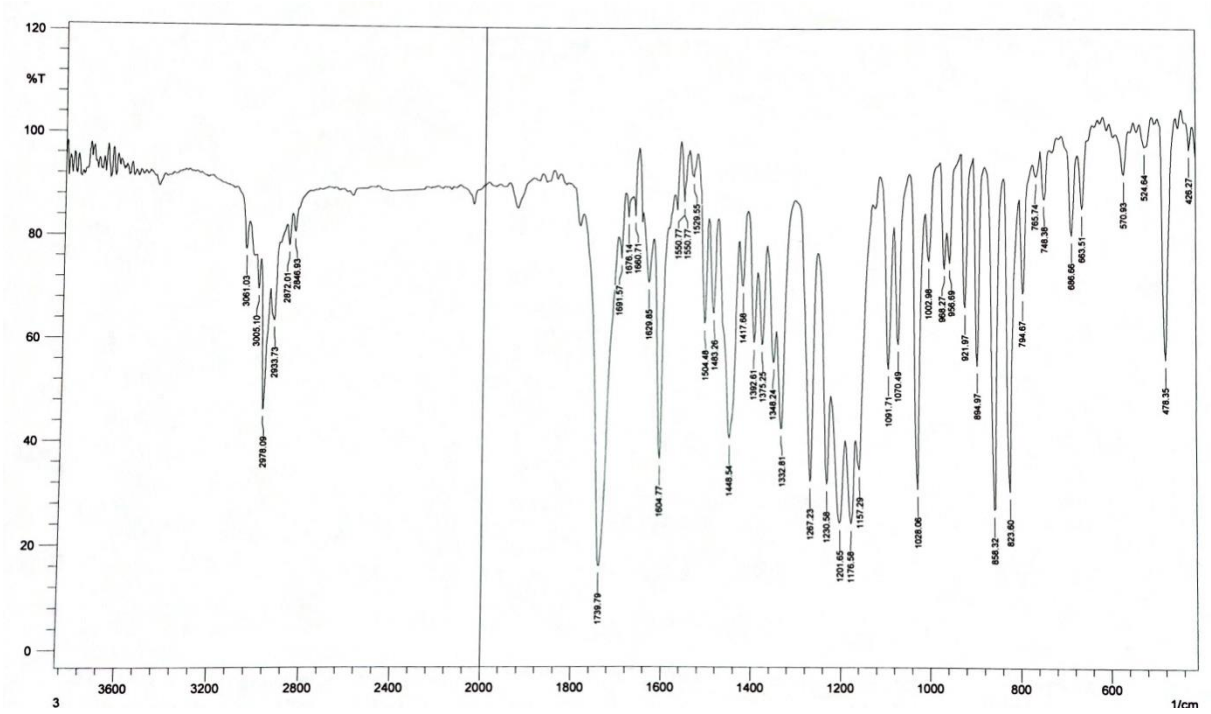


Figure 1: FT-IR spectrum of compound 2

Synthesis of (R)-methyl-2-bromo 2-(6-methoxynaphthalen-2-yl)propanoate (compound 3):

Compound 2 (0.5g, 2.04 mmol) was dissolved in chloroform (15ml), and then NBS (0.36g, 2.04 mmol) was added drop wise with continuous stirring. Then the solution was stirred for additional 3 hours at 25oC. The solvent was evaporated by rotary evaporator. The residue was washed with ether and filtered to afford compound 3 (18). The physicochemical properties in addition to percent yield and Rf values were given in table (1), and FT-IR spectral data was given in table 2.

Synthesis of (R)-methyl-2-(6-methoxy-naphthalen-2-yl)-2-(4-sulfamoylphen-ylamino) propanoate (compound 4):

Compound 3 (0.5g, 1.54 mmol), and sulfanilamide (0.26g, 1.54 mmol) were mixed and dissolved in mixture (30ml) of ethanol 99%: DMF (50:50), which gently refluxed for three hours. Then evaporated the solvent and dissolve the residue in ethyl acetate, washed with 5% w/v NaOH aqueous solution (5×10 ml) and finally

filtered to afford compound 4 (19). The physicochemical properties in addition to percent yield and Rf values were given in table (1), and FT-IR spectral data was given in table 2.

