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Research Article

EVALUATION OF ANTI-INFLAMMATORY ACTIVITIES OF NEWLY SYNTHESIZED ISATIN DERIVATIVES IN RATS

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ABSTRACT

In search of novel anti-inflammatory agents, evaluation of anti-inflammatory activity of a series of new isatin-carbamate derivatives (3a-d) have synthesized previously by condensation isatin(2,3-indolinendione) with piperidine(hexahydropyridine), hydrazine hydrate and Boc-amino acids respectively have evaluated by using fresh egg albumin induced paw edema method. Two sources of diclofenac sodium (Olfen, Germany origin and Almiral, LIMASSOL-CYPRUS origin) as an internal standard. A majority of the synthesized compounds were showing good anti-inflammatory activity and from comparisons of these compounds, compound **3a** was found to exhibit the highest anti-inflammatory activity and **t**he chemical structures have characterized previously by IR spectroscopy and elemental analysis.

KEYWORDS: Isatin, Isatin-3- hydrazine, N-Mannich base, Boc-amino acid, Carbamate derivatives, Anti-inflammatory activity.

INTRODUCTION

Cyclooxygenase (COX) and lipoxygenase produce two groups of arachidonic acid metabolites, prostaglandins (COX products) and leukotrienes (LOX products), that play important role in inflammation. The classical non-steroidal anti-inflammatory drugs (NSAIDs) act via the inhibition of the COX-1 isoenzyme or the combined inhibition of COX-1 and COX-2 isoenzymes. Because COX-1 is mainly responsible for mucus formation in the gastrointestinal (GI) tract, COX-1 inhibition is responsible for inducing GI irritation, the undesired side effect of agents [1]. COX-2 isoenzyme is evident to be over-expressed during inflammatory conditions and was also found to produce a protective role[2]. Thus, inhibition of these enzymes leads to a decreased production of prostaglandins and thromboxanes which lead for the beneficial effects of NSAIDs (e.g. anti-inflammatory, antipyretic, analgesic and cardiovascular effects) as well as their undesirable side effect profiles (e.g. GI irritation). This leads to the concept that inflammation be considered as a multifactor process and all biochemical process should be taken into account[3]. Prevention of leukocyte function and/or lipid mediator biosynthesis could be an important therapeutic intervention in inflammatory diseases and it may be lead to the discovery of new drugs as alternative to conventional anti-inflammatory agents possessing a high incidence of side-effects[4].

Isatins (Indoline-2,3-diones or indole-1H-2,3-diones), have extensively studied due to their diverse pharmacological activities and synthetic versatility. Isatins act as endogenous biological regulators, found in different tissues, and body fluids of humans[5]. The synthetic importance in the chemistry of isatin and its derivatives derived from its easy synthetic accessibility and exhibition of broad spectrum biological effects, including antibacterial, antifungal, anticonvulsant, antiviral, anticancer, antioxidant, anti-inflammatory and anti-proliferative activities[6-8].

On the other hand, Carbamate-bearing molecules has found to have an interesting role in modern drug discovery and medicinal chemistry. Organic carbamates (or urethanes) are structural elements of many approved therapeutic agents. Structurally, the carbamate functionality is related to amide-ester hybrid features and, in general, displays good chemical and proteolytic stabilities. This due to their chemical stability and capability to permeate cell membranes. Another important feature of carbamates is their ability to modulate inter- and intramolecular interactions with the target enzymes or receptors. Therefore a carbamate appear opportunities for modulation of biological properties and improvement in stability and pharmacokinetic properties[9]. The synthesis of a newer class of anti-inflammatory agents is in need of time. Literature survey revealed that isatin have different chemotherapeutic activities such as antibacterial [10], antifungal [11], antiviral [12], anti- HIV [13], anti-mycobacterial [14], anti-cancer [15], anti-inflammatory [16]and anticonvulsant [17]. Carbamate molecules also have many activities such as antibacterial, antifungal, antiviral, anti-mycobacterial, anti-cancer, anti-inflammatory and anticonvulsant[2]. In view of biological importance of these newly synthesized isatin-carbamate derivatives, it was planned to evaluate the new derivatives for their anti-inflammatory activity.

