Academic Sciences International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 6, Issue 1, 2014

Research Article

SYNTHESIS OF NEW DICLOFENAC DERIVATIVES BY COUPLING WITH CHALCONE DERIVATIVES AS POSSIBLE MUTUAL PRODRUGS

SAMER A. HASAN [1] AND AMER N. ELIAS [2, *]

[1]Department of Pharmaceutical Chemistry, College of Pharmacy, University of Kufa, Najaf, Iraq, and [2] Department of Pharmaceutical Chemistry, College of Pharmacy, University of Baghdad, Baghdad, Iraq. Email: amerelias40@yaoo.com

Running title: Diclofenac-chalcones as mutual prodrugs

Received: 23 Sep 2013, Revised and Accepted: 12 Oct 2013

ABSTRACT

Objectives: To synthesize a diclofenac-chalcones derivatives that can act as possible mutual prodrugs of enhanced anti-inflammatory activity and devoid of ulcerogenic side effects.

Methods: Mutual prodrugs were synthesized by conjugation of Diclofenac with a series of eight chalcone derivatives by the Claisen–Schmidt condensation of acetophenone or p-hydroxyacetophenone with benzaldehyde or appropriately substituted benzaldehyde in the presence of $SOCl_2$/EtOH as a catalyst.

Results: The structure of the synthesized derivatives has been characterized by elemental microanalysis (CHN), FTIR Spectroscopy, and other physicochemical properties. The anti-inflammatory activity of the synthesized fluorinated chalcone derivative was performed using the cotton pellet-induced granuloma in rats as a model, and found to be comparable to dexamethasone in this regard.

Conclusion: Chalcones with their pronounced anti-inflammatory activity can synergize the activity of Diclofenac when conjugated with this NSAID.

Keywords: NSAIDs, Diclofenac derivatives, Chalcone derivatives, Antioxidants, Mutual prodrugs.

INTRODUCTION

The non-steroidal anti-inflammatory drugs (NSAIDs) are one of the most common therapeutic groups of agents used worldwide for the treatment of pain, fever and inflammation [1]. However, the usefulness of these agents is limited due to the higher incidences of the observed gastrointestinal (GI) damage that includes gastric ulceration, perforation and their associated complications [2]. These side effects are a result of two different mechanisms, where the first involves a local action comprising of a direct contact effect due to ion trapping mechanism that resulted from the acidic nature of these drugs and their behavior under the local moderately acidic or neutral condition of the stomach[3].The second mechanism which is considered as a key element in the NSAIDs-induced gastropathy is based on their generalized systemic action which follows their absorption and is related to their intrinsic effect in inhibiting the cyclooxygenases (an enzyme-dependent synthesis of prostaglandins that have gastro-protective properties) responsible for their desired anti-inflammatory activity [4].

Recent studies have indicated that local generation of free radicals and various reactive oxygen species (ROS) participate in the formation of gastric ulcers associated with NSAIDs therapy. Based on these observations, it has been suggested that co-administration of NSAIDs and antioxidants might decrease the risk of ulcerogenic side effects by scavenging of ROS or accelerating the healing of peptic ulcers[5, 6]. However, there are potential advantages in giving together such agents having complementary activities, in the form of single chemical entity, i.e. mutual prodrugs which are designed with improved physicochemical properties and capable of releasing the parent drugs at the site of action[7]. Furthermore, the prodrug designing of non-selective COX inhibitors such as diclofenac were devoted to masking the free acidic groups in these molecules in order to protect the gastrointestinal tract (GIT) from local irritation[3]. Amino acids such as L-histidine, L-tyrosine, L-methionine and others are known for their healing effects on gastric toxicity and marked anti-inflammatory activity. Literature review reveals that many efforts to synthesize prodrugs of NSAIDs by conjugation with amino acids have been made, and resulted in products that were characterized by pronounced anti-inflammatory activities and reduced ulcerogenic side effects[8-10] in addition to the marked reduction in their toxicity as manifested by the increase in the LD_{50} of the ibuprofen prodrugs from 708 mg/kg for ibuprofen to a level that exceeds 3000 mg/kg for the synthesized derivatives[10].

Chalcone [1, 3-diphenyl-2-propene-1-one] and related compounds "chalconoids" are those in which two aromatic rings are linked and conjugated together through a reactive keto ethylenic linkage (–CO–CH=CH–), which impart an entirely delocalized π-electron system on both benzene rings in such a way that this system has relatively low redox potentials and has a greater probability of undergoing electron transfer reactions[11]. In addition the colors of these compounds is attributed to the presence of such chromophore (-CO-CH=CH-) and other auxochromes (Scheme 1).

Several strategies such as the Claisen-Schmidt, Knoevenagel condensations and the Meyer-Schuster rearrangement were reported earlier[12-14] for the synthesis of chalcone system and all are based in general on the formation of carbon-carbon bond and here it is the Enone moiety (i.e., the α,β-unsaturated ketone).

Among other strategies, the Claisen-Schmidt condensation appeared to be the most appealing one, where it involves the condensation of an aromatic ketone with an aromatic aldehyde in the presence of suitable condensing agents; accordingly, a variety of methods are available for the synthesis of the chalcones that employs this type of approach and the most important and simplest one is the condensation done under acidic conditions (HCl) produced by using $SOCl_2$/EtOH as a catalyst and followed by dehydration to yield the anticipated chalcone derivative [14]. An interesting feature of the chalcones is that they can serve as precursors in the flavonoid biosynthesis [15], and in addition they may be used as starting materials for the synthesis of a variety of heterocyclic compounds in synthesizing a range of very important therapeutic agents for the treatment of various diseases, in which chalcones impart a key role[16].

