Available online at www.derpharmachemica.com

ISSN 0975-413X
CODEN (USA): PCHHAX

Der Pharma Chemica, 2017, 9(8), 38-45
(http://www.derpharmachemica.com/archive.html)

Design, Synthesis and Biological Evaluation of New Potentially Active Derivatives of Naproxen Linked to Heterocyclic Amines

Alyaa S Naser[1*], Amer N Elias[2]

[1]Donors Division, Deputy Minister Office, Ministry of Health, Baghdad, Iraq
[2]College of Pharmacy, Al-Bayan University, Baghdad, Iraq

ABSTRACT

The synthesis of new derivatives of naproxen through the prodrug strategy is an established part of drug development for the minimization of its side effects and improving its activity, and for this purpose different heterocyclic amines such as 2-aminothiazole, 2-aminobenzimidazole and 2-aminobenzothiazole were used for the synthesis of these derivatives by linking with the parent drug naproxen. After the amidation of these amines they were coupled to naproxen hydrazide. The characterization of the synthesized compounds was done by resorting to Fourier Transform Infrared Spectroscopy (FTIR) and their purity was checked by running the C, H, N and S elemental analysis while other physicochemical properties came in handy in the identification process. The anti-inflammatory activity of naproxen derivatives were evaluated in vivo by using fresh egg white induced paw edema in Wistar albino rat in which the synthesized derivatives have either superior or comparable activity to naproxen.

Keywords: Naproxen, Hydrazide, 2-Aminothiazole, 2-Aminobenzmidazole, 2-Aminobenzothiazole

INTRODUCTION

Pain, fever and inflammation have been associated with mankind since the beginning of life. Non-steroidal Anti-inflammatory Drugs (NSAIDs) have already been considered as the first drugs of choice in the treatment of pain, degenerative inflammatory joint diseases and rheumatic disorders [1]. There are many NSAIDs on the market but still there is an urgent need for new and advanced research focusing on these drugs due to their serious side effects manifested by their imposed and exhibited gastric toxicity and kidney damage. Many of these currently available non-steroidal analgesic and anti-inflammatory agents such as aspirin, naproxen, indomethacin, ibuprofen, diclofenac and others are carboxylic acid derivatives and therefore, they are associated with the ulcerogenic side effect of these drugs. As a result, these NSAIDs show many limitations in their therapeutic use since they share the ulcerogenic side effect among others such as the gastrointestinal upset and renal damage which are inseparable from their pharmacological activities. Recently, approaches that mask the ulcerogenic side effect of these NSAIDs have employed the prodrug concept that utilizes the conversion of the carboxylic acid group into some other functional groups such as an amide, ester, aldehyde or even a ketone [2], so that the synthesis of new compounds devoid of such side effects has become an important goal for the medicinal chemists in recent years [3]. One of the most important NSAIDs used is Naproxen, and although the shown gastrointestinal bleeding and increased Cardiovascular (CV) problems are associated with most of the known NSAIDs, but Naproxen is still yet known for its fewer CV effects with a possible cardio protective role in humans [4].

The amino- derivatives of heterocyclic rings such as the thiazole, benzimidazole and benzothiazole are biologically active compounds which were mentioned earlier in the literature in that they have an extended and various biological activities such as anticancer and antibacterial activities [5].

Aminothiazole is considered as the precursor for the chemical synthesis of a great number of biologically active compounds including fungicides, biocides, sulfur drugs and dyes. 2-aminothiazole derivatives can be used for the treatment of hyperthyroidism by acting as a thyroid inhibitor and as antibacterial [6]. The derivatives of 2-aminothiazole also have antifungal, antiprotozoal, antibacterial [7], anticancer [8,9], and anti-tuberculosis [10] activities.

The benzothiazole nucleus possesses a number of biological activities such as being with an anticancer [11], antimicrobial [12], anticonvulsant [13], anti-diabetic [14], antitubercular [15], antiviral [16], anti-inflammatory [17], anti-leishmanial [18] and antioxidant [19] activities.

2-aminobenzimidazole derivatives are of biological importance since it includes a wide range of biological activities and also it is considered as a precursor for the synthesis of many benzimidazole derivatives. 2-Aminobenzimidazole derivatives is a bioactive compound by having antibacterial, antifungal [20], anticancer [21], anti-inflammatory [22], diuretic [23], H_3-receptor antagonist [24], anti-parasitic [25], anti-obesity and anti-diabetic [26] activities.

The hydrazide derivatives could exhibit various biological activities such as being antibacterial, tuberculostatic, antiviral, antidepressant, antihypertensive, antihistaminic, anti-inflammatory and analgesic [27]. The investigations for new NSAIDs with less or no serious side effects are still a challenge and the goal of many researchers in medicinal chemistry, and so accordingly, in this work we aimed to design new potent and safe Naproxen derivatives.

MATERIALS AND METHODS

Materials and equipment's

2-aminothiazole, 2-aminobenzimidazole and 2-aminobenzothiazole were purchased from Sigma-Aldrich (Germany), chloroacetyl chloride from Merck (Germany), Hydrazine hydrate 99.5% from Alpha medica (India), and thionyl chloride from SCR (South Africa). Naproxen was donated gratefully by The State Company for Drug Industries (SDI, Samara, Iraq).