METERIAL AND METHODS

All solvents used were of laboratory grade, all chemicals used were reagent grade and were used as received without further purification, Ethyl chloroformate (ECF) was obtained from Sigma Aldrich/Germany, Boc-L glycine; Boc-L-alanine, Boc-L-valine and Boc-L-proline were obtained from Shanghai World Yang Chemical/China. Isatin and Piperidine were obtained from Sigma Aldrich/Germany. Melting points (uncorrected) were detected using electrical melting point apparatus, Electro -thermal 9300, USA. The IR spectra were recorded in specac ® Quest ATR (diamond)-IK on FT-IR spectrophotometer /Shimadzu-japan. Compounds have routinely checked for their purity on Silica gel

G (Merck) Thin layer chromatography (TLC) plates. Iodine chamber and UV lamp have used for visualization of TLC spots. Elemental data for C, H, and N have performed by Euro-vector EA 3000A, Italy. All the compound has exhibited satisfactory chemical analysis.

Synthesis of 1-(piperidin-1-ylmethyl)indoline-2,3-dione (compound-1) [18]

The compound 1 has been synthesized as follows, as shown in scheme 1: Isatin(2,3-indolineendione) (1gr,0.00679 mole) was dissolved in (10mL) methanol and then formaldehyde 37%, 2mL was added to the mixture. The reaction mixture was cooled to 0 ^{0}C and then piperidine (hexahydropyridine) (00679 mole, 0.57gr) was added with stirring. The stirring was continues for 1 h at room temperature . the precipitate collected and recrystallized from methanol and the required compound was obtained as orang solid , M.WT=244, M.F=$C_{14}H_{16}N_2O_2$, m.p.=142-144 , Rf :0.56 (ethanol :chloroform, UV active). The elemental Analysis: found C, 68.91 Cal. C, 68.83 ; found H, 6.60, Cal. H, 6.60; found N, 11.48, Cal. N, 11.47 , IR (cm^{-1}) [18] : 2941(C-H str. CH2 Asy.) , 2852(C-H str. CH2 sy.), 1348 (C-N aliphatic), 1469-1412 (C=C Ar.), 3043 (C-H str. Ar.), 1732 (C=O indole), 1612(CO-NH) , 860-762 (HC= Ar. bending).

Synthesis of (Z)-3-hydrazono-1-(piperidin-1-ylmethyl)indolin-2-one(compound2) [18]

The compound 2 has been synthesized as follows, as shown in scheme 1: compound-1 (0.005mole, 0.7gr)was dissolved in methanol (10mL) and added hydrazine hydrate (80%) while shaking. the reaction mixture was refluxed for 30 min. then the solution was allowed to cool to RT and left at refrigerator. overnight and the product obtained was recrystallized from petroleum ether as yellow ppt., m.p.=165-170, M.WT=258, M.F=$C_{14}H_{18}N_4O$, Rf:0.54 (ethanol :chloroform , UV active). The elemental Analysis: found C, 65.17, Cal. C,65.09 ; found H, 7.03, Cal. H, 7.02 ; found N, 21.71, Cal. N, 21.69, IR (cm^{-1}) [(12)] : 1660 (C=N); 1550-1464 (C=C Aromatic); 3357, 3155 (N-H str.), 3064 (C-H Ar.); 1685 (C=O amide isatin), 931-677(HC= Ar. bending), 2931-2850(C-H aliphatic).

General procedure for synthesis of compounds (3a-d)

Compound (3a-d) have been synthesized by the mixed anhydride method[18], as shown in (scheme 1). To a solution of Boc-amino acid (2.28 mmol,0.4gr) was dissolved in Tetrahydrofuran, THF (5mL) containing TEA (2.28 mmol, 0.24gr) at -10 ^{0}c were added Ethyl chloroformate, ECF (2.28 mmol, 0.24gr) drop wise over a period of 10 min. and the mixture was continuously stirred for further 30 min. the solid was filtered off and filtrate was added to the solution of compound 2(2.28 mmol, 0.58gr) containing TEA (2.28 mmol, 0.24gr) in 5 mL DMF for 10 min. and the mixture was stirred for 30 min. at room temperature. The solvent DMF was evaporated and The precipitate was collected and was washed with ether.

