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New bioisosteric derivative of diclofenac sodium resolute gastric ulcer in rats through regulation of pro-inflammatory cytokines "Tumor necrosis factor alpha and Inter-leukin-1"

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Abstract

Background and objective: Gastric ulcer is an important health risk for a human. It is a painful sore in the stomach lining. It is relatively easy to cure, but can cause significant problems if left un-treated. Non-steroidal anti-inflammatory drugs (NSAIDs) are prescribed for millions of people worldwide; however, as their consequences most of individuals suffer from gastric ulcers and related complications. Diclofenac sodium is a medication from NSAIDs class of drugs, is used to relieve joint pain from arthritis but when used chronically, it may cause bleeding and ulcers in the stomach or intestine. This study aimed to test the safety and the antiulcer activity of a new bioisosteric derivative of diclofenac sodium on a rat model.

Methods: 2-Cumaranone 1 had been utilized to prepare the propanamides 2a-e then after the bioisosteric diaryl ethers 3a-e synthesized; then its purity was characterized on the basis of IR, ^{1}HNMR and Mass spectral data. Acute toxicity on albino mice was performed to ensure the safety and an experimental rat model was used to evaluate the anti-ulcer activity. Kidney and liver functions tests were measured, ulcer measurements were reported and pro-inflammatory cytokines tumor necrosis factor alpha (TNFα) and Interleukin 1 beta (IL-1β) levels were tested.

Results: Unlike diclofenac sodium, the bioisosteric diaryl ethers 3a-e is less acidic and produces less damage to the stomach wall. In addition, the structure of amide derivative is also bulky thus it is more selective to cyclooxygenase II enzyme thus the risk of gastric ulcer was less than with diclofenac sodium itself.

Conclusion: Unlike diclofenac, amide derivative of diclofenac is less acidic than diclofenac thus it produces less damage to the stomach wall.

Keywords: Gastric ulcer; Bioisosteric; Diclofenac sodium; TN-α and IL-1β.

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are well known antipyretics and analgesics, however, their caused gastrointestinal morbidity and mortality continues to be a significant problem. NSAIDs in combination with gastric acid have been reported to increase risk of dyspeptic symptoms, damage gastroduodenal mucosa resulting in ulceration, bleeding and perforation.[1-3]

Diclofenac sodium is one of NSAIDs, acts as potent cyclooxygenase inhibition, reduction of arachidonic acid release, and enhancement of arachidonic acid uptake. It thus enclose dual inhibitory effect on both the cyclooxygenase and lipoxygenase pathways.[4] Compounds with a 1,1-diaryl backbone are numerous, and have been found to be used as catalysts and molecular building blocks, however, important drugs and biologically active molecules fall into this structural motif such as: anticancer,[5] antifungal, antiarrhythmic, antidepressant, antihypertensive, anticholinergic, antihistaminic, antimuscarinic, and cholesterol lowering agent.[6] Recently, diaryl ether derivatives had been synthesized

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and tested against COX enzymes and they demonstrated to possess anti-inflammatory activity.[7] Tumor necrosis factors TNF are important keys of the systemic inflammatory reactions secondary to infection, trauma, burns, pancreatitis and hemorrhagic shock. TNF also play a major role in releasing other infectious processes like: ischemia-reperfusion injury, allograft rejection, granuloma development and delayed-type hypersensitivity.[8] Additionally, interleukin-1 performs important host-defense activities in animals such as: stimulation of T and B lymphocytes, protection of bone marrow stem cells and reduction of mortality rate due to fungal and bacterial infections.[9]

The current study aimed to synthesize a new derivative of diclofenac sodium that assumed to be safe on albino mice with no toxicity outcomes and proposed to possess a gastroprotective effect on a rat model.

