Available online at www.scholarsresearchlibrary.com

Scholars Research Library

Der Pharmacia Lettre, 2016, 8 (1):275-280
(http://scholarsresearchlibrary.com/archive.html)

Scholars Research Library
ISSN 0975-5071
USA CODEN: DPLEB4

Synthesis and pharmacological evaluation of some 2-(4-isobutylphenyl)-N-(4-oxo-2-arylthiazolidin-3-yl) propanamides

Anju Goyal[1], Johney Sahewal[2], Neelam Jain[3] and *Sandeep Jain[4]

[1]*Chitkara College of Parmcay, Chitkara University, Rajpura, India*
[2]*Rajendra Institute of Technology and Sciences, Sirsa, India*
[3]*Bhagat Phool Singh Mahila Vishwavidyalay, Khanpur Kalan, Haryana, India*
[4]*Drug Discovery and Research Laboratory, Department of Pharmaceutical Sciences, Guru Jambheshwar University of Sciences & Technology, Hisar, India*

ABSTRACT

*Some derivatives of ibuprofen bearing 4H-thiazolidin-4-one moiety were synthesized from ibuprofen and studied for their pharmacological activities. Methyl ester of ibuprofen **I** was synthesized from ibuprofen and then converted to hydrazide **II** with the reaction of hydrazine hydrate. Hydrazide of ibuprofen then reacted with aromatic aldehydes in the presence of glacial acetic acid to yield the hydrazones **III** which on reaction with thioglycolic acid and dimethyl formamide in presence of catalytic amount of anhydrous zinc chloride furnished the title compounds **IV**. The structures of synthesized compounds were elucidated mainly by spectral evidence. All the synthesized title compounds were screened for their anti-inflammatory activity. Title compounds were also studied for their ulcerogenic potential. The compounds exhibited moderate to significant activities.*

Key words: 4*H*-Thiazolidinone, ibuprofen, anti-inflammatory, ulcerogenic potential.

INTRODUCTION

Ibuprofen, 2-(4-isobutylphenyl) propanoic acid, belongs to class of Non Steroidal Anti-inflammatory Drug (NSAID). The pharmacological activity of NSAIDs is related to suppression of prostaglandins biosynthesis from arachidonic acid by inhibiting the enzymes cyclooxygenases. Long term use of NSAIDs has been associated with gastrointestinal (GI) ulceration, bleeding and nephrotoxicity [1-3]. The GI damage from NSAIDs is generally credited to two factors, locally by carboxylic acid moiety, familiar to most NSAIDs and decreased production of tissue prostaglandin, which weakens the physiological function of cytoprotective prostaglandins in maintaining the GI health and homeostasis [4]. Chronic use of NSAIDs including Ibuprofen, may elicit appreciable GI toxicity, therefore synthetic approaches based on chemical modification of NSAIDs have been carry out with the intention of improving the safety profile of NSAIDs. Studies illustrated that the derivatization of carboxylic functional group of representative NSAIDs, resulted in augmented anti-inflammatory activity with diminished ulcerogenic effect [5, 6]. Certain compounds bearing heterocyclic nucleus like thiazolidinone have been reported to possess significant anti-inflammatory activity [7]. Further, 4*H*-thiazolidinones have been reported to possess diverse biological activities, such as antibacterial [8, 9], anti-inflammatory [10, 11], anti-HIV [12], anticancer [13], anticonvulsant [14], etc. These reports prompt us to undertake the synthesis of some derivatives of ibuprofen bearing 4*H*-thiazolidinone moiety with the expectation that the title compounds might be having the comparable anti-inflammatory activity

with reduced ulcerogenic potential. All the compounds were characterized on the basis of their spectral data. Compounds were studied for their anti-inflammatory activity. They were also screened for ulcerogenic potential.