Chalcones with their unique chemical structure will display a wide range of pharmacological activities depending on the nature, number, and position of the substituent(s) on both benzene rings of the chalcone. Accordingly, some of the chalcone derivatives exhibit numerous biological activities such as anti-inflammatory, analgesic, anti-ulcerative[17-19], antioxidant [20] among a variety of other activities[21-36] and therefore they comprise a class of compounds

with very important therapeutic potentials[37]. Additionally, some of the chalcone derivatives have been found to inhibit several important enzymes in cellular systems, such as xanthine oxidase, mammalian alpha-amylase, cyclooxygenase (COX), 5-lipooxygenase (5-LOX)[38-40], while others demonstrated the ability to block voltage-dependent potassium, and calcium channels[41,42].

Therefore, the present study was designed to synthesize a number of appropriately substituted chalcones which on their conjugation with Diclofenac may serve as possible mutual prodrugs with possible synergistic anti-inflammatory activity and devoid of GIT side effects.

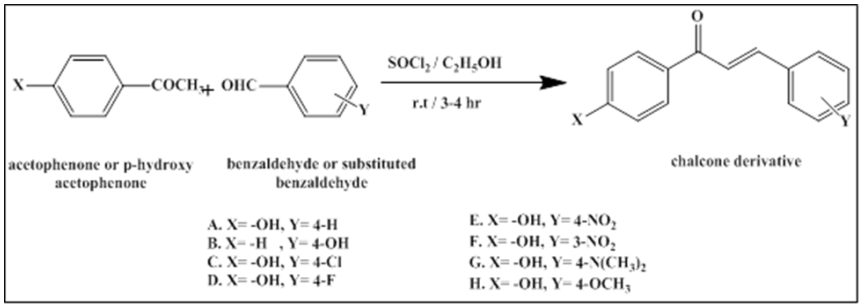
MATERIALS AND METHODS

Acetophenone, benzaldehyde, p-chlorobenzaldehyde, p-dimethylaminobenzaldehyde, p-fluorobenzaldehyde, p-hydroxyacetophenone, p-hydroxybenzaldehyde, p-methoxybenzaldehyde, p-nitrobenzaldehyde, m-nitrobenzaldehyde were purchased from Himedia (India), diclofenac sodium was donated thankfully by The State Company For Drug Industries (SDI, Samara, Iraq), and the quality of all these chemicals together with the other ones used throughout the study and obtained from standard commercial sources were of analar grade and used without further purification. The melting points were determined by the open capillary method using Thomas hoover (England) and were used uncorrected. Cooling of reactions when needed was done using a Julabo chiller VC (F30) (GMBH, Germany). Infra-red spectra were recorded in KBr disc on Shimadzu FTIR 8400 spectrophotometer (Japan), at the College of Pharmacy, University of Al-Mustansiriyah. Elemental microanalysis was performed at the Jordanian University using CHN Elemental Analyzer (Euro-vector EA3000A, Italy). The progress of the reaction was monitored by ascending thin layer chromatography which was run on Kieslgel GF_{254} (60) aluminum plates (E. Merck, Germany), which was used as well to check the purity of the product. The synthesized compound was revealed either by derivatization or reactivity toward iodine vapor or by irradiation with UV_{254} light. Chromatograms were eluted using petroleum spirit (40-60): ethyl acetate (70:30) solvent system.

Chemical synthesis

1. Synthesis of the different chalcone derivatives (A-H)[14, 43, 44]

Chalcones (A-H) were synthesized according to the synthetic pathway depicted in Scheme 1 and in accordance to the previously reported procedure in reference 39. Chalcones (A-H) were prepared using the Claisen-Schmidt condensation procedure by condensing acetophenone [10 mmol/1.16 ml] or p-hydroxyacetophenone [10 mmol/1.36 gm] and benzaldehyde [10 mmol/1.01 ml] or one of the following substituted benzaldehydes (10 mmol): p-hydroxybenzaldehyde (1.22 gm), p-chlorobenzaldehyde (1.4 gm), p-fluorobenzaldehyde (1.07 ml), p-methoxybenzaldehyde (1.21 ml), p-nitrobenzaldehyde (1.51gm), m-nitrobenzaldehyde(1.51 gm) and p-dimethylaminobenzaldehyde (1.49 gm) in dry absolute ethanol (5 ml) using thionyl chloride (8 mmol/ 0.5 ml) to prepare the corresponding chalcone derivatives (Tables 1 and 2).



Scheme 1: Synthetic diagram of the chalcone derivatives (A-H).

2. Chemical conversion of diclofenac sodium into diclofenac[46]

Diclofenac sodium salt (2 gm, 6.28 mmol), was dissolved in a minimum volume of ethanol 99 %: THF (3:1) mixture. The solution was cooled to (18ºC) while stirring for (10 minutes), then 2N HCl (3.1 ml, 6.28 mmol) was added, and followed by the addition of excess cold water (100 ml). The precipitated acid was then filtered and dried to give diclofenac that was used in the next step without further purification (Table 1 and 2).