Synthesis of 3a, tert-butyl-(Z)-(2-oxo-2-(2-(2-oxo-1-(piperidin-1-ylmethyl)indolin-3-ylidene)hydrazinyl)ethyl)carbamate

Compound 3a has been synthesized, as previously described and as shown in (scheme 1). Boc-glycine (2.28 mmol,0.4gr) in THF (5mL) containing TEA (2.28 mmol, 0.24 gr) was reacted with ECF (2.28 mmol 0.24gr). compound 2 (2.28 mmol, 0.58gr) in DMF(5mL) containing TEA (2.28mmol 0.24 gr) was added. The reaction mixture was treated as described earlier. The physical appearance, percent yield and Rf value are listed on Table (1).

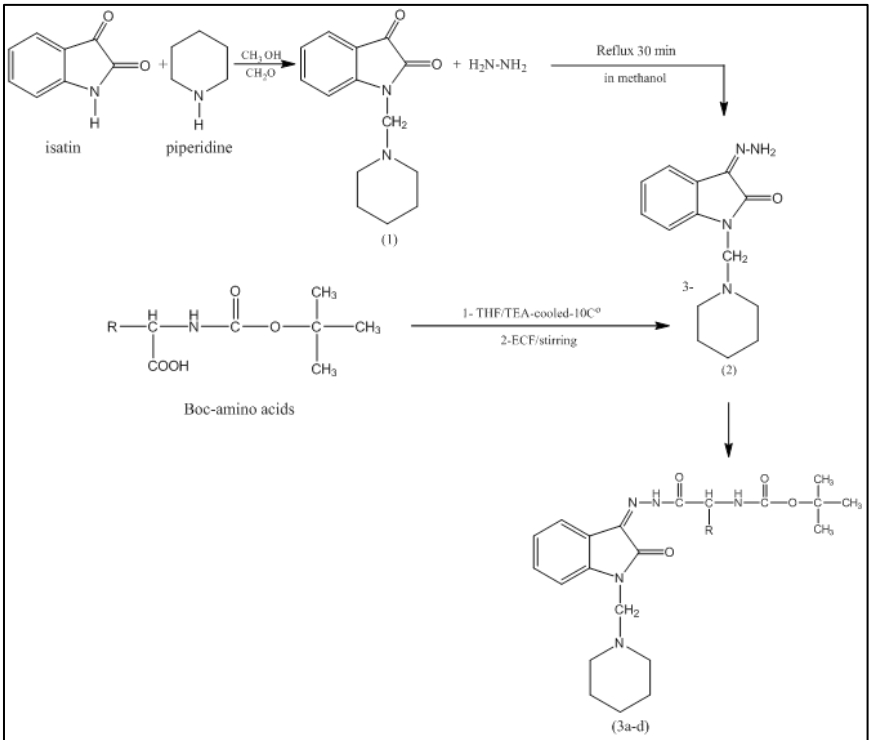
Synthesis of 3b,tert-butyl-(Z)-(1-oxo-1-(2-(2-oxo-1-(piperidin-1-ylmethyl)indolin-3-ylidene)hydrazinyl)propan-2-yl)carbamate

Compound 3b has been synthesized, as follows and as shown in (scheme1): Boc-alanine (2.1 mmol,0.4gr) in 5 mL of THF containing TEA (2.1 mmol, 0.22gr) reacted with ECF (2.1mmol, 0.22gr). compound 2(2.1mmol,0.54gr) in DMF(5mL) containing TEA (2.1mmol,0.22gr) was added. The reaction mixture was treated as previously described. The physical appearance, percent yield and Rf value are listed on Table (1).

Synthesisof3c,tert-butyl-(Z)-(3-methyl-1-oxo-1-(2-(2-oxo-1-(piperidin-1-ylmethyl)indolin-3-ylidene)hydrazinyl)butan-2-yl)carbamate

Compound 3c has been synthesized, as follows and as shown in (scheme1): Boc-valine (1.842 mmol, 0.4gr) in 5 mL of THF containing TEA (1.842 mmol,0.186gr) reacted with ECF (1.842 mmol, 0.2gr). compound 2(1.842 mmol, 0.48gr) in DMF(5mL) containing TEA (1.842 mmol,0.186gr) was added. The mixture was treated as previously described. The physical appearance, percent yield and Rf value are listed on Table (1).