MATERIALS AND METHODS

The chemicals used in the present study were of AR/LR grade obtained from Spectrochem, Qualigens, Rankem, Titanic, S.D. Fine, Hi-Media and Merck and were used without further purification. All the reactions were carried out under pescribed laboratory conditions and the products were purified by recrystallization. Melting points were determined in open capillaries in an electric apparatus and were uncorrected. Purity of the synthesized compounds were checked by TLC using silica gel G as a stationary phase in different solvent systems as a mobile phase and iodine vapors as a detecting agent. Methyl ester I, hydrazide II and aryl hydrazones III of ibuprofen were prepared according to the procedure given in the literature [15].

***General procedure for the synthesis of* 2-(4-isobutylphenyl)-N-(4-oxo-2-arylthiazolidin-3-yl) propanamides (IVa-g)**

A mixture of hydrazide hydrazones (0.025 M) and thioglycolic acid (0.025 M, 2.25 mL) were taken in DMF (50 mL) containing a pinch of anhydrous $ZnCl_2$ and refluxed for about 6 hours. The reaction mixture was cooled and poured on to crushed ice. The solid thus obtained was filtered, washed with water and the product was re-crystallized from rectified spirit. Physico-chemical data of the title compounds are presented in the Table I.

Table I: Physico-chemical data of 2-(4-isobutylphenyl)-N-(4-oxo-2-arylthiazolidin-3-yl) propanamides (IVa-g)

Compound Code	R	Molecular Formula	M.P. (°C)	Yield (%)
IVa	H	C21H24N2O2S	110-112	81
IVb	Cl	C21H23ClN2O2S	106-108	83
IVc	Br	C21H23BrN2O2S	103-105	82
IVd	F	C21H23FN2O2S	132-134	80
IVe	OH	C21H24N2O3S	165-167	78
IVf	OCH3	C22H26N2O3S	114-116	79
IVg	NO2	C21H23N3O4S	145-147	85

Spectral Data of the title compounds:

2-(4-isobutylphenyl)-N-(4-oxo-2-phenylthiazolidin-3-yl) propanamide (IVa):

IR (KBr, cm^{-1}): 3370 (N-H stretching for amide group), 1680 (C=O stretching for amide carbonyl), 2886 (Alkyl CH stretching).

1H NMR (300 MHz CDCl3, δ ppm): 7.02-7.61 (m, Ar), 8.14 (s, NH), 8.78 (s, CH), 3.93 (s, 2H, benzyl CH_2).

2-(4-isobutylphenyl)-N-(4-oxo-2-(4-chlorophenyl) thiazolidin-3-yl) propanamide (IVb):

IR (KBr, cm^{-1}): 3371 (N-H stretching for amide group), 1682 (C=O stretching for amide carbonyl), 2885 (Alkyl CH stretching).

1H NMR (300 MHz CDCl3, δ ppm): 7.06-7.67 (m, Ar), 8.14 (s, NH), 8.78 (s, CH), 3.93 (s, 2H, benzyl CH_2).

2-(4-isobutylphenyl)-N-(4-oxo-2-(4-bromophenyl) thiazolidin-3-yl) propanamide (IVc):

IR (KBr, cm^{-1}): 3369 (N-H stretching for amide group), 1684 (C=O stretching for amide carbonyl), 1188 (C-Br stretching for aromatic Bromine), 2884 (Alkyl CH stretching).

1H NMR (300 MHz CDCl3, δ ppm): 7.05-7.68 (m, Ar), 8.15 (s, NH), 8.79 (s, CH), 3.92 (s, 2H, benzyl CH_2).