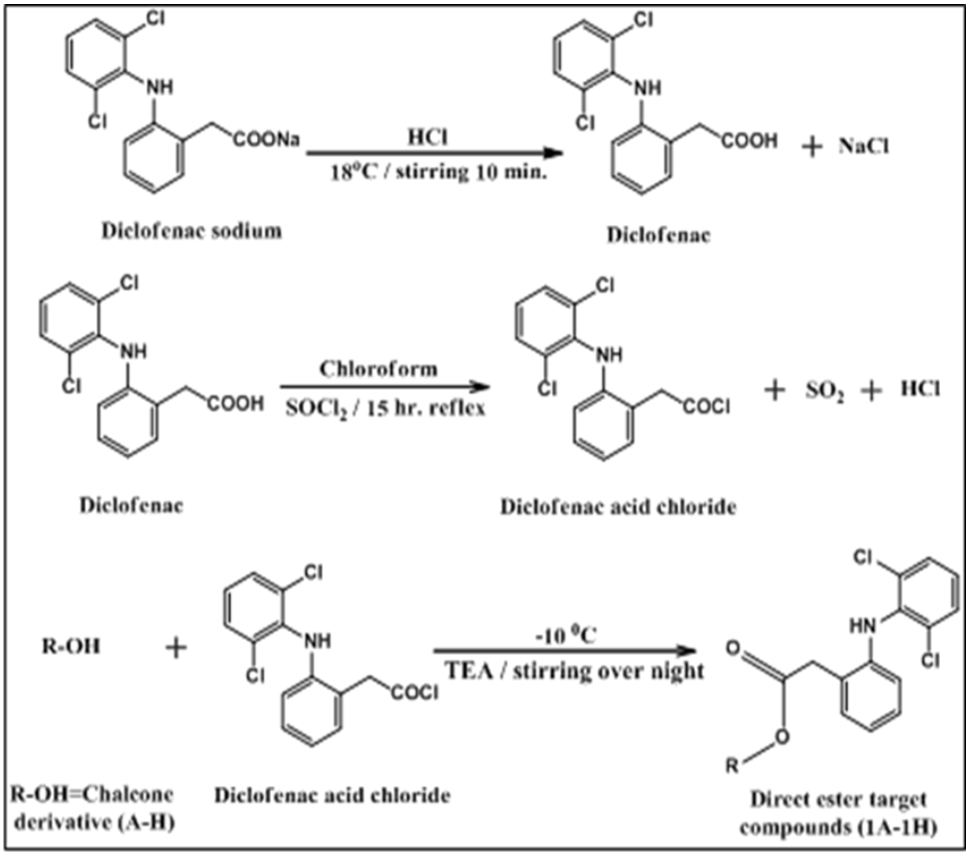
3. Synthesis of the direct ester derivatives of diclofenac-chalcone target compounds (1A-1H)[47, 48]

Diclofenac (10 mmol/2.96 gm) dissolved in the minimum amount of dry chloroform (50 ml), was placed in a two necks round bottom flask, and cooled down to (-15ºC). A slight excess of thionyl chloride (16 mmol/1 ml) was then added drop wise over a period of (15-20 minutes) with stirring while the temperature was kept below (-10ºC). After completion of the addition of thionyl chloride, the reaction mixture was refluxed for (15 hours) at (60-70ºC) with continuous stirring on magnetic stirrer. The reaction progress was monitored by means of using a gas trap. Later the solvent was evaporated to dryness, re-dissolved in dry chloroform and evaporated. The process was repeated several times to ensure complete removal of thionyl chloride. Then the residue (diclofenac acid chloride) was re-dissolved in (10 ml) of dry chloroform. The obtained acid chloride solution was added drop wise to a mixture of either one of the following chalcone derivatives (10 mmol): A (2.24 gm), B (2.24 gm), C (2.58 gm), D (2.42 gm), E (2.69 gm), F (2.69 gm), G (2.67 gm), H (2.54 gm), and triethylamine (10 mmol/ 1.4 ml) in dry dichloromethane (10 ml), previously cooled to (-10ºC), with constant stirring over a period of 1 hr., while maintaining a constant temperature. The reaction mixture was stirred overnight, washed with 5% v/v HCl (3×50 ml), 5% w/v NaOH (3×50 ml) and finally with distilled water (2×50 ml). The organic layer was dried over anhydrous sodium sulphate, filtered and the solvent was removed under reduced pressure to obtain the final products (1A-1H) (Scheme 2 and Tables 1 and 2), that were recrystallized from petroleum spirit (40-60) and ethyl acetate.

4. Synthesis of the di-ester derivatives of diclofenac-chalcone target compounds (2C1 and 2D1) through a spacer molecule (glycolic acid)

A: Synthesis of chalcone-chloroacetyl derivatives (2C and 2D) [5,49]

A mixture of either one of the following appropriate chalcone derivatives (10 mmol): C (2.58 gm), or D (2.42 gm), and triethylamine (10 mmol/ 1.4 ml) in dry dichloromethane (25 ml) was cooled in an ice salt mixture at (-10°C). Chloroacetyl chloride (10 mmol/ 0.8 ml) in dry chloroform (25 ml) was added drop wise to the above mentioned mixture with constant stirring over a period of (1 hour), at (-10°C), and the stirring of the mixture was continued over night at (-10°C). The reaction mixture was then washed with 5% v/v HCl (3×50 ml), 5% w/v $KHCO_3$ (3×50 ml) and finally with distilled water (2×50 ml). The organic layer was dried over anhydrous sodium sulphate, filtered and the solvent was removed under reduced pressure to obtain the corresponding substituted chalcone-chloroacetyl derivative (chalcone-chloroethanoate esters) (2C and 2D) (Scheme 3 and Tables 1 and 2). These derivatives were recrystallized from petroleum spirit (40-60) and ethyl acetate.



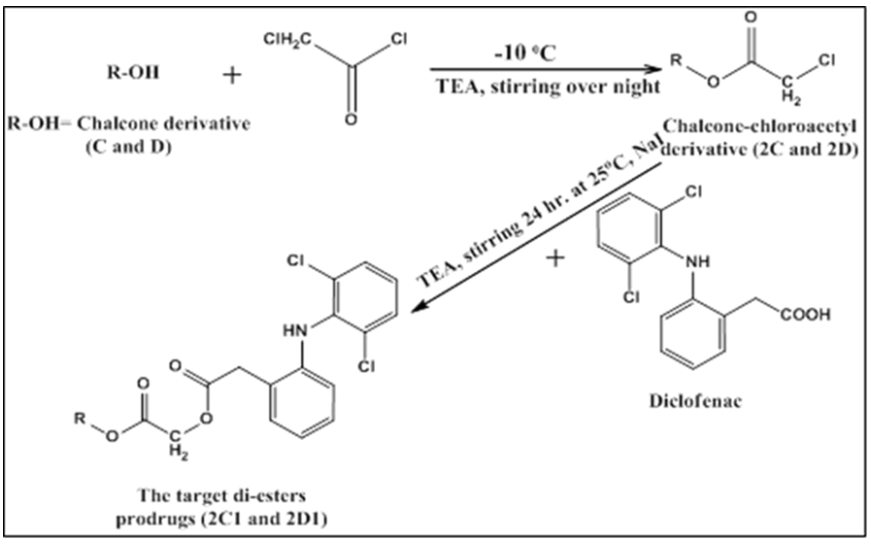
Scheme 2: Synthetic diagram of the direct ester derivatives of diclofenac (1A-1H)