Synthesis of 3d, tert-butyl-(Z)-2-(2-(2-oxo-1-(piperidin-1-ylmethyl)indolin-3-ylidene)hydrazine-1-carbonyl)pyrrolidine-1-carboxylate. Compound 3d has been synthesized, as follows and as shown in (scheme1): Boc-proline (1.86 mmol, 0.4gr) in THF (5mL) containing TEA (1.86 mmol, 0.188gr) was reacted with ECF (1.86 mmol, 0.2gr). compound 2(1.86 mmol, 0.48gr) in DMF(5mL) containing TEA (1.86 mmol, 0.188 gr) was added. The mixture was treated as previously described. The physical appearance, percent yield and Rf value are listed in Table (1).



Scheme 1. Synthesis of compound 3a-d[18]

RESULTS AND DISCUSSION

Spectral data of synthesized compounds (3a–d)

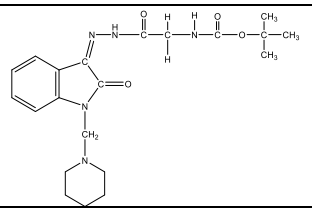
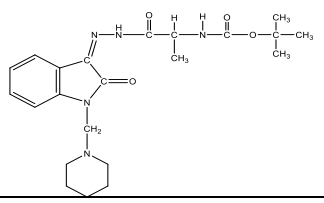
The IR characteristic bands of compound 3a [18], 1745(C=O of urethane), 1672 (C=O of 20 Amide), 3336 (N-H of urethane), 1537 (N-H bending of urethane), 1622 (C=N), 1165 (C-O-C str. of urethane), 3036 (C-H str. Ar.) , 2939(C-H str. CH2 Asy), 2880 (C-H str. CH2 sy.) , 1454,1369 (C-H ben. CH3 of urethane Asy,sy)

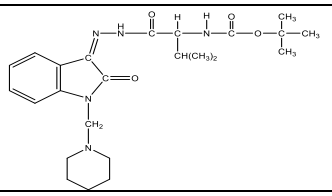
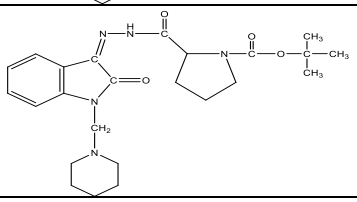
The IR characteristic bands of compound 3b [18], 1738(C=O of urethane), 1691 (C=O of 20 Amide), 1165 (C-O-C str. of urethane), 3384 (N-H of urethane), 1518 (N-H bending of urethane), 1612 (C=N) , 3084 (C-H str. Ar.) , 2941(C-H str. CH2 Asy), 2841 (C-H str. CH2 sy), 1456,1371 (C-H ben. CH3 of urethane Asy, sy)

The IR characteristic bands of compound 3c [18], 1707(C=O of urethane), 1651 (C=O of 20 Amide), 1161(C-O-C str. of urethane), 3340 (N-H of urethane), 1549 (N-H bending of urethane), 1549 (C=N), 3026 (C-H str. Ar.) , 2939(C-H str. CH2 Asy), 2885 (C-H str. CH2 sy) , 1462,1371 (C-H ben. CH3 of urethane Asy,sy) .

The IR characteristic bands of compound 3d [18], 1741(C=O of urethane), 1639 (C=O of 20 Amide),1130 (C-O-C str. of urethane), 3330 (N-H of urethane)), 1549 (C=N) , 3020 (C-H str. Ar.), 2976(C-H str. CH2 Asy), 2897 (C-H str. CH2 sy), 1431,1363 (C-H ben. CH3 of urethane Asy., sy.)