2-(4-isobutylphenyl)-N-(4-oxo-2-(4-florophenyl) thiazolidin-3-yl) propanamide (IVd):

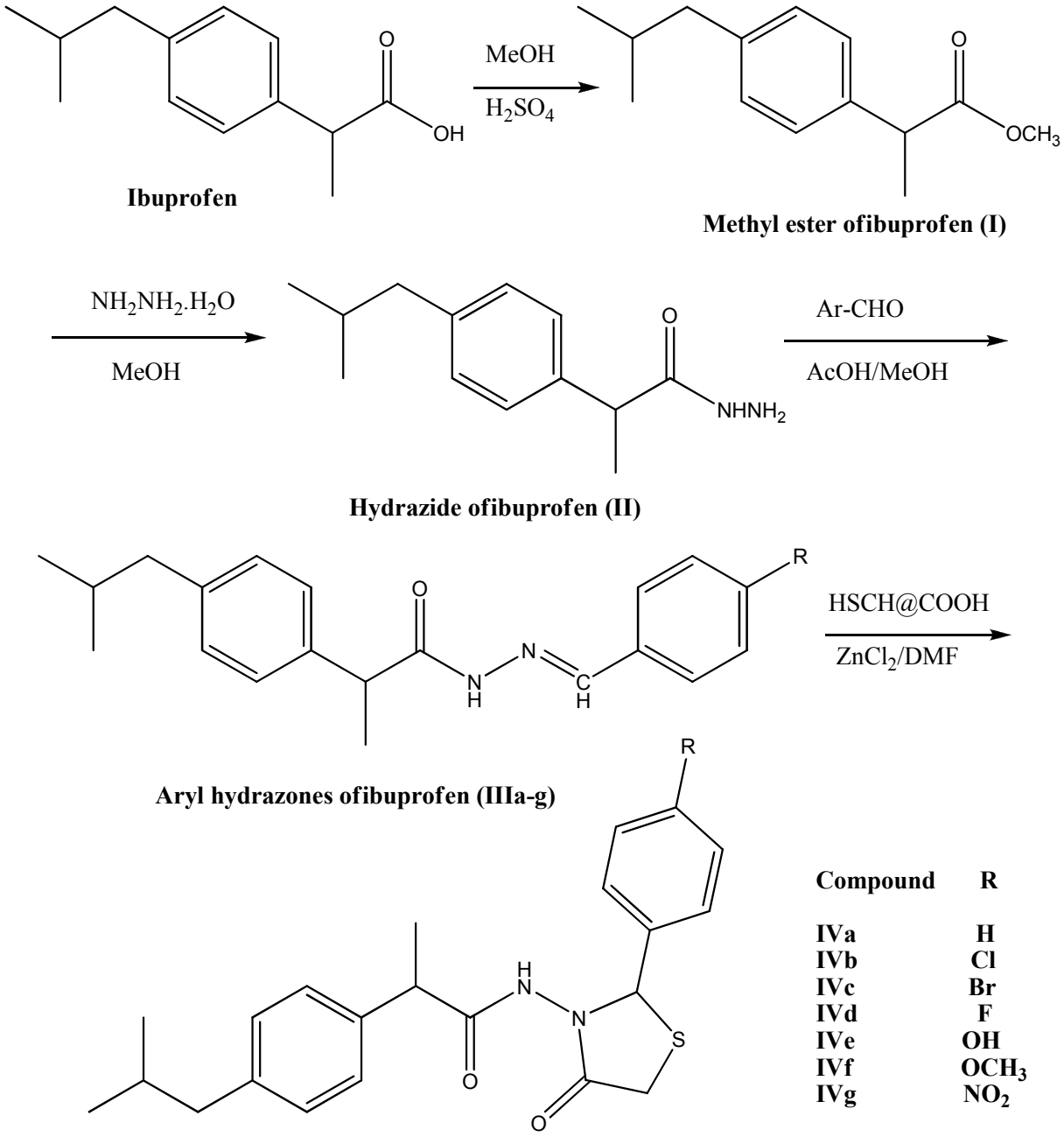
IR (KBr, cm^{-1}): 3371 (N-H stretching for amide group), 1678 (C=O stretching for amide carbonyl), 1550 (-N-O stretching for aromatic nitro group), 2880(Alkyl CH stretching).

1H NMR (300 MHz CDCl3, δ ppm): 7.04-7.62 (m, Ar), 8.13 (s, NH), 8.75 (s, CH), 3.89 (s, 2H, benzyl CH_2).