B: Synthesis of the di-ester derivatives of diclofenac-chalcone target compounds (2C1 and 2D1)[5]

A mixture of either one of the following appropriate chalcone-chloroacetyl derivatives (10 mmol): 2C (3.35 gm), or 2D (3.18 gm), diclofenac (10 mmol/2.96 gm), triethylamine (10 mmol/1.4 ml) and sodium iodide (10 mmol/1.5 gm) in DMF (25 ml) was stirred overnight at room temperature. The reaction mixture was poured into crushed ice with stirring and extracted with chloroform (4×25 ml). The combined organic layer was washed with 2% w/v sodium thiosulphate (3×50 ml), 5% v/v HCl (3×50 ml), 5% w/v $KHCO_3$ (3×50 ml) and finally with distilled water (2×50 ml). The organic layer was dried over anhydrous sodium sulphate, filtered and the solvent was removed under reduced pressure to obtain the diclofenac-chalcone derivatives as possible mutual di-esters prodrugs (2C1 and 2D1) (Scheme 3 and tables 1 and 2). These target products were recrystallized from petroleum spirit (40-60) and ethyl acetate.

Evaluation of the anti-inflammatory activity of the fluorinated chalcone derivative

The anti-inflammatory activity of this chalcone derivative was reported in an earlier study [45] using the cotton pellet-induced granuloma in rats as a model in comparison with diclofenac and dexamethasone as standards.



Scheme 3: Synthetic diagram of the di-esters derivatives of diclofenac (2C1 and 2D1).

Table 1: Physicochemical characterization data for synthesized compounds

Sym.	Molecular Formula	Molecular Weight	% Yield	Melting point °C	R_f	Elemental analysis found (calculated)%		
						C	H	N
Diclofenac	$C_{14}H_{11}Cl_2NO_2$	296	95	160-162	0.15	-	-	-
A	$C_{15}H_{12}O_2$	224	88	173-175	0.5	80.34 81.243	5.39 5.381	-
B	$C_{15}H_{12}O_2$	224	88	184-185	0.35	80.34 82.437	5.39 5.370	-
C	$C_{15}H_{11}ClO_2$	258	94	190-192	0.34	69.64 70.112	4.29 4.312	-
D	$C_{15}H_{11}FO_2$	242	92	192-194	0.2	74.37 74.558	4.58 4.603	-
E	$C_{16}H_{15}NO_4$	269	60	247-249	0.38	66.91 67.295	4.12 4.296	5.20 5.330
F	$C_{16}H_{15}NO_4$	269	66	231-233	0.36	66.91 68.103	4.12 4.299	5.20 5.225
G	$C_{17}H_{17}NO_2$	267	76	184-186	0.28	76.38 77.119	6.41 6.520	5.24 5.323
H	$C_{16}H_{14}O_3$	254	82	187-189	0.1	75.57 75.581	5.55 5.634	-
1A	$C_{29}H_{21}Cl_2NO_3$	502	85	122-124	0.34	69.33 68.903	4.21 4.268	2.79 2.669
1B	$C_{29}H_{21}Cl_2NO_3$	502	72	122-125	0.59	69.33 70.773	4.21 4.232	2.79 2.737
1C	$C_{29}H_{20}Cl_3NO_3$	536	77	114-117	0.29	64.88 64.470	3.76 3.751	2.61 2.631
1D	$C_{29}H_{20}Cl_2FNO_3$	521	79	115-118	0.32	66.93 65.557	3.87 3.859	2.69 2.749
1E	$C_{29}H_{20}Cl_2N_2O_5$	547	62	121-124	0.59	63.63 63.918	3.68 3.721	5.12 5.078
1F	$C_{29}H_{20}Cl_2N_2O_5$	547	69	123-125	0.76	63.63 62.624	3.68 3.507	5.12 5.226
1G	$C_{31}H_{26}Cl_2N_2O_3$	545	82	124-126	0.46	68.26 69.861	4.80 4.628	5.14 5.036
1H	$C_{30}H_{23}Cl_2NO_4$	532	65	122-125	0.33	67.68 68.444	4.35 4.472	2.63 2.673
2C	$C_{17}H_{12}Cl_2O_3$	335	85	164-164.5	0.66	60.92 61.782	3.61 3.622	-
2D	$C_{17}H_{12}ClFO_3$	318	88	140-142	0.58	64.06 65.769	3.79 3.802	-
2C1	$C_{31}H_{22}Cl_3NO_5$	594	56	114-115	0.42	62.59 62.723	3.73 3.670	2.35 2.369
2D1	$C_{31}H_{22}Cl_2FNO_5$	578	63	117-118	0.45	64.37 63.778	3.83 3.739	2.42 2.537