The quality of all these chemicals together with the other ones used throughout the study and obtained from standard commercial sources were of the highest purity and quality available. The purity of the synthetic starting materials was ensured by measuring their corresponding melting points and performing their IR spectroscopy, so these compounds together with the other reagents were used without further purification.
The progress of the reaction was monitored together with the process of checking the purity of the synthesized products was done by ascending Thin Layer Chromatography (TLC) that runs on Kieslgel G60 F_{254}, pre-coated with 0.2 mm thickness aluminum plates (Spain). The chromatograms were eluted by using one or more of the following mobile phases: Solvent system (A): Hexane: Ethyl acetate (4:6); System (B): Hexane: Ethyl acetate (2:8); and System (C): Ethyl acetate: Methanol (6:4). The synthesized final products together with their intermediates compounds were revealed by irradiating the plates with UV_{254} light.
The melting points were determined by the open capillary method using Stuart SMP30 (USA) and results were used uncorrected. Cooling when needed during reactions was performed by the use of Julabo chiller VC (F30) (GMBH, Germany). IR were recorded in KBr disc on Shimadzu FTIR 8400 spectrophotometer (Japan), at the College of Pharmacy, University of Baghdad and on Shimadzu FTIR 8400-S spectrophotometer (Japan), at the College of Pharmacy, University of Al-Mustansiriyah. Elemental microanalysis was performed at the College of Science, University of Al-Mustansiriyah using CHN Euro EA Elemental Analyzer (Italy).

The biological evaluation of the anti-inflammatory activity of the final target compounds was performed at the Department of Pharmacology and Toxicology, College of Pharmacy, University of Baghdad.

Experimental work

Chemical synthesis

The procedures described and followed below for the synthetic processes were improved from those reported earlier in the literature when used with few minor changes.

The synthesis of naproxen methyl ester (Intermediate compound A)

A suspension of naproxen (7 g, 0.0304 mol) in 80 ml of absolute methanol contained in a 250 ml round bottom flask was cooled down to -10°C and then to which thionyl chloride (2.2 ml, 0.0304 mol) was added drop wise with stirring, that was performed at -10°C. After the completion of addition the mixture was heated with stirring for 3 h at 45°C, then refluxed for 3 h at 70°C, and after the refluxing period the mixture was kept stirring over night at room temperature. Later the excess solvent was evaporated under vacuum, and the precipitated material was re-dissolved in absolute methanol which was followed by evaporating the solvent again under vacuum. This process was repeated for three times and the product was then re-crystallized from absolute ethanol [28,29].

The synthesis of naproxen hydrazide (Intermediate compound B)

An accurately weighed amount of naproxen methyl ester (intermediate compound A) (5 g, 0.02 mol) was added to 75 ml of absolute ethanol contained in a 250 ml round bottom flask, and to this mixture an excess of hydrazine hydrate 99.5% (4.5 ml, 0.14 mol) was then added in a drop wise manner, followed by leaving the reaction stirred overnight at room temperature. After that it was kept under reflux for 8 hr. at 80°C and at the end of the refluxing period the mixture was left to be stirred overnight at room temperature. Later, 20 ml of cold distilled water was added to precipitate the product (intermediate compound B) which was obtained by filtration and left to dry. The product was then re-crystallized from absolute ethanol [30,31].

The synthesis of the intermediate compounds C, D and E

(a) For the synthesis of intermediate compound C (α-chloroamide of 2-aminothiazole) and accurately weighed amount of 2-aminothiazole (5 g, 0.05 mol) was dissolved in 50 ml of chloroform placed in a 250 ml round bottom flask and to this solution (6.9 g, 0.05 mol) of anhydrous potassium carbonate was added with stirring. The reaction flask was later placed in an ice bath at 0°C, and chloroacetyl chloride (5 ml, 0.06 mol) was then added with stirring in a drop wise fashion and the mixture was left at room temperature for a few minutes then it was refluxed for 18 h at 85°C [32].

At the end of the refluxing period, the excess amounts of the solvent and chloroacetyl chloride were evaporated under reduced pressure. The residual material thus obtained was washed with 3 × 15 ml of (5%) sodium bicarbonate and subsequently with 3 × 30 ml of cold water and after filtration; the obtained precipitate was left to dry and later re-crystallized from absolute ethanol.