2-(4-isobutylphenyl)-N-(4-oxo-2-(4-hydroxyphenyl) thiazolidin-3-yl) propanamide (IVe):

IR (KBr, cm^{-1}): 3379 (N-H stretching for amide group), 1667 (C=O stretching for amide carbonyl), 3401(O-H stretching of aromatic ring), 2891(Alkyl CH stretching).

1H NMR (300 MHz CDCl3, δ ppm): 7.01-7.66 (m, Ar), 8.02 (s, NH), 8.77 (s, CH), 3.94 (s, 2H, benzyl CH_2).



Scheme 1: Synthesis of 2-(4-isobutylphenyl)-N-(4-oxo-2-arylthiazolidin-3-yl) propanamides

2-(4-isobutylphenyl)-N-(4-oxo-2-(4-methoxyphenyl) thiazolidin-3-yl) propanamide (IVf):
IR (KBr, cm^{-1}): 3374 (N-H stretching for amide group), 1659 (C=O stretching for amide carbonyl), 2890 (Alkyl CH stretching), 1240 (C–O of Methoxy).
1H NMR (300 MHz CDCl3, δ ppm): 1.14 (d, CH3), 9.91 (q, CH), 7.00-7.59 (m, Ar), 8.02 (s, NH), 3.78 (s, 3H, OCH_3), 3.87 (s, 2H, benzyl CH_2).

2-(4-isobutylphenyl)-N-(4-oxo-2-(4-nitrophenyl) thiazolidin-3-yl) propanamide (IVg)
IR (KBr, cm^{-1}): 3382 (N-H stretching for amide group), 1678 (C=O stretching for amide carbonyl), 1550 (-N-O stretching for aromatic nitro group), 2880(Alkyl CH stretching).
1H NMR (300 MHz CDCl3, δ ppm): 7.04-7.62 (m, Ar), 8.13 (s, NH), 8.75 (s, CH), 3.84 (s, 2H, benzyl CH_2).

Pharmacological Evaluation
All the protocol of the animal activity has been approved by Institutional Animal Ethics Committee of HAU, Hisar and all the compounds synthesized were evaluated for anti-inflammatory activity and ulcerogenic potential.

Anti-inflammatory activity
This method depends on inhibition of edema caused by carrageenan. The edema was measured by plethysmometer. All animals were weighed and numbered. A mark was made on one of the hind paw beyond tibiotarsal junction, so that every time hind paw was dipped in column up to the fixed mark to ensure constant paw volume. The initial paw volume of each rat was noted by mercury displacement. The animals were divided into nine groups. In each group, six rats were kept. One group was taken as control (carrageenan induced), one standard (Ibuprofen) and remaining seven groups for the compound to be tested. To a group, Standard Ibuprofen orally administered and to rest of groups the test compounds (100mg/kg) were given in equimolar quantities (based on weights of rats) orally. Paw edema was induced in unanesthesized rats by injection of carrageenan (0.1 mL of 1% w/v carrageenan distill water solution) into the plantar region of right hind paw after 30 min of drug administration. Paw volume was measured using plethysmometer after the injection of carrageenan at 2 hr and 4 hr intervals of drug administration [16, 17]. The percentage inhibition of inflammation was calculated for Ibuprofen sodium and test compounds by following formula:

(%) Inhibition = 1- Vt/Vc

Where Vt and Vc are the mean relative changes in the volume of paw edema in the test and control respectively. All the results were expressed as mean ± standard deviation (SD). Data was analyzed using student unpaired t-test and critical range for significance difference between two groups of observations was taken as $p < 0.001$, $p < 0.01$ and $p < 0.05$. Biological activity data of synthesized compounds is summarized in Table II.