Table 2: IR spectral data of synthesized compounds

Sym.	Chemical Name	Characteristics IR spectral bands (KBr) v cm^{-1} with its Interpretation
Diclofenac	2-(2-((2,6-dichlorophenyl) amino)phenyl)acetic acid	3323 (-NH), the signals between 2580 and 2900 (–COOH), 1693 (C=O) of the carbonyl group
A	(E)-3-(phenyl)-1-(4-hydroxy phenyl)prop-2-en-1-one	3122 (-OH), 1645 (C=O), 1604 (C=C) trans alkene
B	(E)-3-(4-hydroxyphenyl)-1-phenylprop-2-en-1-one	3234 (-OH), 1649 (C=O), 1599 (C=C) trans alkene
C	(E)-3-(4-chlorophenyl)-1-(4-hydroxyphenyl)prop-2-en-1-one	3095 (-OH), 1645 (C=O), 1600 (C=C) trans alkene, 1085 aromatic (C-Cl) stretching vibration
D	(E)-3-(4-fluorophenyl)-1-(4-hydroxyphenyl)prop-2-en-1-one	3134 (-OH), 1649 (C=O), 1608 (C=C) trans alkene, 1161 (C-F)
E	(E)-3-(4-nitrophenyl)-1-(4-hydroxy phenyl)prop-2-en-1-one	3387 (-OH), 1653 (C=O), 1610 (C=C) trans alkene, 1514 (N-O) asym. Stretching, 1336 (N-O) sym. Stretching
F	(E)-3-(3-nitrophenyl)-1-(4-hydroxyphenyl)prop-2-en-1-one	3161 (-OH), 1651 (C=O), 1606 (C=C) trans alkene, 1556 (N-O) asym. Stretching, 1346 (N-O) sym. Stretching
G	(E)-3-(4-dimethylaminophenyl)-1-(4-hydroxyphenyl)prop-2-en-1-one	3122 (-OH), 2970, 2810 (C-H) asym. and sym. stretching vibration of $-CH_3$ group, 1635 (C=O), 1604 (C=C) trans alkene, 1348 aromatic (C-N) stretching vibration
H	(E)-3-(4-methoxyphenyl)-1-(4-hydroxyphenyl)prop-2-en-1-one	3120 (-OH), 2940, 2860 (C-H) asym. and sym. stretching vibration of $-CH_3$ group, 1645 (C=O), 1600 (C=C) trans alkene, 1253 (C-O-C) ether
1A	(E)-4-cinnamoylphenyl2-(2-((2,6-dichlorophenyl)amino) phenyl) acetate	3325 (N-H), 1732 (C=O) ester, 1612 (C=C) trans alkene overlap with (C=O) stretching vibration of ketone*, 1091 aromatic (C-Cl) stretching vibration
1B	(E)-4-(3-oxo-3-phenylprop-1-en-1-yl)phenyl 2-(2-((2,6-dichlorophenyl)amino)phenyl) acetate	3325 (N-H), 1732 (C=O) ester, 1610 (C=C) trans alkene overlap with (C=O) stretching vibration of ketone*, 1089 aromatic (C-Cl) stretching vibration
1C	(E)-4-(3-(4-chlorophenyl) acryloyl)phenyl2-(2-((2,6-dichlorophenyl)amino) phenyl)acetate	3325 (N-H), 1732 (C=O) ester, 1645 (C=O) ketone, 1614 (C=C) trans alkene, 1091 aromatic (C-Cl) stretching vibration
1D	(E)-4-(3-(4-fluorophenyl) acryloyl) phenyl2-(2-((2,6-	3325 (N-H), 1732 (C=O) ester, 1614 (C=C) trans alkene overlap with (C=O)

	dichlorophenyl)amino) phenyl)acetate	stretching vibration of ketone*, 1091 aromatic (C-Cl) stretching vibration
1E	(E)-4-(3-(4-nitrophenyl) acryloyl)phenyl2-(2-((2,6-dichlorophenyl) amino) phenyl)acetate	3450 (N-H), 1732 (C=O) ester, 1612 (C=C) trans alkene overlap with (C=O) stretching vibration of ketone*, 1359 (N-O) sym. Stretching, 1091 aromatic (C-Cl) stretching vibration
1F	(E)-4-(3-(3-nitrophenyl) acryloyl) phenyl2-(2-((2,6-dichlorophenyl) amino) phenyl)acetate	3450 (N-H), 1732 (C=O) ester, 1612 (C=C) trans alkene overlap with (C=O) stretching vibration of ketone*, 1359 (N-O) sym. Stretching, 1089 aromatic (C-Cl) stretching vibration
1G	(E)-4-(3-(4-(dimethylamino) phenyl) acryloyl)phenyl2-(2-((2,6-dichloro phenyl)amino) phenyl)acetate	3452 (N-H), 2949 (C-H) asym. stretching vibration of -CH_3 group , 1732 (C=O) ester, 1610 (C=C) trans alkene overlap with (C=O) stretching vibration of ketone*, 1089 aromatic (C-Cl) stretching vibration
1H	(E)-4-(3-(4-methoxyphenyl) acryloyl)phenyl2-(2-((2,6-dichlorophenyl)amino) phenyl)acetate	3448 (N-H), 2950 (C-H) asym. stretching vibration of -CH_3 group, 1732 (C=O) ester, 1612 (C=C) trans alkene overlap with (C=O) stretching vibration of ketone*, 1089 aromatic (C-Cl) stretching vibration
2C	(E)-4-(3-(4-chlorophenyl) acryloyl)phenyl 2-chloro acetate	2955 (C-H) asym. stretching vibration of -CH_2 group, 1774 (C=O) ester, 1656 (C=O) ketone, 1606 (C=C) trans alkene, 817 aliphatic (C-Cl) stretching vibration
2D	(E)-4-(3-(4-fluorophenyl) acryloyl)phenyl 2-chloro acetate	2955 (C-H) asym. stretching vibration of -CH_2 group, 1776 (C=O) ester, 1658 (C=O) ketone, 1604 (C=C) trans alkene , 1222 aromatic (C-F) stretching vibration, 821 aliphatic (C-Cl) stretching vibration
2C1	(E)-2-(4-(3-(4-chlorophenyl) acryloyl)phenoxy)-2-oxoethyl 2-(2-((2,6-dichlorophenyl) amino)phenyl)acetate	3448 (N-H), 2916 (C-H) asym. stretching vibration of -CH_2 group, 1732 (C=O) ester, 1612 (C=C) trans alkene overlap with (C=O) stretching vibration of ketone*, 1093 aromatic (C-Cl) stretching vibration
2D1	(E)-2-(4-(3-(4-fluorophenyl) acryloyl)phenoxy)-2-oxoethyl 2-(2-((2,6-dichlorophenyl) amino)phenyl)acetate	3448 (N-H), 2918 (C-H) asym. stretching vibration of -CH_2 group, 1732 (C=O) ester, 1608 (C=C) trans alkene overlap with (C=O) stretching vibration of ketone*, 1093 aromatic (C-Cl) stretching vibration