Table 1: Physicochemical data of all synthesized test compounds (3a–d)[18]

Compound	Structure	Physical appearance	% Yield	m.p. (C°)	Rf value	Molecular formula	Analysis (%), found (calc.): C; H; N
3a		**Pale yellow**	**77**	**250-253**	**0.50**	**$C_{21}H_{29}N_5O_4$ (415)**	**60.70(60.71) 7.041(7.04) 16.87(16.86)**
3b		**Pale yellow**	**62**	**266-269**	**0.55**	**$C_{22}H_{31}N_5O_4$ (429)**	**61.59(61.52) 7.291(7.28) 16.32(16.31)**

3c		**pale yellow**	**55**	**289-292**	**0.46**	**$C_{24}H_{355}O_4$ (457)**	**63.07(63.00) 7.719(7.71) 15.32(15.31)**
3d		**Pale yellow**	**35**	**295-298**	**0.44**	**$C_{24}H_{33}N_5O_4$ (455)**	**63.31(63.28) 7.31(7.30) 15.39(15.37)**

PHARMACOLOGY

The anti-inflammatory activity of the synthesized compounds(3a-d)

Dimethylsulfoxide (DMSO) use as solvent and two sources of diclofenac sodium (Olfen, Germany origin and Almiral, LIMASSOL-CYPRUS origin) as an internal standard. Albino rats of both sexes their weight (180-220 g), were supplied by the Animal House of the College of Pharmacy/ University of Baghdad. They are housed in the same location under standardized condition of temperature, humidity and light/dark cycle 2 weeks before experiment. They were fed standard rodent pellet diet and they have free access to water. The local Research Ethics Committee in College of Pharmacy, University of Baghdad, approved the research protocol. They were divided into seven groups (six rats each) as follows:

Group I: Six rats were received single dose of 2ml/kg of dimethylsulfoxide (DMSO) intraperitoneaIly. This group served as a negative control [19] .

Group II: Six rats were treated intraperitoneally with diclofenac sodium(Olfen) as a standard (I) in a dose of 25 mg/kg) .

Group III: Six rats were treated intraperitoneally with diclofenac sodium(Almiral) as a standard (II) in a dose of 25 mg/kg).

Group IV-VII: Six rats are treated intraperitoneally with the synthesized compounds (3a, 3b, 3c and 3d), in dose 200 mg/kg and each one dissolved in dimethylsulfoxide (DMSO).
The anti-inflammatory activity of the synthesized compounds was studied by using fresh egg-albumin induced-edema model. Acute inflammation was induced by a subcutaneous (S.C.) injection of 0.1 ml of undiluted egg-albumin into the planter side of the left hind paw of the rats 30 minutes after intraperitoneal (I.P.) administration of each compound, drugs and the vehicle. The paw thickness was measured by means of verneacliber at six-time intervals (0, 30, 60, 120, 180 and 240 min.) after compounds and drugs administration. The data were expressed as the mean ± SD.

Note: at 0 min, consider as a baseline were the compounds and drugs injected after measuring the paw thickness for each rat, and at 30 min, the edema were induced into paw of each rat by using the fresh egg-albumin and then measuring paw thickness.

Statistical Analysis

Data were expressed as mean ± standard deviation (SD). The Statistical significance of the differences between various groups was determined by unpaired student t-test. Differences were considered statically significant for p-value< 0.05**.**
The percent of inhibition of inflammation was calculated according to the following equation:

Percentage of inhibition (%) = 100 X [1-(x/y)]
Where:
X= mean increase in paw volume, the thickness of treated rats of either (group II, III, IV, V, VI, VII).
y= mean increase in paw volume, the thickness of group I rats (negative control).

Table 2 and **Fig. 1** showed the effects of the synthesized compounds(3a,3b,3c and 3d) treated groups against fresh egg albumin-induced acute inflammation compared to negative control group (I), and standard groups (II and III) (diclofenac sodium 25mg/kg) -treated rats. Percentage of inhibition (%) compared to the negative control (group I) was shown in table 2.

All tested compounds are effectively reduced the increase in paw edema thickness of treated rats, where their effect started at 120 minutes and continues until the end of the experiment time(at 240 min) except the compound **3c,** which shows its effect at 60 min and continues until the end of the experiment with respect to control group(1).