Synthesis of (R) – methy l-2- (4-(N-acetylsul-famoyl) phenylamino)-2-(6-methoxyna-phthalen-2-yl)propanoate (compound 5):

Compound 3 (0.5g, 1.54 mmol), and sulfacetamide (0.66g, 1.54 mmol) were mixed and dissolved in mixture (40ml) of ethanol99%: DMF (50:50) mixture (40ml), which gently refluxed for three hours. Then evaporated the solvent and dissolve the residue in ethyl acetate, washed with 5% w/v NaOH aqueous solution (5×10 ml) and finally filtered to afford compound 5 (19). The physicochemical properties in addition to percent yield and Rf values were given in table (1), and FT-IR spectral data was given in table 2.

Synthesis of (R)-2-(6-methoxyna-phthalen-2-yl)-2-(4-sulfamoylph-enylamino) propanoic acid (compound 6):

20 ml of tetrahyrofuran: ethanol 99% (1:3) was used to dissolve Compound 4 (0.3g, 0.72 mmol). The solution was kept at 18o C, and then NaOH (2N) solution (0.35 ml, 0.72 mmol) was added gradually, with continuous stirring through 45 minutes. Stirring was continued at the same temperature for two hours. Then acidify the reaction mixture by the addition of HCl (2N) solution (0.35 ml, 0.72 mmol), after that the acidic compound was precipitated by the addition of excess ice water and filtered to afford compound 6 (20). The physicochemical properties in addition to percent yield and Rf values were given in table (1), FT-IR spectral data was given in table 2, and Figure 2 represent these spectrums. CHN Calculated: C, 59.99; H, 5.03; N, 7.00. Found C, 59.95; H, 5.07; N, 7.36.