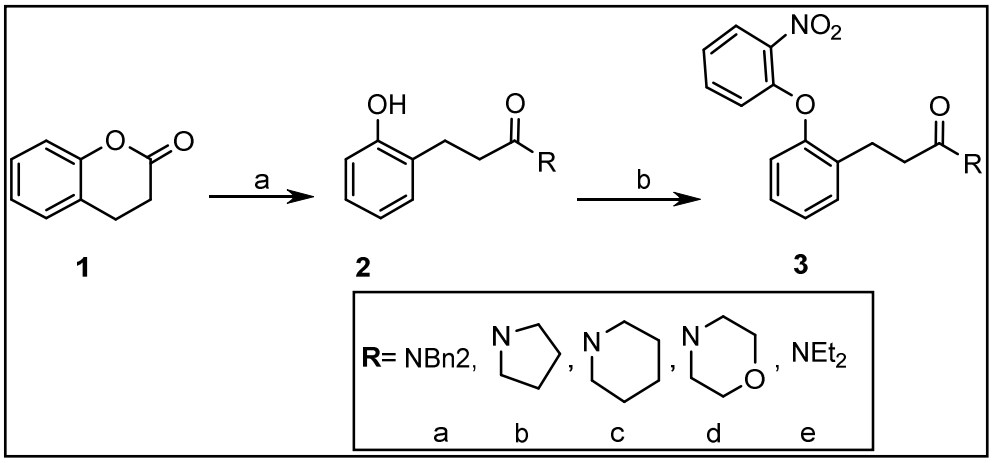
Methods

Chemistry:

The diclofenac derivatives have been synthesized at College of Pharmacy- Pharmaceutical and Organic Chemistry lab. Commercially available reagents were used without purification (from Sigma). ^{1}H and ^{13}C NMR spectra were recorded on a BrukerUltra Shield 300 (300 MHz) spectrometer at Central Lab., University of Jordon). Melting points of the synthesized compounds were measured on Gallen Kampelectrothermal melting point apparatus and are uncorrected. IR spectra were recorded on a JASCO, Japan (Pharmaceutical Chemistry Department, College of Pharmacy, Hawler Medical University/Erbil).

General procedure for the synthesis of propanamides2a-e

To a solution of 2-chromanone 1(1 eq.) in toluene (0.1 M) was added the amine R (1.5 eq.). The resulting solution was stirred at 110^{o}C for 6 hours, after which it was allowed to cool, acidified (1 M HCl), and extracted with ethyl acetate. The combined organic layers were washed with distilled water and brine, dried ($MgSO_4$), filtered and the solvent evaporated in*vacuo* to afford the pure amide2 directly or after flash column chromatography.[10]



Scheme 1 Synthesis of bioisosteric derivatives of diclofenac. (Reaction conditions: i) amines R (1.5 eq.), 2-chromnanone1 (1 eq.), toluene (0.1 M), reflux, 6 hours; ii) propanamides2a-e (1 eq.), 1-fluoro-2-nitrobenzene (10 eq.), K_2CO_3 (2.5 eq.), DMSO (0.1 M), 25° C, 24 hours

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General procedure for the synthesis of bioisostericdiarylethers3a-e

To a solution of the prepared amide 2 (1 eq.) in DMSO (0.1 M) was added potassium carbonate (2.5 eq.) and the resulting solution was stirred at 25° C for 30 minutes. 1-Fluoro-2-nitrobenzene FNB (10 eq.) was added and the reaction stirred for 24 hours at 25°C. After which, the mixture was acidified with hydrochloric acid solution (1 M). The product 3 was extracted with ethyl acetate and the combined organic layers were washed with distilled water, brine, dried ($MgSO_4$), filtered and the solvent evaporated in *vacuo* to afford the crude residue which was purified by flash column chromatography.[10]

Acute toxicity study

This test aimed to confirm the safety of bioisosteric diaryl ethers 3a-e on experimental mice based on the OECD 423 guideline.[11] All mice were not allowed for food intake for 24 hours and water was withdrawn 2 hours prior to the experiment. Thirty mice were divided in to three groups (five female and five male mice in each group): (Normal control group received 5 ml/kg 10% Tween 20), (Low dose group received 2g/kg BIDD) and (high dose group received 5g/kg 3a-e). A single dose of the samples was administered to the mice then the animals were observed for abnormal behavior (convulsions, sedation, respiratory distress, changes in skin, and fur salivation) for the first three hours and 24 hours continuously and at least once daily thereafter for 14 days, mortality was recorded if there is any. The animals were sacrificed on the 15th day of the study and blood samples were collected for biochemical tests including kidney and liver functions.