All tested compounds showed non-significant changes compared with standard groups (II and III), Also there is non-significant differences among the synthesized compounds, as shown in Table 2 and Fig 1. But as a percent of anti-inflammatory activity, the compound **(3a),** shows slightly more inhibition than standard groups(II and III) and other tested compounds(3b, 3c and 3d) at 180 and 240 min, as shown in Table 2.

Acute Inflammation is a general pattern of immune response to cell Injury characterized by rapid accumulation of immune cells at the site of injury. It's response is initiated by both immune and parenchymal cells at the site of injury and is coordinated by a wide variety of soluble mediators. A classical signs of heat, redness, swelling, pain, and loss of function, and in which vascular and exudative processes predominate. This study shows the anti-inflammatory activity of the synthesized compounds against egg-albumin induced edema in rats.

Table 2: The Effect Of Control, Standard(1), Standard(2) And Compounds (3-d)On Albumin Induced Paw Edema In Rats

Groups	Mean increase in paw thickness (mm)						% of inhibition				
	0 min	30 min	60 min (1hr)	120 min (2hr)	180 min (3hr)	240 min (4hr)	30 min	60 min	120 min	180 min	240 min
Control%	3.8167± 0.0339	5.5133± 0.5233	6.1433± 0.247	6.430± 0.2813	6.050± 0.2685	5.5933± 0.6437	--	--	--	--	--
Stand.(1) olfen	3.6017± 0.3450	5.3050± 0.7681	6.0367± 1.015	*5.6017± 0.825	*5.0633± 0.691	*4.8± 0.3673	--	1.7%	13%	16.3%	14%
Stand.(2) Almiral	3.7117± 0.2603	*4.775± 0.3975	5.803± 0.725	*5.0783± 0.5849	*4,795± 0.475	*4.468± 0.4141	--	5.5%	21%	20.7%	20%
3 a	3.58± 0.252	*4.851± 0.387	6.328± 0.391	*5.553± 0.262	*4.723± 0.609	*4.348± 0.39	--	--	13.6%	22%	22%
3 b	3.688± 0.261	*4.9± 0.277	5.795± 0.664	*5.163± 0.660	*5.036± 0.147	*4.673± 0.181	--	5.6%	19.7%	16.7%	16.4%
3 c	*3.501± 0.147	*4.493± 0.255	*5.556± 0.252	*5.645± 0.493	*5.038± 0.468	*4.476± 0.357	--	9.6%	12%	16.7%	19.9%
3d	3.691± 0.312	4.856± 0.5	5.655± 0.496	*5.496± 0.366	*5.061± 0.185	*4.843± 0.262	--	7.9%	14.5%	16.3%	13.4%

*Data were expressed as mean ±SD, *P 0.05;significant difference compared to the negative control group
*Percent inhibition (%) compared to the negative control (group I). *Number of animals= 6

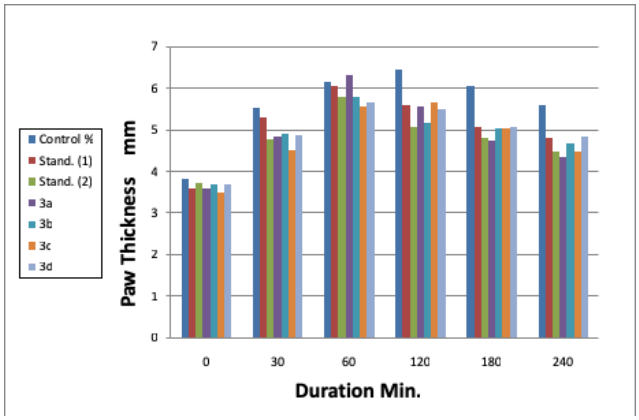


Figure 1: The Effect Control, Standard(1), Standard(2) And Compound (3a-d)on Albumin Induced Paw Edema In Rats

CONCLUSION

A series of new derivatives of isatin have been synthesized successfully previously in appreciable yields and screened for their anti-inflammatory activity using fresh egg albumin induced paw edema method. It is concluded that the new carbamate derivatives of isatin possess anti-inflammatory activity. Furthermore, the new derivative (compound 3a) has significant activity.

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