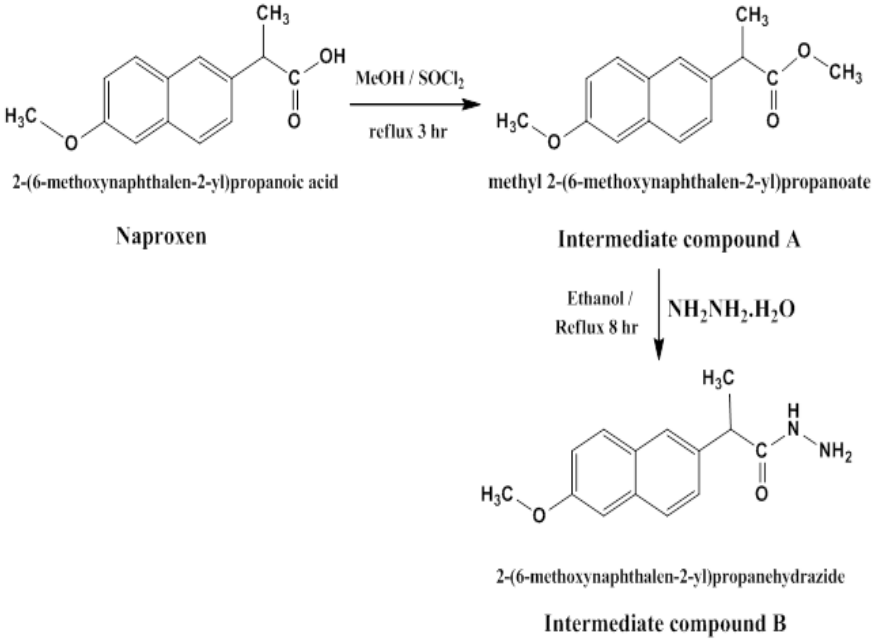
(b) For the synthesis of intermediate compound D (α-chloroamide of 2-aminobenzimidazole), an accurately weighed amount of 2-aminobenzimidazole (5 g, 0.037 mol) was added to 50 ml of chloroform in a 250 ml round bottom flask, then (5.1 g, 0.037 mol) of anhydrous potassium carbonate was added to the mixture with stirring. Later, the reaction mixture was placed in an ice bath at 0°C and after acquiring the required temperature (3.79 ml, 0.0469 mol) of chloroacetyl chloride was added with stirring in a drop wise manner. After the addition of chloroacetyl chloride was completed, the mixture was kept stirred under reflux for 22 h at 85°C. Then, it was followed by removing the excess amount of the solvent and chloroacetyl chloride by evaporation under reduced pressure. The residue thus obtained was washed with 3 × 15 ml of (5%) sodium bicarbonate and subsequently with 3 × 30 ml of cold water, and after filtration the obtained precipitate was dried and re-crystallized from absolute ethanol.

(c) Intermediate compound E (α-chloroamide of 2-aminobenzothiazole) was synthesized by dissolving an accurately weighed amount of 2-aminobenzothiazole (5 g, 0.033 mol) in 50 ml of chloroform contained in a 250 ml round bottom flask, then (4.6 g, 0.033 mol) of anhydrous potassium carbonate was added to this solution with stirring. The reaction flask was placed later in ice bath at 0°C, and chloroacetyl chloride (3.36 ml, 0.041 mol) was then added with stirring in drop wise fashion. After the addition of the chloroacetyl chloride was completed, the mixture was kept stirred under reflux for 18 h at 85°C. Later, the excess amount of the solvent and chloroacetyl chloride was evaporated under reduced pressure. The residue thus obtained was washed with 3 × 15 ml of (5%) sodium bicarbonate and subsequently with 3 × 30 ml of cold water and after filtration the precipitate obtained was left to dry and re-crystallized from absolute ethanol.

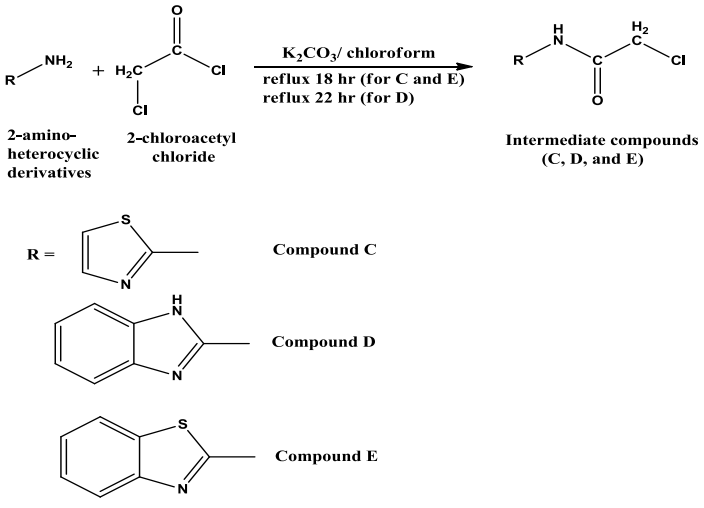
The synthesis of the final target compounds (M1-M3)

To a solution of the intermediate compound B (1 g, 0.004 mol) in 40 ml acetone contained in a 250 ml round bottom flask, an accurately weighed amount of the intermediate compounds C, D, and E intermediate compound C: (0.7 g, 0.004 mol); intermediate compound D: (0.83 g, 0.004 mol) and intermediate compound E: (0.9 g, 0.004 mol), was added with stirring that was kept for 15 min. Then, (1.1 g, 0.008 mol) of anhydrous potassium carbonate was added with stirring to this mixture which was refluxed later for 24 h at 80°C. At the end of the refluxing period, the precipitate obtained in the reaction solution was collected by filtration, and then it was washed with 3 × 15 ml of distilled water, dried and later re-crystallized from aqueous ethanol to produce the corresponding target compounds M1-M3 [32,33].

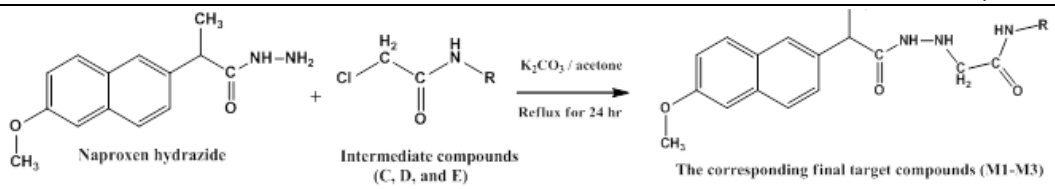
The general synthetic route illustrated in Schemes 1-3 was followed to synthesize the entire intermediate and final target compounds described earlier starting from Naproxen. The physicochemical characterization data (i.e., the physical appearance, percent yield, melting point (m.p. °C) and R_f values) of these compounds together with the elemental microanalysis (C, H, N analysis) of the final target compounds (M1-M3) are given in Table 1. The FTIR spectral data (KBr) υ cm^{-1} of both the intermediate and final target compounds are listed below in Table 2.



