Academic Sciences International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 5, Issue 4, 2013

Research Article

DESIGN, SYNTHESIS AND CHARACTERIZATION OF NOVEL OXO-[2-(ARYLAMINO)-4-PHENYL-THIAZOL-5-YL]-ACETIC ACID ETHYL ESTERS AS POTENTIAL ANTI-INFLAMMATORY AGENTS

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Received: 01 Aug 2013, Revised and Accepted: 02 Sep 2013

ABSTRACT

Objective: A series of Oxo-[2-(arylamino)-4-phenyl-thiazol-5-yl]-acetic acid ethyl esters were designed, synthesized and evaluated for their anti-inflammatory activity.

Methods: The target molecule were synthesized with the help of 3-chloro-2-oxo-propanoate and thiourea derivatives. Synthesized molecules were evaluated for anti-inflammatory activity using Human Red Blood cell membrane stabilizing activity and carrageenan induced paw edema model of acute inflammation.

Results: The compounds 6a, 6b and 6f showed significant anti-inflammatory activity in both *in vitro* and *in vivo* model. The compound 6e showed significant anti-inflammatory only in *in vitro* model. Electron donating substituent on the 4 position of 2-phenylamino of thiazole proved to be crucial for good activity. The best compound among the series was Oxo-[2-(4-Methoxy-phenylamino)-4-phenyl-thiazol-5-yl]-acetic acid ethyl ester (6b) with good *in vitro* HRBC membrane stabilizing action and *in vivo* anti-inflammatory activity.

Conclusion: The results suggest the suitability of the designed molecular framework as a potential anti-inflammatory molecular framework which also exhibits HRBC membrane stabilizing action.

Keywords: Thiazole, Anti-inflammatory agents, Membrane stabilizing action.

INTRODUCTION

Inflammation is a localized protective reaction of cells or tissues of the body to allergic or chemical irritation, injury and/or infections. The inflammation is characterized by pain, heat, redness, swelling and loss of function that result from dilation of the blood vessels leading to an increased blood supply and from increased intercellular spaces resulting in the movement of leukocytes, protein and fluids into the inflamed regions [1]. Even though the innate cascade process of inflammation is complex, it is mainly divided into two parts i.e. acute and chronic. Acute inflammation is characterized by rapid onset and is of short duration. It is characterized by the exudation of fluids and plasma proteins; and the migration of leukocytes, most notably neutrophils into the injured area. This acute inflammatory response is believed to be a defense mechanism aimed at killing of bacteria, virus and parasites while still facilitating wound repairs. Chronic inflammation is of a more prolonged duration and manifests histologically by the presence of lymphocytes and macrophages, resulting in fibrosis and tissue necrosis. The persistent chronic inflammation increases the development of the degenerative diseases such as rheumatoid arthritis, atherosclerosis, heart disease, Alzheimer, asthma, acquired immunodeficiency disorder (AIDS), cancer, congestive heart failure (CHF), multiple sclerosis (MS), diabetes, infections (bacteria, fungi, parasites), gout, IBD-inflammatory bowel disease, aging and other neurodegenerative CNS depression, all of which are associated with immunopathological changes that appears to play a key role in the onset of the condition [2,3] Therefore, although there are a number of anti-inflammatory drugs available in the market, there is a need to develop novel drugs with better safety profile. Inhibiting the p38 MAP kinase pathway *in vivo* is known to be effective in controlling the release of various proinflammatory cytokines, most notably TNF-α and IL-1β [4]. As a result, small molecule p38 inhibitors have attracted interest within the pharmaceutical industry due to the potential to effectively treat significant inflammatory diseases such as rheumatoid arthritis. The 2-aminothiazoles are reported to be the potent p38 inhibitors [4]. The structural scaffold of 2-aminothaizole moiety has been established to have the molecular periphery to confer drug-like properties in diverse therapeutic areas including modulations of inflammation. Thiazole ring has also been indicated to be a substitute for phenyl in anti-inflammatory agents [5, 6], Figure 1 (1) is the minimum pharmacophoric requirement for the anti-inflammatory action [5]. In present study synthesis, and anti-inflammatory activity of 2-aminothiazole analogue maintaining the minimal pharmacophoric requirement for anti-inflammatory action is reported.

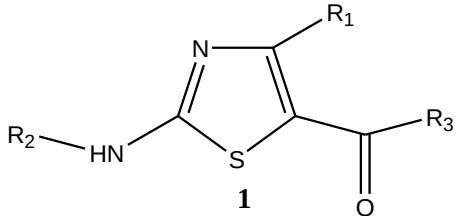

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Fig. 1: Minimal pharmacophoric requirement for anti-inflammatory activity

MATERIAL AND METHODS

Chemistry

Melting points were measured on Veego digital melting point apparatus. Mass spectra were recorded on Shimadzu LCMS 2010. IR spectra were recorded on a Shimadzu IR-Affinity 1 spectrometer. ^{1}H NMR Spectra were recorded on a Bruker Advance spectrometer 400 MHz; chemical shifts (δ scale) are reported in parts per million (ppm). 1H NMR Spectra are reported in order: number of protons, multiplicity and approximate coupling constant (*J* value) in hertz (Hz); signals were characterized as s (singlet), d (doublet), t (triplet), m (multiplet), br s (broad signal) and Ar (aryl). The ^{13}C NMR spectra were recorded at 100.6 MHz; chemical shifts (δ scale) are reported in parts per million (ppm). All the products are new compounds, which were characterized by IR, ^{1}H NMR and ^{13}C NMR spectra and Mass spectral data. The purity of the compound was checked by TLC using silica gel G. The general procedure for synthesis of Oxo-[2-(arylamino) -4-phenyl-thiazol-5-yl] -acetic acid ethyl esters are as follows 0.01moles of Thiourea derivatives 4 in 5 ml of acetonitrile was added to a stirred solution of 0.01moles of ethyl 3-chloro-2-Oxo-propanoate at room temperature. The reaction mixture was stirred at room temperature for 1 to 2 h. Pure product precipitated was filtered off and dried.