Gastroprotective activity

Thirty-two adult male rats were divided randomly (following simple randomization method) into four groups by using simple random table. First group received a high dose bioisosteric derivatives of diclofenac 3a-e (200mg/kg) orally by intra-gastric gavage. While the second group received a lower dose (100mg/kg). The third group received 10% Tween 20 while the forth group received the selective and irreversible proton pump inhibitor “esomeprazole”. The animals were left for one hour then, one ml of ethanol (95%) was given orally to induce gastric ulcer. The animals were left for another one hour then; they were anesthetized by ketamine and xylazine and sacrificed. Blood samples were collected then the abdomens were opened and the stomach were removed and opened along the greater curvature. All rats’ stomachs were washed with cold saline to examine the degree of gross mucosal damage and the mucosa was immediately fixed with formalin (10%) and the pH of the gastric juice was measured.

Statistical Analysis

All data were expressed as Mean ± SEM. The statistical analysis was achieved using one-way ANOVA, in the IBM statistical package for the social sciences (SPSS, version 23) program. A *P*-value ≤ 0.05 as considered statistically significant.

Results

The propanamides2a-e had been prepared from 2-cumaranone 1 and corresponding amines R with a good yield percentage and fully characterized by different spectroscopic methods, as shown in Tables 1 and 2.

Table 1 Physical data and yields of the amides 2a-e

Entry	Yield (%)	Color	Melting point °C
3a	93	colorless	148-150
3b	100	colorless	151-153
3c	78	colorless	130-132
3d	82	colorless	129-131
3e	100	Yellow	128-130

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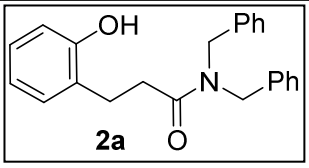
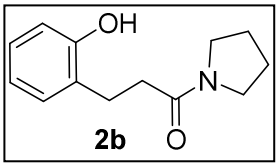
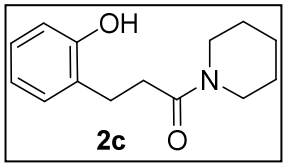
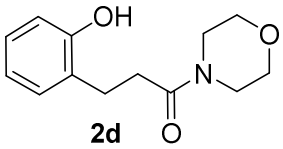
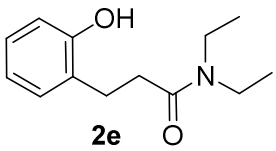
Table 2 Diagnostics peaks and values in IR and NMR of the propanamides 2a-e

Compounds	IR (neat,cm^{-1}): ν_{max}	^1H NMR ($CDCl_3$, 300MHz): δ_H	^{13}C NMR ($CDCl_3$, 75MHz): δ_C
 **2a**	1613 (C=O stretching), 3181 (O-H stretching), 1142 (C-O stretching).	2.82 (t, 2H), 3.01 (t, 2H), 4.41 (s, 2H), 4.58 (s, 2H), 9.31 (s, 1H).	25.00, 35.11, 48.98, 49.97 (CH_2).
 **2b**	1622 (C=O stretching), 1039 (C-N stretching), 3283 (OH stretching).	1.78-1.98 (m, 4H), 2.66 (t, 2H), 2.94 (t, 2H), 3.33 (t, 2H), 3.45 (t, 2H).	24.40, 24.44, 26.05, 36.74, 46.31, 46.66 (CH_2).
 **2c**	1619 (C=O stretching), 3278 (OH stretching), 1013 (C-O stretching).	1.55-1.62 (m, 6H), 2.71 (t, 2H), 2.94 (t, 2H), 3.34 (t, 2H), 3.55 (t, 2H).	24.39, 24.82, 25.51, 26.21, 35.25, 43.39, 46.45, (CH_2).
 **2d**	1618 (C=O stretching), 2974 (OH stretching), 1035 (C-O stretching).	2.71 (t, 2H), 2.96 (t, 2H), 3.42 (t, 2H), 3.62 (m, 6H).	24.59, 35.11, 42.48, 45.73, 66.34, 66.76 (CH_2).
 **2e**	1613 (C=O stretching), 3175 (OH stretching), 1071 (C-O stretching).	1.08 (t, 3H, *J*= 4.5Hz), 1.11 (t, 3H, *J*= 4.5Hz), 2.71 (t, 2H, *J*= 6.0Hz), 2.94 (t, 2H, *J*= 6.0Hz), 3.26 (q, 2H, *J*= 9.0Hz), 3.36 (q, 2H, *J*= 9.0Hz).	13.02, 13.88 (CH_3), 24.90, 35.04, 40.95, 42.09 (CH_2).