Scheme 1: The synthetic diagram of intermediate compounds A and B



Scheme 2: The synthetic diagram of intermediate compounds C, D and E



Scheme 3: The synthetic diagram of the corresponding final target compounds (M1-M3)

Table 1: Physicochemical characterization data of the synthesized intermediates (A-E) and the final target compounds (M1-M3)

Sym.	Molecular formula	Molecular weight	% yield	Melting point (°C)	Physical appearance	R_f value	Elemental analysis (calculated/found)%			
							C	H	N	S
A	$C_{15}H_{16}O_3$	244	96	89-92	White crystals	0.9 B	-	-	-	-
B	$C_{14}H_{16}N_2O_2$	244	85	139-140	White fluffy powder	0.14 B	-	-	-	-
C	$C_5H_5ClN_2OS$	176	96	176-179	Light-brown crystals	0.69 A	-	-	-	-
D	$C_9H_8ClN_3O$	209	40	197-198	Light-brown crystals	0.87 A	-	-	-	-
E	$C_9H_7ClN_2OS$	226	62	158-161	Light-brown crystals	0.8 A	-	-	-	-
M1	$C_{19}H_{20}N_4O_3S$	384	35	258-261	Light-brown powder	0.34 C	59.36 58.707	5.24 5.33	14.57 14.846	8.34 8.248
M2	$C_{23}H_{23}N_5O_3$	417	65.5	276-279	Off-white powder	0.46 C	66.17 64.78	5.55 5.555	18.78 18.873	-
M3	$C_{23}H_{22}N_4O_3S$	434	55	257-260	Off-white powder	0.41 C	63.58 63.198	5.1 5.079	12.89 13.006	7.38 7.335

Table 2: The IR spectral data of the synthesized target and intermediate compounds

Sym.	Chemical name	Characteristic IR spectral bands (KBr) ν cm^{-1} with their interpretations
A	methyl 2-(6-methoxynaphthalen-2- yl)propanoate	3061 Aromatic (C-H) stretching vibration, 1737 (C=O) stretching vibration of ester and 1174 (C-O) stretching vibration of ester
B	2-(6-methoxynaphthalen-2-yl)propanehydrazide	3292 and 3282 (N-H) asym. and sym. stretching vibration of secondary amide, 1639 (C=O) stretching vibration of amide (amide I band) and 1525 (N-H) bending vibration of (amide II band)
C	2-chloro-*N*-(thiazol-2-yl)acetamide	3385 (N-H) stretching vibration of secondary amide, 1653 (C=O) stretching vibration of secondary amide (amide I band), 1518 (N-H) bending vibration of secondary amide (amide II band) and 767 (C-Cl) stretching vibration of -CH_2Cl group
D	*N*-(1*H*-benzo[*d*]imidazole-2-yl)-2-chloroacetamide	3234 (N-H) stretching vibration of secondary amide, 1691(C=O) stretching vibration of secondary amide (amide I band), 1512 (N-H) bending vibration (amide II band) and 767 (C-Cl) stretching vibration of CH_2Cl group
E	*N*-(benzo[*d*]thiazol-2-yl)-2-chloroacetamide	3506 (N-H) stretching vibration of secondary amide, 1693(C=O) stretching vibration of secondary amide (amide I band), 1562 (N-H) bending vibration (amide II band) and 775 (C-Cl) stretching vibration of -CH_2Cl group
M1	2-(2-(2-(6-methoxynaphthalen-2-yl)propanoyl)hydrazinyl)-*N*-(thiazol-2-yl)acetamide	3115 (N-H) stretching vibration of secondary amide, 1651 and 1626 Two overlapping absorption bands (C=O) stretching vibration of amides (amide I band) and 1240 (C-N) stretching vibration
M2	*N*-(1*H*-benzo[*d*]imidazole-2-yl)-2-(2-(2-(6-methoxynaphthalen-2-yl)propanoyl)hydrazinyl)acetamide	3257 (N-H) stretching vibration of secondary amide, 1687 and 1640 (C=O) stretching vibration of secondary amide (amide I band) and 1220 (C-N) stretching vibration
M3	*N*-(benzo[*d*]thiazol-2-yl)-2-(2-(2-(6-methoxynaphthalen-2-yl)propanoyl)hydrazinyl)acetamide	3396 (N-H) stretching vibration of secondary amide, 1668 and 1620 (C=O) stretching vibration of amide (amide I band) and 1232 (C-N) stretching vibration

Evaluation of anti-inflammatory activity of the synthesized compounds (M1-M3)

The research protocols and animal care measures was approved by the local research ethics committee, College of Pharmacy, University of Baghdad and in accordance with the standard requirements for the care and use of experimental animal stated elsewhere. Thirty wistar rat of either sex weighing 180-220 g were obtained from the local bred of the animal house, department of pharmacology and toxicology, College of Pharmacy, University of Baghdad and were fed standard chaw and had free access to water and *libitum*. The animals were housed in the same location under slandered conditions.