*The C=O stretching vibration of the target compounds (1A-1H and 2C1 and 2D1) was overlapped with that of the adjacent stretching vibration (C=C) of the trans alkene, which is in contrast to that shown by their original chalcones (A-H).

RESULTS AND DISCUSSION

The chalcone derivatives were prepared as intermediate compounds for synthesizing the various target conjugates with Diclofenac by using the Claisen-Schmidt condensation method. The present study was designed, in part, to develop an efficient procedure for the synthesis of the chalcone derivatives using the $SOCl_2$/ EtOH catalytic system, that involves the condensation under acidic condition (HCl) that is formed *in situ* by the reaction of $SOCl_2$ with absolute ethanol followed by dehydration to yield the intended chalcone derivative[14,43]. It was previously reported that the use of (0.05 ml) of $SOCl_2$ in the catalytic system was accompanied with a good product yield [50], while in this study the use of such volume of $SOCl_2$ was proven inadequate to produce good yields of the chalcone derivatives. Attempts to improve the yields of the chalcone derivatives were made by manipulating the volume of $SOCl_2$ and (0.5 ml) was shown to be the optimal volume to be used of this catalyst with (5 ml) of absolute ethanol during the reaction. This protocol gave an excellent yield of the intended product in a short span of time without the formation of any side product(s).

Recently, we reported the synthesis of a fluorinated chalcone derivative namely (E)-3-(4-flourophenyl)-1-(4-hydroxy phenyl) prop-2-en-1-one, which demonstrated an effective anti-inflammatory activity in terms of attenuation of granulation tissue formation, which is comparable to that produced by dexamethasone, greater than the influence on edema formation. This fluorinated chalcone derivative showed a marked anti-inflammatory activity compared to dexamethasone and Diclofenac when tested as an example of the prepared chalcones [45]. This activity may illustrate a synergistic effect to that shown by Diclofenac when testing the anti-inflammatory activity of the compounds, as an outcome of coupling the NSAID with the synthesized chalcones.

In an earlier study, the fluorinated chalcone derivative has been reported to possess anti-inflammatory activity due to its influence on nitric oxide production[51]. The beneficial changes in such type of biological activity are often resulted from the introduction of fluorine into the molecule, which may be attributed to alterations in the physico-chemical properties of these derivatives [52]. Similar results were reported by Yadav *et al* (2011), who indicated that the anti-inflammatory activity of the chalcone derivatives was increased when electron-withdrawing groups (Halogen or hydroxyl moiety) are included in the chalcone nucleus [53]. Similarly, the compound '4-fluoro/4-chloro chalcone showed more activity comparable to indomethacin due to the -F/-Cl group present in the compound.

The present study was also performed to synthesize new derivatives of Diclofenac, which may serve as possible mutual prodrugs either by direct esterification with the synthesized chalcone derivatives or by using a glycolic acid spacer arm; where the choice of these chalcones is mainly due to their known antioxidant and gastro-protective properties, in an attempt to decrease the GI side effects, illustrated by the gastric ulceration shown by Diclofenac.

The structures of the synthesized compounds were confirmed by using IR, elemental microanalysis (CHN), and other physicochemical parameters (Tables 1 and 2). The synthesized chalcone derivatives (A-H) showed several characteristic sharp bands in the IR region, where the bands in the range between 1635-1660 cm^{-1} indicated the appearance of the carbonyl C=O group of the formed ketone, which was conjugated to both the aromatic and the alkene systems. The synthesized direct ester and di-esters derivatives of Diclofenac showed characteristic sharp bands around 1732 cm^{-1} which indicates the presence of the C=O group of the formed esters, that is also confirmed by the disappearance of signals between 2580 and 2900 cm^{-1} of Diclofenac (Table 2). The elemental microanalysis revealed good agreement with the calculated percentages. The percent deviations of the observed/calculated values were found to be within the limits of accurate analysis (Table 1).

CONCLUSION

In conclusion, the results obtained in this study strongly suggest that chalcones with their pronounced anti-inflammatory activity can synergize the activity of Diclofenac when conjugated with this NSAID. This synergism can allow the use of smaller doses of diclofenac within its chalcone conjugates to obtain a greater anti-inflammatory activity than that manifested by the ordinary doses of diclofenac. Consequently, this will be accompanied with the reduction of the systemic gastrointestinal side effects caused by diclofenac.