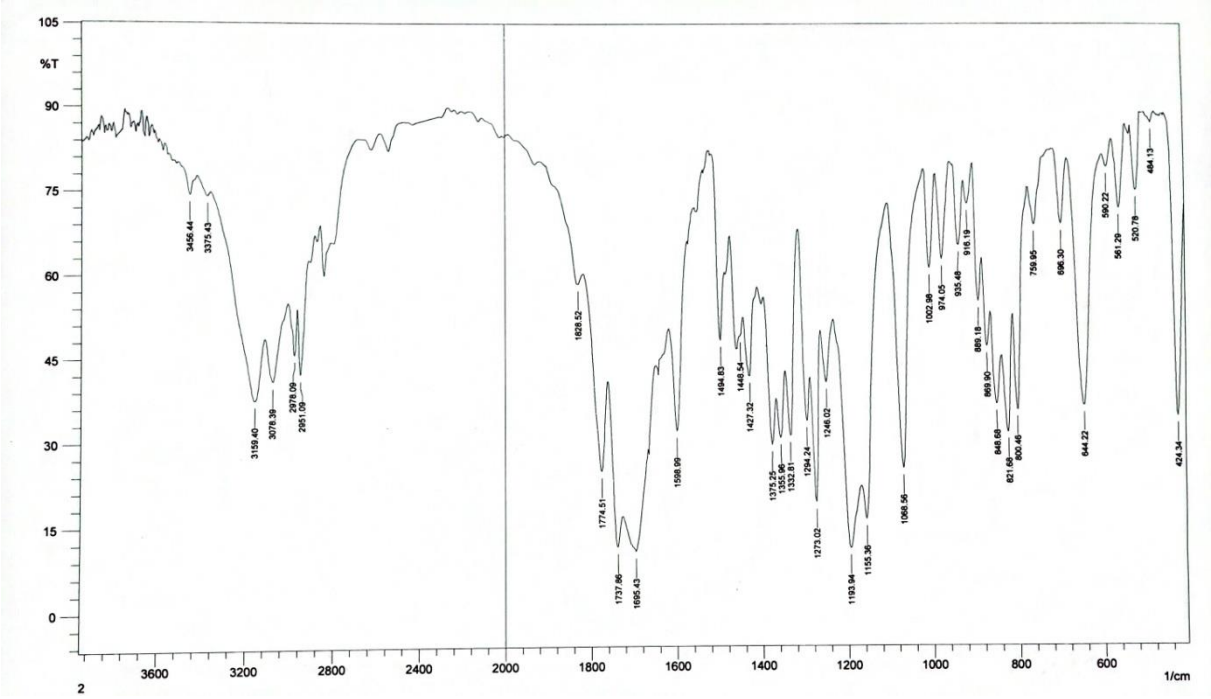


Figure-2:FT-IR spectrum of compound 6.

Synthesis of (R)-2-(4-(N-acetylsulfamoyl) phenylamino)-2-(6-methoxynaphthalen-2-yl) propanoic acid (compound 7):

30 ml of tetrahyrofuran: ethanol 99% (1:3) was used to dissolve Compound 5 (0.4g, 0.87mmol). The reaction mixture was kept at 18o C, and then NaOH (2N) solution (0.42ml, 0.87mmol) was added gradually, with continuous stirring through 45 minutes. Stirring was continued at the same temperature for two hours. Then acidify the reaction mixture by the addition of HCl (2N) solution (0.42ml, 0.87mmol), after that the acidic compound was precipitated by the addition of excess ice water and filtered to afford compound 7 (20). The physicochemical properties in addition to percent yield and Rf values were given in table (1), FT-IR spectral data was given in table 2, and Figure 3 represent these spectrums. CHN Calculated: C, 59.72; H, 5.01; N, 6.33. Found: C, 59.80; H, 5.5; N, 6.36.