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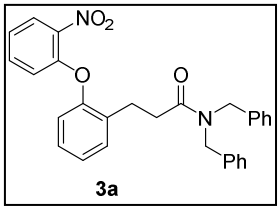
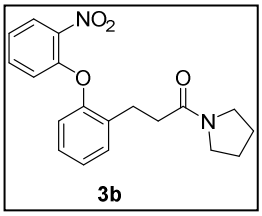
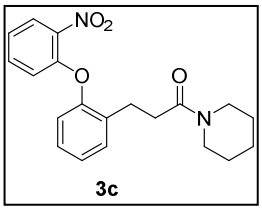
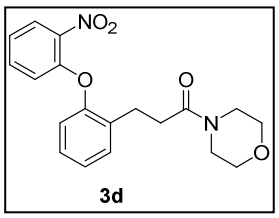
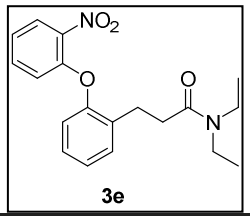
The next step after the successful preparation of the propanamide substrates 2a-e, was their reaction with FNB to afford the diarylether derivatives 3a-e in their maximum percent's of yield, as shown in Table 3 and 4.

Table 3 Physical data and yields of the bioisosteric diarylethers 3a-e

Entry	Yield (%)	Color	Melting point °C
3a	100	yellow	Oily
3b	94	Yellow	Oily
3c	90	Yellow	Oily
3d	91	Yellow	Oily
3e	90	Yellow	Oily

Table 4 Diagnostics peaks and values in IR, NMR of the diarylethers 3a-e

Chemical Name and structure	IR (neat,cm^{-1}): ν_{max}	^{1}H NMR ($CDCl_3$, 300MHz): δ_H	^{13}C NMR ($CDCl_3$, 75MHz): δ_C
 **3a**	1644 (C=O stretching), 1101 (C-O stretching), 1524, 1347 (N-O stretching).	2.82 (t, 2H, *J*= 7.5Hz), 3.06 (t, 2H), 4.42 (s, 2H), 4.57 (s, 2H).	26.95, 33.43, 48.23, 49.90 (CH_2).
 **3b**	1604 (C=O stretching), 1039 (C-N stretching), 1100 (C-O stretching), 1523, 1344 (N-O stretching).	1.80 (tt, 2H), 1.88 (tt, 2H), 2.65 (t, 2H), 2.95 (t, 2H), 3.34 (t, 2H), 3.42 (t, 2H).	24.52, 26.20, 26.49, 35.02,45.74, 46.56 (CH_2).
 **3c**	1631 (C=O stretching), 1098 (C-O stretching), 1583, 1348 (N-O stretching).	1.55-1.67 (m, 6H), 2.77 (t, 2H), 3.01 (t, 2H), 3.42 (t, 2H), 3.60 (t, 2H).	24.39, 25.44, 26.18, 26.76, 33.32, 42.52, 46.42 (CH_2).
 **3d**	1639 (C=O stretching), 1023 (C-O stretching), 1582, 1349 (N-O stretching).	2.72 (t, 2H), 2.94 (t, 2H), 3.42 (t, 2H), 3.53 (t, 2H), 3.61 (t, 4H).	26.72, 32.75, 41.73, 45.73, 66.36, 66.58 (CH_2).
 **3e**	1631 (C=O stretching), 1098 (C-O stretching), 1524, 1349 (N-O stretching).	0.95-1.01 (m, 6H), 2.59 (t, 2H), 2.87 (t, 2H), 3.15 (q, 2H), 3.24 (q, 2H).	12.92, 14.01 (CH_3), 26.69, 33.14, 39.96, 41.75 (CH_2).

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A single oral administration of bioisosteric derivatives 3a-e at two doses (2g/kg and 5g/kg) did not show any toxic effect or mortality for 24 hours and the mice behavior was normal (no sign of changes in eyes, respiration, skin, fur, convulsion or sedation) throughout 14 days of observation. The biochemical measurements of blood serum revealed that there are no significant differences (P >0.05) between all groups as shown in Tables 5 and 6.