The animals were divided into five groups each group consists of six rats as follows: Group A: Six rats served as the control and were treated with the vehicle Dimethyl Sulfoxide (DMSO) with a dose of 2 ml/kg [34]. Group B: Six rats were treated with Naproxen in a dose of 10 mg/kg [35,36] dissolved in DMSO and served as a reference substance. Groups (C-E): Each group of six rats was treated with the tested compounds (synthesized target compounds M1-M3) respectively, in doses that are equivalent by weight to 10 mg/kg of Naproxen and dissolved in dimethyl sulfoxide. The calculated doses of the tested compounds M1-M3 are 16.69 mg/Kg, 18.13 mg/Kg, and 18.848 mg/Kg respectively.

Experimental design

The acute anti-inflammatory activity of the target compounds was studied by the use of fresh egg-white induced paw edema model [37]. An acute inflammation was created by the injection of 0.1 ml fresh undiluted egg-white subcutaneously into the planter side of left hind paw of Wister albino rats, 30 min after the intra-peritoneal administration of the tested compounds or their vehicle. The paw thickness was measured in millimeter by using a Vernier caliper [38] at eight time intervals (0, 30, 60, 120,180, 240, 300 and 360) and these measurements were taken after the intra-peritoneal administration of the tested compounds or their vehicle (control), which was considered as time zero.

The data are expressed as the standard error of the mean (± SEM) and the results were analyzed by using student t-test for their statistical significance (two samples that assuming equal variance). Probability (P) values<0.05 were considered as significant.

RESULTS AND DISSCUSION

The pharmacological evaluation of the final target compounds (M1-M3) was performed by studying anti-inflammatory activity using paw edema model. After subcutaneous injection of fresh egg white a progressive edema will be induced. This edema is an acute inflammation and characterized by increased blood flow and vascular permeability along with the accumulation of fluid, leukocytes and inflammatory mediators such as cytokines [39]. To consider the rationality of paw edema method used for the anti-inflammatory evaluation of newly synthesized compounds, Naproxen was used as a reference compound of a recognized anti-inflammatory activity profile.

The difference in paw thickness readings, between Naproxen which was used as a reference material and dimethyl sulfoxide which is considered as a control, on the fresh egg white induced paw edema in rats is shown in Table 3. Both control and Naproxen groups' indicates that the paw edema method used in this study is a valid method and can effectively be used for the evaluation of the anti-inflammatory effect of the newly synthesized compounds as shown in Figure 1.

Table 3: The effect of Naproxen (reference) and dimethyl sulfoxide (control) on the fresh egg white induced paw edema in rats

	Time (min)	DMSO (n=6)	Naproxen (n=6)
Paw thickness (mm)	0	3.76 ± 0.27	3.72 ± 0.17
	30	5.32 ± 0.32	5.35 ± 0.34
	60	5.67 ± 0.33	5.61 ± 0.36
	120	6 ± 0.12	5.61 ± 0.36*
	180	5.54 ± 0.32	5.12 ± 0.28*
	240	5.5 ± 0.13	5.1 ± 0.3*
	300	5.33 ± 0.19	4.93 ± 0.35*
	360	5.22 ± 0.26	4.86 ± 0.23*

Data are expressed in mm paw thickness as mean ± SEM. n=number of animals. Time (0) is the time of i.p. injection of Naproxen (reference) and dimethyl sulfoxide (control). Time (30) is the time of injection of fresh egg white for induction of paw edema. *Significantly different compared to control (P<0.05)

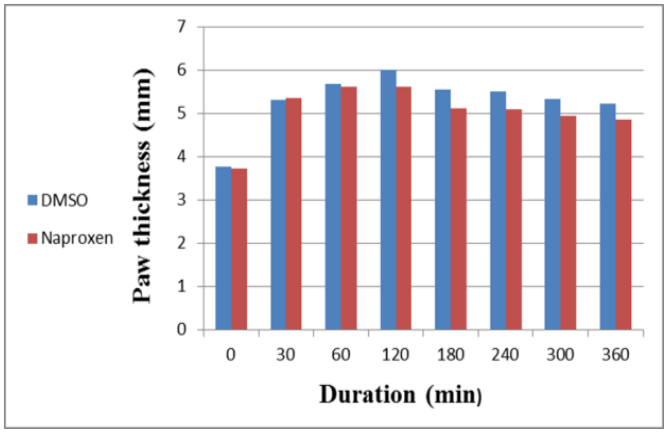


Figure 1: The effect of naproxen (reference) and dimethyl sulfoxide (control) on the fresh egg-white induced paw edema in rats, time (30) is the time of egg-white injection

The effect of the tested compounds (M1-M3) with respect to the control (DMSO) group and the reference (naproxen) group are shown in Table 4. All tested compounds were successfully limited the increase in paw edema, and the effect of the synthesized compounds started at 120 min (significantly different compared to control) and their effect continued till the end of the experiment with statistically significant reduction (P value is less than 0.05) in paw edema, as shown in Figure 2.