ACKNOLEDGEMENT

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

REFERENCES

1. Scheiman JM. Non-steroidal anti-inflammatory drugs, aspirin, and gastrointestinal prophylaxis: an ounce of prevention. Rev. Gastroenterol. Disord. 2005; 5 Suppl 2: S39–S49
2. Derle DV, Gujar KN, and Sagar BSH. Adverse effects associated with the use of non-steroidal anti-inflammatory drugs: An overview. Indian J. Pharm. Sci. 2006; 68(4): 409-414.
3. Jones R, Rubin G, Berenbaum F, and Scheiman J. Gastrointestinal and cardiovascular risks of non-steroidal anti-inflammatory drugs. Am. J. Med. 2008; 121(6): 446-474
4. Qandil AM. Prodrugs of Non-steroidal Anti-Inflammatory Drugs (NSAIDs), More Than Meets the Eye: A Critical Review. Int. J. Mol. Sci. 2012; 13(12): 17244-17274
5. Manon B, and Sharma PD. Design, synthesis and evaluation of diclofenac-antioxidant mutual prodrugs as safer NSAIDs. Indian J. Chem. 2009; 48B (9): 1279-1287
6. Sawraj S, Bhardwaj TR, and Sharma PD. Design, synthesis and evaluation of novel indomethacin–flavonoid mutual prodrugs as safer NSAIDs. Med. Chem. Res. 2011; 20(6): 687–694
7. Bhosle D, Bharambe S, Gairola N, and Dhaneshwar SS. Mutual prodrug concept: fundamentals and applications. Indian J. Pharm. Sci. 2006; 68(3): 286-294
8. Levit GL, Anikina LV, Vikharev YuB, Demin AM, Safin VA, Matveeva TV *et al*. Synthesis and Anti-inflammatory and Analgesic Activity of Naproxen Amides with Amino Acid Derivatives. Pharm. Chem. J. 2002; 36(5): 232-236
9. Rasheed A, and Kumar CK A. Synthesis, hydrolysis and pharmacodynamics profiles of novel prodrugs of mefenamic acid. Int. J. Curr. Pharm. Res. 2009; 1(1): 47-55
10. Anikina LV, Levit GL, Demin AM, Vikharev YuB, Safin VA, Matveeva TV*et al*. Synthesis and Anti-inflammatory and Analgesic Activity of Amino Acids Acylated with Ibuprofen. Pharm. Chem. J. 2002; 36(5): 237-239
11. Patil CB, Mahajan SK, and Katti SA. Chalcone: A versatile molecule. J. Pharm. Sci. Res. 2009; 1(3): 11-22
12. Knoevenagel E. Condensation von Malonsäure mit Aromatiachen Aldehyden durch Ammoniak und Amine. Chem. Ber. 1898; 31(3): 2596–2619
13. Li JJ. Meyer–Schuster rearrangement. In Name Reactions: A Collection of Detailed Reaction. 3rd ed. Berlin: Springer; 2006. p. 380-381
14. Hu Z, Liu J, Dong Z, Guo L, Wang D, and Zeng P. Synthesis of chalcones catalyzedby $SOCl_2$/EtOH. J. Chem. Res. 2004; 35(34): 158-159
15. Xue Y, Zheng Y, An L, Zhang L, Qian Y, Ding Y*et al*. A theoretical study of the structure–radical scavenging activity of hydroxychalcones. Comput. Theor. Chem. 2012; 982: 74–83
16. Prashar H, Chawla A, Sharma AK, and Kharb R. Chalcone as a versatile moiety for diverse pharmacological activities. Int. J. Pharm. Sci. Res. 2012; 3(7): 1913-1927
17. Zhang XW, Zhao DH, Quan YC, Sun LP, Yin XM, and Guan LP. Synthesis and evaluation of anti-inflammatory activity of substituted chalcone derivatives. Med. Chem. Res. 2010; 19(4): 403-412
18. Heidari MR, Foroumadi A, Amirabadi A, Samzadeh-Kermani A, Azimzadeh BS, and Eskandarizadeh A. Evaluation of anti-inflammatory and analgesic activity of a novel rigid 3,4-dihydroxy chalcone in mice. Ann. N Y Acad. Sci. 2009; 1171: 399-406
19. Okunrobo LO, Usifoh CO, and Uwaya JO. Anti-inflammatory and gastroprotective properties of some chalcones. Acta Pol. Pharm. 2006; 63(3): 195-199
20. Kashyap SJ, Garg VK, Dudhe R, Sharma PK, and Kumar N. Synthesis and in-vitro antioxidant activity of substituted chalcone derivatives. Int. J. Drug Formul. Res. 2011; 2(4): 324-336
21. Ko HH, Hsieh HK, Liu CT, Lin HC, Teng CM, and Lin CN. Structure-activity relationship studies on chalcone derivatives: potent inhibition of platelet aggregation. J. Pharm. Pharmacol. 2004; 56(10): 1333-1337
22. Ilango K, Valentina P, and Saluja GS. Synthesis and in-vitro anti-cancer activity of some substituted chalcone derivatives. Res. J. Pharm. Biol. Chem. Sci. 2010; 1(2): 354-359
23. Wu JH, Wang XH, Yi YH, and Lee KH. Anti-AIDS agents 54. A potent anti-HIV chalcone and flavonoids from genus Desmos. Bioorg. Med. Chem. Lett. 2003; 13(10): 1813–1815
24. Paramesh M, Niranjan MS, Niazi S, Shivaraja S, and Rubbani MS. Synthesis and antimicrobial study of some chlorine containing chalcones. Int. J. Pharm. Pharm. Sci. 2010; 2(2): 113-117
25. Avila HP, Fatima Ed, Smania A, Monache FD, and Junior AS. Structure-activity relationship of antibacterial chalcones. Bioorg. Med. Chem. 2008; 16(22): 9790–9794
26. Opletalová V, and Sedivý D. Chalcones and their heterocyclic analogs as potential antifungal chemotherapeutic agents. Ceska. Slov. Farm. 1999; 48(6): 252-255
27. Lahtchev KL, Batovska DI, Parushev SP, Ubiyvovk VM, and Sibirny AA. Antifungal activity of chalcones: a mechanistic study using various yeast strains. Eur. J. Med. Chem. 2008; 43(10): 2220-2228
28. Yadav N, Dixit SK, Bhattacharya A, Mishra LC, Sharma M, Awasthi SK*et al*. Antimalarial activity of newly synthesized chalcone derivatives in vitro. Chem. Biol. Drug. Des. 2012; 80(2): 340-347
29. Aponte JC, Castillo D, Estevez Y, Gonzalez G, Arevalo J, Hammond GB*et al*. In vitro and in vivo anti-Leishmania activity of polysubstituted synthetic chalcones. Bioorg. Med. Chem. Lett. 2010; 20(1): 100-103
30. Sivakumar PM, Seenivasan SP, Kumar V, and Doble M. Synthesis, anti-mycobacterial activity evaluation, and QSAR studies of chalcone derivatives. Bioorg. Med. Chem. Lett. 2007; 17(6): 1695–1700
31. Nielsen SF, Chen M, Theander TG, Kharazmi A, and Christensen SB. Synthesis of anti-parasitic licorice chalcones. Bioorg. Med. Chem. Lett. 1995; 5(5): 449-452
32. Chen M, Christensen SB, Blom J, Lemmich E, Nadelmann L, Fich K, Theander TG*et al*. Licochalcone A, a novel antiparasitic agent with potent activity against human pathogenic protozoan species of Leishmania. Antimicrob. Agents Chemother. 1993; 37(2): 2550-2556
33. Wang J, Wang N, Yao X, and Kitanaka S. Structures and anti-histamine activity of chalcones & aurones compounds from Bidens parviflora Willd. Asian J. Tradit. Med. 2007; 2(1): 23-29
34. Hsieh CT, Hsieh TJ, El-Shazly M, Chuang DW, Tsai YH, Yen CT*et al*. Synthesis of chalcone derivatives as potential anti-diabetic agents. Bioorg. Med. Chem. Lett. 2012; 22(12): 3912-3915
35. Ducki S. Antimitotic chalcones and related compounds as inhibitors of tubulin assembly. Anticancer Agents Med. Chem. 2009; 9(3): 336-347
36. Cho S, Kim S, Jin Z, Yang H, Han D, Baek NI*et al.* Isoliquiritigenin, a chalcone compound, is a positive allosteric modulator of GABAA receptors and shows hypnotic effects. Biochem. Biophys. Res Commun. 2011; 413(4): 637-642
37. Dimmock JR, Elias DW, Beazely MA, and Kandepu NM. Bioactivities of chalcones. Curr. Med. Chem. 1999; 6(12): 1125-1149
38. Rahman MA. Chalcone: a valuable insight into the recent advances and potential pharmacological activities. Chem. Sci. J. 2011; 2011(29): 1-16
39. Katsori AM, and Hadjipavlou-Litina D. Recent progress in therapeutic applications of chalcones. Expert Opin. Ther. Pat. 2011; 21(10): 1575-1596
40. Parente L. Pros and cons of selective inhibition of cyclooxygenase-2 versus dual Lipoxygenase/cyclooxygenase inhibition: Is two better than one? J. Rheumatol. 2001; 28(11): 2375-2382
41. Cianci J, Baell JB, Flynn BL, Gable RW, Mould JA, Paul D*et al.* Synthesis and biological evaluation of chalcones as inhibitors of the voltage-gated potassium channel Kv1.3. Bioorg. Med. Chem. Lett. 2008; 18(6): 2055-2061
42. Lin CN, Hsieh HK, Ko HH, Hsu MF, Lin HC, Chang YL*et al.* Chalcones as potent antiplatelet agents and calcium channel blockers. Drug Dev. Res. 2001; 53(1): 9–14
43. Petrov O, Ivanova Y, and Gerova M. SOCl2/EtOH: Catalytic system for synthesis of chalcones. Catal. Commun. 2008; 9(2): 315-316
44. Jayapal MR and Sreedhar NY. Synthesis and characterization of 4-hydroxy chalcones by Aldol condensation using SOCl2/EtOH. Int. J. Curr. Pharm. Res. 2010; 2(4): 60-62
45. Hasan SA, Elias AN, Jwaied AH, Khuodaer AR, and Hussain SA. Synthesis of new fluorinated chalcone derivative with anti-inflammatory activity. Int. J. Pharm. Pharm. Sci. 2012; 4 Suppl 5: 430-434
46. Bodansky M, Klausner YS, and Ondetti MA. Peptide synthesis. 2nd Ed. New York: John Wiley & Sons, Inc.; 1976
47. Rasheed A, and Ashok Kumar CK. Synthesis, hydrolysis and pharmacodynamic profiles of novel prodrugs of mefenamic acid. Int. J. Curr. Pharm. Res. 2009; 1(1): 47-55