Table II: Anti-inflammatory activity of synthesized title compounds (IVa-g)

Compound Name	% Anti-inflammatory activity ± SD	
	2 hours	4 hours
Control		
Standard (Ibuprofen)	41.59 ± 4.39	52.53 ± 3.55
Iva	22.88 ± 4.22	30.74 ± 2.44
IVb	26.84 ± 4.32	34.72 ± 3.18
IVc	24.40 ± 5.51	32.33 ± 2.11
IVd	32.66 ± 3.64	51.34 ± 3.76
IVe	31.63 ± 4.12	49.58 ± 5.93
IVf	30.19 ± 3.97	49.30 ± 1.69
IVg	25.30 ± 4.54	30.36 ± 3.43

Evaluation of Ulcerogenic Potential
Ulcerogenic test was done according to Cioli et al [18]. Rats were divided into different groups consisting of six animals each. Ulcerogenic activity was evaluated after oral administration of test compounds 20 mg kg–1 body mass. Control rats received orally, the vehicle (suspension of 1% carboxy methylcellulose). Food but not water was removed 24 h before administration of the test compounds. After the drug treatment, the rats were fed normal diet for 17 h and were then sacrificed. The stomach was removed and opened along the greater curvature, washed with distilled water and cleaned gently by dipping in saline. The mucosal damage was examined by means of a magnifying glass. For each stomach the mucosal damage was assessed according to the following scoring system: 0.5 redness; 1.0 spot ulcer; 1.5 hemorrhagic streaks; 2.0 ulcers > but ≥5; 3.0 ulcers > 5. The mean score of each treated group minus the mean score of control group was regarded as the severity of gastric mucosal damage. Biological activity data of synthesized compounds is summarized in Table III.

Table III: Anti-ulcer activity of synthesized title compounds (IVa-g)

Compound Name	Ulcerogenic activity (mean severity index ± SEM)
Control	0.0± 0.0
Standard (Ibuprofen)	1.8 ± 0.2
IVa	0.5 ± 0.1
IVb	0.6 ± 0.1
IVc	0.6 ± 0.2
IVd	0.8 ± 0.2
IVe	0.5 ± 0.1
IVf	0.6 ± 0.2
IVg	0.5 ± 0.1

RESULTS AND DISCUSSION

The various thiazolidinone derivatives of Ibuprofen were synthesised according to the **scheme 1**. Reaction of ibuprofen with excess of methanol presence of concentrated sulfuric acid gave methyl ester of ibuprofen I which on further treatment with excess of hydrazine hydrate and methanol yielded ibuprofen hydrazide II. Compund II so formed on refluxing with required aromatic aldehydes in methanol in the presence of few drops of glacial acetic acid yielded aryl hydrazones III which on further reaction with of thioglycolic acid in DMF, containing a pinch of anhydrous $ZnCl_2$ furnished the title compounds IV. The compounds were obtained in good to excellent yield. The melting points of compounds varied from 98-168°C. The completion of each reaction was monitored by TLC spotting with the Rf values duly calculated. The result of the physico-chemical properties of all five synthesized compounds is as shown in Table I. The structures of newly synthesized compounds were characterized by spectroscopic techniques. Infrared spectra show N-H stretching peak in the range of 3370-3385 cm^{-1} whereas amide carbonyl (C=O) peak was observed in the range of 1660-1680 cm-1. Proton NMR spectra spectra of the title compounds exhibited the downfield singlet ~ δ 8.2 ppm onwards indicating the presence of azomethane protons. Compounds also exhibited a singlet at ~ δ 4.0 ppm due to (S-CH2-C) and another singlet at ~ δ 6.0 ppm due to (N-CH-S) thereby revealing the formation of 1,3-thiazolidin-4-one ring. All the synthesised title compounds were screened for their anti-inflammatory and ulcerogenic potential. The compounds exhibited moderate to significant anti-inflammatory activities whereas all the compounds were found to exhibit less ulceration than the standard drug.