Table 4: The effect of control, naproxen and tested compounds M1-M3 on egg-white induced paw edema in rats

Time (min)	DMSO (n=6)	Naproxen (n=6)	M1 (n=6)	M2 (n=6)	M3 (n=6)
0	3.76 ± 0.27	3.72 ± 0.17	3.59 ± 0.16	3.56 ±0.13	3.62 ± 0.1
30	5.32 ± 0.32	5.35 ± 0.34	5.26 ± 0.24	5.58 ± 0.25	5.5 ± 0.33
60	5.67 ± 0.33	5.61 ± 0.36	5.39 ± 0.21	5.65 ± 0.24	5.79 ± 0.26
120	6 ± 0.12	5.61 ± 0.36^{*a}	4.8 ± 0.33^{*b}	5.14 ± 0.28^{*b}	5.38 ± 0.32*
180	5.54 ± 0.32	5.12 ± 0.28^{*a}	4.63 ± 0.41^{*b}	4.78 ± 0.21^{*b}	5.03 ± 0.39*
240	5.5 ± 0.13	5.1 ± 0.3^{*a}	4.46 ± 0.4^{*b}	4.52 ± 0.23^{*b}	4.81 ± 0.15*
300	5.33 ± 0.19	4.93 ± 0.35^{*a}	4.44 ± 0.4^{*b}	4.42 ± 0.17^{*b}	4.69 ± 0.2*
360	5.22 ±0.26	4.86 ± 0.23^{*a}	4.31 ± 0.39^{*b}	4.27 ± 0.16^{*b}	4.27 ± 0.25^{*b}

Data are expressed in mm paw thickness as mean ± SEM. n=Number of animals. Time (0) is the time of i.p. injection of tested compounds, Naproxen and dimethyl sulfoxide (control). Time (30) is the time of injection of fresh egg white (induction of paw edema). *Significantly different compared to control (P<0.05). Non-identical superscripts (a and b) among different groups are considered significantly different (P<0.05)

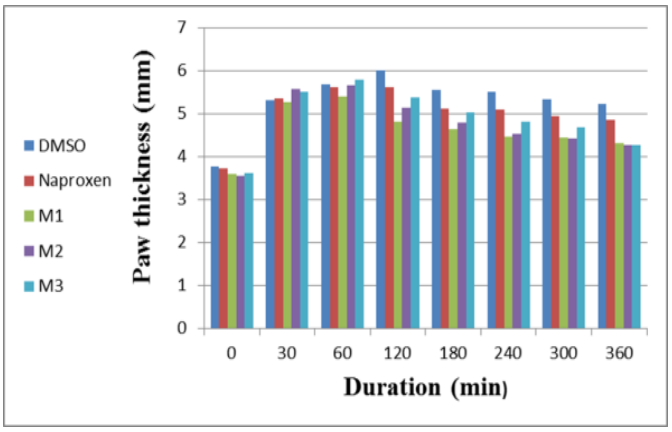


Figure 2: The effect of Naproxen, dimethyl sulfoxide, compounds M1, M2, and M3 on the egg-white induced paw edema in rats. Results are expressed as mean ± SEM (n=6 for each group). Time (30) is the time of fresh egg-white injection

The comparison between the reference drug (naproxen) and tested compounds (M1-M3) indicate that all the tested compounds were efficiently potent to limit the rise in paw edema, usually their effect started 120 (min) after the i.p. injection this revealed early onset of action of these compounds and their anti-inflammatory effect continued for the end of the experiment. It was found that M1 and M2 compounds were significantly more effective than Naproxen as anti-inflammatory agent, while compound M3 showed comparable effect to that of naproxen. The percent of inhibition of the tested compounds (M1-M3) was calculated according to the equation:

$$\% \text{ of Inhibition} = 100\ (1 - Vt/Vc)\ \%$$

Where Vc represents edema volume in the control and Vt the edema volume in the group treated with the tested compound and are shown in Table 5. It was found that M1 and M2 compounds have greater % of inhibition for the inflammation than M3 compound as shown in Figure 3. During the *in vivo* study it was noticed that compound M3 has a diuretic effect in rats [40].

Table 5: The % inhibition of inflammation in paw edema exhibited by the action of the tested compounds (M1-M3)

Time (min)	M1	M2	M3
30	1.13	4.89	3.38
60	4.94	0.4	2.12
120	20	14.33	10.33
180	16.43	13.72	9.21
240	18.91	17.82	12.55
300	16.7	17.1	12
360	17.43	18.2	18.2

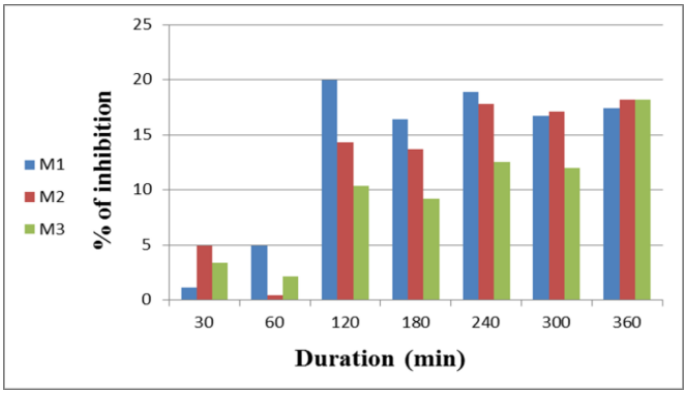


Figure 3: The % inhibition of inflammation in paw edema exhibited by the action of the tested compounds (M1-M3)