Table 5 Effect of bioisosteric derivatives 3a-e on serum biochemical analysis (Liver function test)

Animal groups	**Liver biochemical parameters**				
Female	**Total Bilirubin (mg/dL)**	**Direct Bilirubin (mg/dL)**	**AST (U/L)**	**ALT (U/L)**	**ALP (U/L)**
Vehicle	0.06 ± 0.1	0.02 ± 0.2	166 ± 1.0	32.5± 0.2	94.5 ± 0.1
LD (2 g/kg)	0.06± 0.4	0.02± 0.3	170 ± 0.2	34.7± 0.3	93.3 ± 0.4
HD (5 g/kg)	0.07 ± 1.0	0.02 ± 0.1	169.7± 0.5	33 ± 0.4	92 ± 0.1
***P* value**	0.064	0.087	0.066	0.099	0.111
Male	**Total Bilirubin (mg/dL)**	**Direct Bilirubin (mg/dL)**	**AST (U/L)**	**ALT (U/L)**	**ALP (U/L)**
Vehicle	0.08±0.1	0.02±0.1	154±0.11	33±0.2	107±0.3
LD (2 g/kg)	0.07±0.09	0.01±0.2	166±0.08	37±0.2	99.5±0.23
HD (5 g/kg)	0.08±0.1	0.01±0.22	159±0.11	38±0.13	101±0.11
***P* value**	0.062	0.091	0.071	0.120	0.092

Values expressed as mean ± SEM. The results did not show any significant difference between groups. ALT:alanine aminotransferase; AST:aspartate aminotransferase; ALP:alkaline phosphatase.

Table 6 Effect of effect of 3a-e on serum biochemical analysis (renal function test)

Animal groups	**Kidney biochemical parameters**				
Female	**Urea (mg/dL)**	**Creatinine (mg/dL)**	**Uric acid (mg/dL)**	**Calcium**	**Phosphorus (mg/dL)**
Vehicle	33.5 ± 0.1	0.38 ± 0.2	6.3 ± 0.1	9.95 ± 0.4	7 ± 0.4
LD (2 g/kg)	34.33 ± 0.2	0.39 ± 0.1	5.9 ± 0.5	10.3 ± 0.7	7.7 ± 0.1
HD (5 g/kg)	35.00± 0.1	0.41 ± 0.03	6.0 ± 0.4	10.00 ± 0.11	7.9 ± 0.3
***P* value**	0.061	0.992	0.0666	0.074	0.0783
Male	**Urea (mg/dL)**	**Creatinine (mg/dL)**	**Uric acid (mg/dL)**	**Calcium**	**Phosphorus (mg/dL)**
Vehicle	37.5 ± 0.4	0.40 ± 0.11	5.1 ± 01	9.8 ± 0.5	8.9 ± 0.4
LD (2 g/kg)	36.7±0.02	0.39±0.2	4.9±0.1	10.3±0.2	8.5±0.2
HD (5 g/kg)	38.4±0.1	0.41±0.3	5.3±0.1	9.3±0.3	8.3±0.1
***P* value**	0.056	1.000	0.0675	0.098	0.081

Values expressed as mean ± SEM. The results did not show any significant difference between groups.

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The gastro-protective effect of bioisosteric derivatives 3a-e was tested against ethanol induced gastric ulcer in rats (Table 7) in terms of ulcer area, ulcer inhibition percentage, mucus weight and pH of stomach. Pre-treatment with 100 mg/kg and 200 mg/kg of bioisosteric derivatives 3a-e was found to inhibit gastric lining injury induced by ethanol (48.7% and 61%) for high dose and low doses respectively. Also our results revealed that bioisosteric derivatives 3a-e can decrease the pH significantly ($P < 0.05$) that represent the acidity which plays a major role in stimulating stomach ulcer. Gastric mucus layer that is covering the gastric lining plays an important role in preserving the inner layer of stomach from exogenous aggressive factors (Table 7).

The macroscopic observations of the stomachs showed significant differences between groups (Figure 1). Rats in the low dose and high dose treated groups reduced areas of gastric lesions compared to rats in positive control group. Lesions were significantly reduced in term of size and severity in rats pre-treated with esomeprazole as shown in Figure 1.