CONCLUSION

Present study describes the synthesis of ibuprofen derivatives bearing 4*H*-thiazolidinone derivatives. All the title compounds were characterized by physic-chemical and spectral techniques. Compounds were evaluated for their anti-inflammatory activity. All the compounds exhibited moderate to significant activity. These were also screened for ulcerogenic potential. All the compounds were found to show less ulceration than the standard drug. These findings suggest the synthesis of some more derivatives of ibuprofen bearing thiazolidinone and evaluate them for anti-inflammatory activity and ulcerogenic potential.

Acknowledgements
Authors are thankful to the Director, Rajendra Institute of Technology and Sciences, Sirsa-125055, INDIA for providing necessary facilities to carry out the present study. Thanks are due to Institutional Animal Ethics Committee of HAU, Hisar for giving permission to carry out animal studies.

REFERENCES

[1] M. Amir, H. Kumar, S. A. Javed, *Eur. J. Med. Chem.*, **2004**, 39, 535.
[2] J. Smith, Y. Zhang, C. M. Koboldt, J. Muhammad, B. S. Zwefel, A. Shaffer, J. J. Talley, J. L. Masferrer, K. Serbert, P. C. Isakson, *Proc. Natl. Acad. Sci.* USA, **1998**, 95, 13313.
[3] T. D. Warner, F. Giuliano, I. Vaynovie, A. Bukasa, J. A. Mitchell, J. R. Vave, *Proc. Natl. Acad. Sci*. USA, **1999**, 96, 7563.
[4] Hawkey, L. Laine, T. Simon, A. Beaulieu, J. Maldonado-Cocco, E. Acevedo, A. Shahane, H. Quan, J. Bolognese, E. Mortensen, *Arthritis Rheum.*, **2000**, 43, 370.
[5] S. Kalgutkar, A. B. Marnett, B. C. Crews, R. P. Remmel, *J. Med. Chem.*, **2000**, 43, 2860.

[6] M. Duflos, M. R. Nourrisson, J. Brelet, J. Courant, G. Le Baut, N. Grimaud, J. Y. Petit, *Eur. J. Med. Chem.*, **2001**, 36, 545.
[7] S. J. Gilani, S. A. Khan, O. Alam, V. Singh, A. Arora, *J. Serb. Chem. Soc.*, **2011**, 76, 1057.
[8] Deep, S. Jain, P. C. Sharma, S. K. Mittal, P. Phogot, M. Malhotra, *Arabian J. Chem.*, **2014**, 7, 287.
[9] S. Jain, A. Kumar, M. Kumar, N. Jain, Arabian J. Chem., 2011, doi:10.1016/ j.arabjc. 2011.04.009 (In Press).
[10] Deep, S. Jain, P. C. Sharma, *Acta Pol. Pharm. Drug Res.*, **2010**, 67, 63.
[11] Sharma, V. Kumar, S. Jain, P. C. Sharma, *J. Enzyme Inhib. Med. Chem.*, **2011**, 26, 546.
[12] Rao, J. Balzarini, A. Carbone, A. Chimirri, E. Clercq, A. M. Monforte, P. Monforte, C. Pannecouque, M. Zappala, *Farmaco*, **2004**, 59, 33.
[13] O. Guzel, N. Terzioglu, G. Capan, A. Salman, *Arkivoc*, **2006**, xii, 98.
[14] F. A. Ragab, N. M. Eid, H. A. El-Tawab, *Pharmazie*, **1997**, 52, 926.
[15] H. L. Yale, K. Losee, J. Martins, M. Holsing, F. M. Perry, J. Berstein, *J. Am. Chem. Soc.*, **1953,** 75, 1933.
[16] Amir, S. Kumar, *Acta Pharm.*, **2007**, 57, 31.
[17] B.A. Winter, E. A. Risley, G. W. Nuss, *Proc. Soc. Exp. Biol. Med.*, **1962**, 111, 544.
[18] V. Cioli, S. Putzolu, V. Rossi, P. Scorza Barcellona, C. Corradino, *Toxicol. Appl. Pharmacol.*, **1979**, 50, 283.