48. Rasheed A, Theja I, Ashok Kumar CK, Lvanya Y, Ravindra P, and Vamsee Krishna S. Synthesis, hydrolysis studies and pharmacodynamic profile of novel colon-specific mutual prodrug of Aceclofenac with amino acids. Der Pharm. Chemic. 2009; 1(2): 59-71
49. Furniss BS, Hannaforg AJ, Smith PWG, and Tatchell AR. Vogal's Textbook of Practical Organic Chemistry. 5th Ed. New York: John Wiley & Sons, Inc.; 2005. p. 395
50. Jayapal MR, and Sreedhar NY. Synthesis of 2,6-dihydroxy substituted chalcones by Aldol condensation using $SOCl_2$/EtOH. Int. J. Pharm. Pharm. Sci. 2011; 3(1): 127-129
51. Rojas J, Payá M, Dominguez JN, and Luisa Ferrándiz M. The synthesis and effect of fluorinated chalcone derivatives on nitric oxide production. Bioorg. Med. Chem. Lett. 2002; 12(15): 1951-1954
52. Kirk KL. Biomedical Chemistry, Applying chemical principles to understanding and treatment of disease. 2nd Ed. New York: John Wiley & Sons, Inc.; 2001
53. Yadav HL, Gupta P, Pawar RS, Singour PK, and Patil UK. Synthesis and biological evaluation of anti-inflammatory activity of 1,3 diphenyl propenone derivatives. Med. Chem. Res. 2011; 20(4): 461-465.