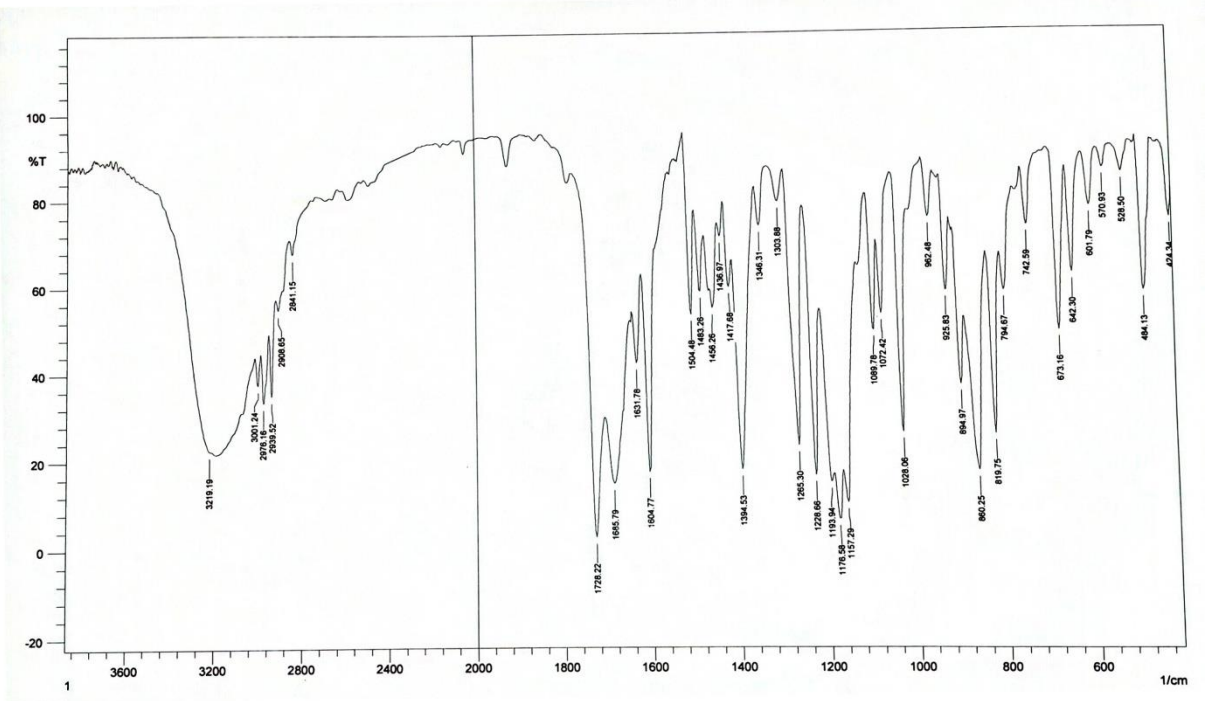


Figure 3; FT-IR spectrum of compound 7.

Results and Discussion:

Naproxen derivatives were synthesized through linking its α-carbon with amine derivatives (4-aminobenzene sulfonamide, and (4-aminobenzenesulfonyl)acetamide, by the scheme that shown above. They were subjected to physico-chemical characterization, the data are shown in Table 1, and their structures were confirmed by the FT-IR spectroscopy, and were represented by Table 2. IR spectra of compound 2 showed the characteristic absorption band for ester C=O stretching at 1739 cm-1, thus confirmed the formation of ester bonds in the synthesized compound, while compounds 6, and 7 showed C=O stretching, that characterized the acid at 1695 cm-1, and 1728 cm-1 respectively.

Table 1: Physicochemical properties of the synthesized compounds.

Compounds	Chemical Formula	Molecular weight	Appearance	Percent Yield	Melting point ^{o}C	R_f values
2	$C_{15}H_{16}O_3$	244.11	Yellow crystals	75.5	88-91	0.75
3	$C_{15}H_{15}BrO_3$	323.18	Pale brown crystals	80.2	77-79	0.78
4	$C_{21}H_{22}N_2O_5S$	414.47	Brown powder	79.1	93-95	0.83
5	$C_{23}H_{24}N_2O_6S$	456.14	Yellow powder	74	160-162	0.89
6	$C_{20}H_{20}N_2O_5S$	400.45	Brown powder	45	98-101	0.73
7	$C_{22}H_{22}N_2O_6S$	442.12	Deep yellow powder	24	175-176	0.82

Table 2: FT-IR spectral data of the synthesized compounds.

Compounds	Bands (cm-1)	Interpretation
2	3061	C-H stretching vibration of aromatic
	1739	C=O stretching vibration of ester
	1332	C-O stretching vibration of ester
4	3456	C-H stretching vibration of alkane
	3361 and 3372	N-H stretching vibration of primary sulfonamide
	1741	C=O stretching of ester
	1581 and 1479	C=C stretching vibration of aromatic
	1311 and 1150	S=O stretching of sulfonamide
5	3352	N-H stretching of secondary amine
	1734	C=O stretching of ester
	1326 and 1153	S=O stretching vibration of secondary sulfonamide
6	3456 and 3375	N-H stretching of primary sulfonamide
	3159-2951	Broad, moderately absorption region result from overlapping of O-H stretching vibration of carboxylic acid and N-H stretching vibration of secondary amine.
	1695	C=O stretching vibration of acid
	1332 and 1193	S=O stretching vibration of primary sulfonamide
7	3219-2939	Broad, moderately absorption region result from overlapping of O-H stretching vibration of carboxylic acid and N-H stretching vibration of amine.
	1728	C=O stretching of carboxylic acid
	1394 and 1157	S=O stretching vibration.

Conclusion:

The synthesis of the designed compounds has been successfully achieved, and their purity and structural formulas were confirmed by melting points determination, Rf values, FT-IR spectroscopy and elemental microanalysis.

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The synthesis of the designed compounds has been

We are grateful to pharmaceutical chemistry depart