The FTIR spectral data confirmed the structure of the synthesized intermediate and final target compounds (M1-M3), where it revealed the synthesis of the Naproxen methyl ester (Intermediate compound A) since it showed the formation of corresponding ester bond through the appearance of the characteristic sharp band of the (C=O) stretching vibration at 1737 cm^{-1}, which is accompanied by the disappearance of characteristic broad band of the (O-H) group of carboxylic acid of Naproxen. The naproxen hydrazide (intermediate compound B) showed the appearance of the characteristic sharp band around 1639 cm^{-1} which indicates the formation of the (C=O) group of the formed hydrazide (amide I band) and accompanied with the disappearance of the characteristic sharp band of the (C=O) stretching vibration of the ester at 1737 cm^{-1}. IR absorption bands of intermediate compounds (C, D, and E) indicate the formation of amide through the appearance of characteristic sharp amide I band (C=O stretching vibration) in the range between 1700-1640 cm^{-1} and the appearance of amide II band (N-H bending vibration) in the range between1570-1510 cm^{-1} for a secondary amide. The synthesized derivatives (M1-M3) showed some characteristic sharp bands in the IR region, where the bands in the range between 1360-1080 cm^{-1} indicate the appearance of the (C-N) group stretching vibration of the amine accomplished by the disappearance of the band range between 800-600 cm^{-1} which belong to the stretching vibration of $-CH_2Cl$ group.
For the confirmation of the basic chemical structure of the synthesized derivatives (M1-M3), elemental microanalysis is performed. The results are reported in Table 2. Good results were obtained and agree with the calculated percentages in which the percent deviation of the observed / calculated values was found to be within the limits of the correct analysis.

CONCLUSION

It was found that the synthesis of naproxen derivatives by using heterocyclic amines like 2-amino thiazole, 2-aminobenzimidazole and 2-aminobenzothiazole may enhance the anti-inflammatory activity of Naproxen depending on the type of amine used. *In vivo* study for the anti-inflammatory activity through fresh egg white paw edema model indicate that compounds M1 and M2 are significantly more active than naproxen, while compound M3 has comparable activity to that of naproxen.

ACKNOWLEDGEMENTS

The data was abstracted from MSc thesis submitted to the Department of Pharmaceutical Chemistry, College of Pharmacy/University of Baghdad. The authors wish to thank the University of Baghdad for supporting this study.

REFERENCES

[1] A.S. Mehanna, *AJPE.*, **2003**, 67, 1-7.
[2] D.S. Bele, I. Singhvi, *IJRPC.*, **2011**, 1(4), 1058-1065.
[3] M. Asif, C. Asthana, *Int. J. Chem. Tech. Res*., **2009,** 1(4), 1200-1205.
[4] C. Bombardier, L. Laine, A. Reicin, D. Shapiro, R. Burgos-Vargas, B. Davis, R. Day, M.B. Ferraz, C.J. Hawkey, M.C. Hochberg, T.K. Kvien, T.J. Schnitzer, *N. Engl. J. Med*., **2000**, 343, 1520-1528.
[5] G.Y. Nagesh, K. Mahendra Raj, B.H.M. Mruthyunjayaswamy, *J. Mol. Struct.*, **2015**, 1079, 423-432.
[6] Q. Al-Balas, N.G. Anthony, B. Al-Jaidi, A. Alnimir, G. Abbott, A.K. Brown, R.C. Taylor, G.S. Besra, T. D. McHugh, S.H. Gillespie, B.F. Johnston, S.P. Mackay, G.D. Coxon, *PLoS ONE.*, **2009**, 4(5), e5617, 1-9.
[7] M.V. Papadopoulou, W.D. Bloomer, H.S. Rosenzweig, S.R. Wilkinson, J. Szular, M. Kaiser, *Eur. J. Med. Chem.*, **2016**, 117, 179-186.
[8] C.Y. Tsai, M. Kapoor, Y.P. Huang, H.H. Lin, Y.C. Liang, Y.L. Lin, S.C. Huang, W.N. Liao, J.K. Chen, J.S. Huang, M.H. Hsu, *Molecules.*, **2016,** 21, 145, 1-9.
[9] H. Kaur, H. Kaur, A. Chawla, U.S. Baghel, R.K. Dhawan, *J. Glob. Trend. Pharm. Sci.*, **2014**, 5, 2, 1684-1691.
[10] E.A. Kesicki, M.A. Bailey, Y. Ovechkina, J.V. Early, T. Alling, J. Bowman, E.S. Zuniga, S. Dalai, N. Kumar, T. Masquelin, P.A. Hipskind, J.O. Odingo, and T. Parish, *PLoS ONE.*, **2016**, 11(5), e0155209, 1-25.
[11] S. Saeed, N. Rashid, P.G. Jones, M. Ali, R. Hussain, *Eur. J. Med. Chem.*, **2010**, 45(4), 1323-1331.
[12] K.R.A. Abdellatif, G.A. Abd El Wareth, O.M. El-Badry, H.M. Ragab, M.M. El-Enany, *Beni-Suef. Uni. J. Basic. Appl. Sci.*, **2015**, 4, 52-59.
[13] M.Z. Hassan, S.A. Khan, M. Amir, *Eur. J. Med. Chem.*, **2012**, 58, 206-213.
[14] A. Ammazzalorso, A. Giancristofaro, A.D. Angelo, *Bioorg. Med. Chem. Lett.*, **2011**, 21(16), 4869-4872.
[15] G.A. Pereira, A.C. Massabni, E.E. Castellano, L.A.S. Costa, C.Q.F. Leite, F.R Pavan, A. Cuin, *Polyhedron.*, **2012**, 38(1), 291-296.
[16] S.R. Nagarajan, G.A. De Crescenzo, D.P. Getman, *Bioorg. Med. Chem.*, **2003**, 11, 22, 4769-4777.
[17] S. Shafi, M.M. Alam, N. Mulakayala, *Eur. J. Med. Chem.*, **2012**, 49, 324-333.
[18] F. Delmas, A. Avellaneda, C.D. Giorgio, *Eur. J. Med. Chem.*, **2004**, 39(8), 685-690.
[19] T. Tzanova, M. Gerova, O. Petrov, M. Karaivanova, D. Bagrel, *Eur. J. Med. Chem.*, **2009**, 44(6), 2724-2730.