Table 7 Antiulcer activity of bioisosteric derivatives of diclofenac 3a-e against ethanol-induced gastric injury

	Pre-treatment (5 ml/kg)	Ulcer area (mm2)	Inhibition (%)	Mucus weight (mg)	PH (mEq/l)
Vehicle(Ulcer Positive)	10% Tween 20	220.8±2.9	…	957±1.9	5.7±1.3
Control (Ulcer Negative)	20 Mg/kg Esomperazole	55.2±1.6	68	365±5.8	3.7±1.6
Low Dose	100 mg/kg **3a-e**	144± 6.6	48.7	929.3±2.3	4.8±3.4
High Dose	200 mg/kg **3a-e**	86.4±0.6	61	438.7± 6.4	4.3±0.4
***P* value**		0.037	0.050	0.001	0.041

Values are expressed as the mean ± SEM.

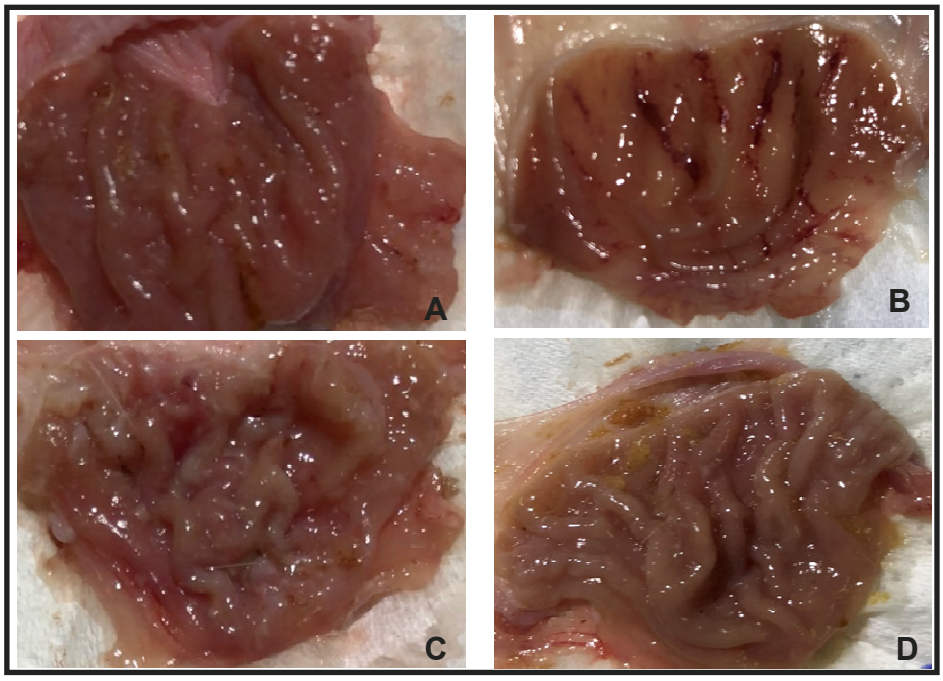

Figure 1 Effect of bioisosteric derivatives of diclofenac3a-e on macroscopic appearance of the gastric mucosa

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The esomeprazole group show no injuries to the gastric mucosa (A). Severe injuries are observed in the gastric mucosa of the ulcer control group (B). The HD group shows mild injuries to the gastric mucosa (C) while LD group shows moderate injuries in the gastric mucosa (D).

Moreover, regarding the results of the tested cytokines (Interleukin-1β and tumor necrosis factor α) the esomeprazole group (the negative control group) showed high concentration of both cytokines (O) in comparison to the ulcer positive control group (T) in which the cytokines concentrations were very low. The high dose group showed comparable results to the esomeprazole group while the low dose group showed moderate concentration as illustrated in Figure 2.

Discussion

The results of this study revealed that 3a-e doses of 100 and 200 mg/kg are safe because none died during the study period and none of the animals produced toxic signs and symptoms. Also there were no significant differences in biochemical parameters of liver and kidney with the vehicle group. Similarly, several researchers used various synthesized derivatives of diclofenac and showed no toxicity.[12,13] Based on these findings the doses of 3a-e used for the gastroprotective study was safe and of no toxicity to rats. Moreover, the results showed that 3a-e was able to produce ulcer inhibition in gastric tissue in rats (48.7% in low dose and 61% in high dose). These results are consistent with the previous studies that showed various synthesized compound had anti ulcerogenic effects against ethanol-induced gastric damage.[14] Esomeprazole was used as antiulcer reference drug in this study against gastric ulcer induced by ethanol. Omeprazole is one of the proton pump inhibitor drug that prescribe to control gastric acid secretion and thereby prevention or treatment of gastric ulcer.[15]

In this study the ulcer negative group is treated with esomeprazole (20 mg/kg) showed a controlled ulcer inhibition percentage and decreased ulceration area. The proton pump inhibitors prolong their preventive and healing effects on stomach by double action Thus, in addition to inhibiting acid secretion, the gastro protective effect of esomeprazole can be ascribed to a reduction in gastric oxidative injury.[16] The pro-inflammatory cytokines, Tumor Necrosis Factor-alpha (TNFα) and Interleukin-β (IL-β) mediate the innate immune response and the dysregulation of their response contributes to the

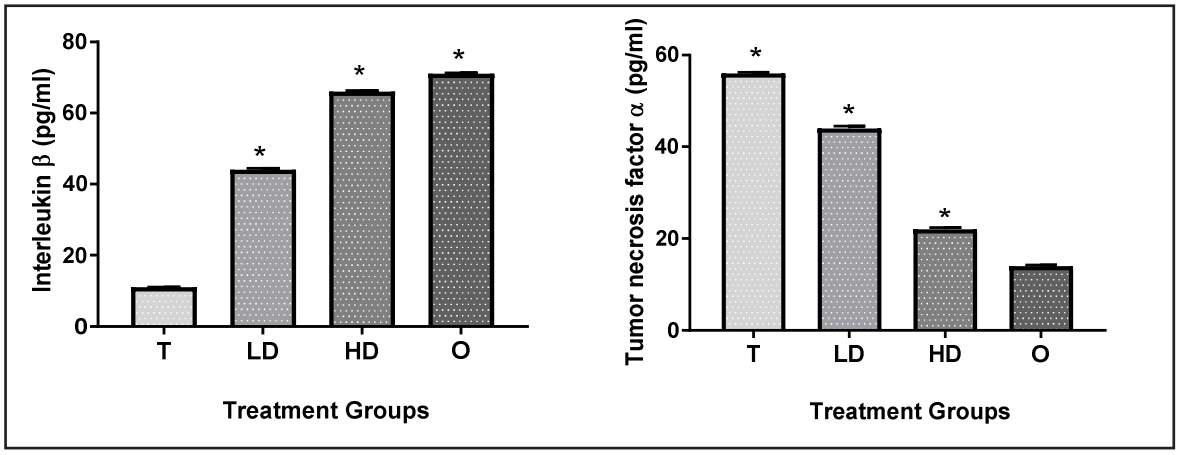

Figure 2 Effect of bioisosteric derivatives of diclofenac3a-e on the concentration of Interleukin β and Tumor necrosis factor α.

The esomeprazole group (O), ulcer control group (T), the High Dose group (HD) and the Low Dose group (LD). *P* value for Il-β test is 0.013 and for TNFα is 0.02)

pathogenesis of diseases like arthritis, cancer, and congestive heart failure.[17] In this study the amide derivative of diclofenac has been found to recover the levels of these cytokines up to their normal levels, this is similar to other studies[18] which showed that *S*-diclofenac (2-[(2,6-dichlorophenyl)amino] benzeneacetic acid 4-(3*H*-1,2,dithiol-3-thione-5-yl) phenyl ester; ACS 15) administration inhibited lipopolysaccharide-induced inflammation, reduced plasma IL-1β/TNF-α and caused significantly less gastric toxicity than diclofenac.

Conclusion

Unlike diclofenac, amide derivative of diclofenac 3a-e is less acidic than diclofenac thus it produces less damage to GIT stomach wall. In addition, the structure of amide derivatives 3a-eis bulkier which makes them more selective toward cyclooxygenase II enzyme, thus, the risk of gastric ulcer less in comparison with diclofenac.

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Competing interests

The author declares that she has no competing interests.

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