[20] H. Lopez-Sandoval, M.E. Londono-Lemos, R. Garza-Velasco, I. Poblano-Melendez, P. Granada-Macias, I. Gracia-Mora, N. Barba-Behrens, *J. Inorg. Biochem.*, **2008**, 102, 1267-1276.
[21] A.Ts. Mavrova, D. Wesselinova, N. Vassilev, J.A. Tsenov, *Eur. J. Med. Chem.*, **2013**, 63, 696-701.
[22] Z. Wang, D. Sun, S. Johnstone, Z. Cao, X. Gao, J.C. Jaen, J. Liu, S. Lively, S. Miao, A. Sudom, C. Tomooka, N.P. Walker, M. Wright, X. Yan, Q. Ye, J.P. Powers, *Bioorg. Med. Chem. Lett.*, **2015**, 25(23), 5546-5550.
[23] H. Wahe, P.F. Asobo, R.A. Cherkasov, A.E. Nkengfack, G.N. Folefoc, Z.T. Fomum, D. Doepp, *ARKIVOC.*, **2003**,170-177.
[24] M. Rivara, V. Zuliani, G. Cocconcelli, G. Morini, M. Comini, S. Rivara, M. Mor, F. Bordi, E. Barocelli, V. Ballabeni, S. Bertoni, P.V. Plazzia, *Bioorg. Med. Chem.*, **2006**, 14(5), 1413-1424.
[25] A. Ts. Mavrova, P. Denkova, Y.A. Tsenov, K.K. Anichinaa, D.I. Vutchevc, *Bioorg. Med. Chem.*, **2007**, 15(18), 6291-6297.
[26] H.J. Kwak, Y.M. Pyun, J.Y. Kim, H.S. Pagire, K.Y. Kim, K.R. Kim, S.D. Rhee, W.H. Jung, J.S. Song, M.A. Bae, D.H. Lee, J.H. Ahn, *Bioorg. Med. Chem. Lett.*, **2013**, 23(16), 4713-4718.
[27] R. Paprocka, B. Modzelewska-Banachiewiczi, M. Wiese, A. Eljaszewicz, J. Michalkiewicz, *Acta Pol. Pharm.-Drug Res.*, **2012**, 69(6), 1390-1394.
[28] E.R. Vogel, W. Jackson, D.S. Masterson, *Molecules.*, **2015**, 20(6), 10487-10495.
[29] I.A. Bello, G.I. Ndukwe, J.O. Amupitan, R.G. Ayo, F.O. Shode, *Int. J. Med. Chem.*, **2012**, 1-6.
[30] R.A. Elrayess, N. Gareb, M.M. Azab, M.M. Said, *Life. Sci. J.*, **2013**, 10(3), 1784-1793.
[31] A. El-Faham, Z. Al Marhoon, A. Abdel-Megeed, M. Siddiqui, *J. Chem*., **2013**, 1-6.
[32] N. Singh, U.S. Sharma, N. Sutar, S. Kumar, U.K. Shamra, *J. Chem. Pharm. Res.*,**2010**, 2(3), 691-698
[33] R.T. Morrison, R.N. Boyd, Englewood Cliffs, NJ 07632, USA, **1992**, 845-883.
[34] A.A. Sulaiman, S.A. Hussain, K.M. Jum'ma, A.H. Sigar, *Iraqi J. Pharm. Sci*., **2009**, 18, 1-6.
[35] R. Blackler, S. Syer, M. Bolla, E. Ongini, J.L. Wallace, *PLoS ONE*., **2012**, 7(4), 1-8.
[36] E. Ekundi-Valentim, F.P.N. Mesquita, K.T. Santos, M.A. Vieira de Paula, J. Florenzano, C.I. Zanoni, *Med. Gas Res*., **2013**, 3(24), 1-9.
[37] P. Flecknell, *Anim. Welfare Inf. Cent. News Lett.*, **1997-1998**, 8(3-4), 8-14.
[38] M. Singh, V. Kumar, I. Singh, V. Gauttam, A.N. Kalia, *Pharm. Res.*, **2010**, 2(6), 364-367.
[39] A. Kumar, S. Gaur, K. Jha, K. Sharma, *J. Sci. Innov. Res.*, **2012**, 1(3), 71-79.
[40] J.Y. Su, Q.C. Li, L. Zhu, *Excli. J.*, **2011**, 10, 110-116.