Comp. No. 6a. Oxo-[2-(4-Methoxy-benzoylamino)-4-phenyl-thiazol-5-yl)- acetic acid ethyl ester

% Yield: 63.50, Melting point: 194-196°C, Rf: 0.59 (Dichloromethane: Methanol-9.9:0.1), I.R. (cm $^{-1}$) 3055.24, 3024.38 (CH-str., Ar.), 2902.87, 2850.79, 2808.36 (C-H str., sp^3) 1720.50, 1618.28 (-C=O-str.), 1593.2, 1558.48, 1541.12, 1517.98, 1471.69 (C=C-str.). ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 1.281-1.317(t, 3H, CH_3CH_2OCO-, J=7.2Hz), 3.804 (s, 3H, OCH_3), 4.189-4.207 (m, 2H, CH_3CH_2OCO-, J=7.2Hz), 6.970-7.006 (m,2H, H-Ar), 7.181-7.204 (m, 2H, H-Ar), 7.258-7.426 (m, 5H, H-Ar), 9.840 (s, 1H, -NH) ^{13}C NMR: (100.6 MHz, $CDCl_3$) δ [ppm]: 13.90(-CH_3), 55.54(-OCH_3), 59.21(-CH_2-), 114.17, 123.39, 123.51, 128.11, 128.44, 128.69, 129.45, 129.94, 132.10, 134.94,140.96, 161.37 (Ar-C and C=O),170.66, 182.24 (C=O) . MS (ESI) (M+1): 411.15

Comp. No. 6b. Oxo-[2-(4-Methoxy-phenylamino)-4-phenyl-thiazol-5-yl]-acetic acid ethyl ester

% Yield: 66.50, Melting point: 204-206°C, Rf: 0.64 (Dichloromethane: Methanol-9.9:0.1), I.R. (cm $^{-1}$) 2950.67, 2850.79, (C-H str., sp^3) 1735.93, 1620.21 (-C=O-str.), 1560.41, 1517.98, 1508.33, 1477.47, 1458.18, 1436.97 (C=C-str.).^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 1.301-1.337(t, 3H, CH_3CH_2OCO-, J=7.2Hz), 3.830 (s, 3H, OCH_3), 4.214-4.232 (m, 2H, CH_3CH_2OCO-, J=7.2Hz), 6.838-6.860 (m,2H, H-Ar), 7.082-7.130 (m, 2H, H-Ar), 7.222-7.305 (m, 5H, H-Ar), 8.824 (s, 1H, -NH) ^{13}C NMR: (100.6 MHz, $CDCl_3$) δ [ppm]: 14.10 (-CH_3), 56.04, (-OCH_3) 59.24 (-CH_2-), 114.21, 123.41, 123.53, 128.13, 128.47, 128.72, 129.48, 129.97, 132.13, 134.97, 140.98, 161.39 (Ar-C and C=O),170.69, 182.27 (C=O) . MS (ESI) (M+1): 383.05

Comp. No. 6c. Oxo-(4-phenyl-2-0-tolylamino-thiazol-5-yl) - acetic acid ethyl ester

% Yield: 64.33, Melting point: 189-192°C, Rf: 0.59 (Dichloromethane: Methanol-9.9:0.1), I.R. (cm $^{-1}$) 3057.17, 3028.24 (CH-str., Ar.), 1718.58, 1651.00 (-C=O-str.), 1552.70, 1521.84, 1506.41, 1458.18, 1423.47 (C=C-str.).^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 1.314-1.350 (t, 3H, CH_3CH_2OCO-, J=7.2Hz), 2.220 (s, 3H, OCH_3), 4.193-4.207 (m, 2H, CH_3CH_2OCO-, J=7.2Hz), 7.176-7.540 (m, 9H, H-Ar), 8.650 (s, 1H, -NH) ^{13}C NMR: (100.6 MHz, $CDCl_3$) δ [ppm]: 13.73 (-CH_3), 17.66(-OCH_3),59.21 (-CH_2-), 114.23, 123.43, 123.55, 128.15, 128.49, 128.74, 129.50, 129.99, 132.15, 134.99, 140.97, 161.41 (Ar-C and C=O), 182.23 (C=O) . MS (ESI) (M+1): 367.05

Comp. No. 6d. Oxo-(4-phenyl-2-phenylamino-thiazol-5-yl)-acetic acid ethyl ester

% Yield: 61.21, Melting point: 225-227°C, Rf: 0.56 (Dichloromethane: Methanol-9.9:0.1), I.R. (cm $^{-1}$) 3067.80, 3029.41 (CH-str., Ar.), 2958.80, 2926.04(C-H str., sp^3) 1718.58, 1653.00 (-C=O-str.), 1589.34, 1556.55, 1506.41, 1492.90, 1463.97, 1452.40, 1423.47 (C=C-str.).^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 1.287-1.323 (t, 3H, CH_3CH_2OCO-, J=7.2Hz), 4.211-4.229 (m, 2H, CH_3CH_2OCO-, J=7.2Hz), 6.830-6.856 (m,2H, H-Ar), 7.079-7.128 (m, 4H, H-Ar), 7.222-7.308 (m, 4H, H-Ar), 8.824 (s, 1H, -NH) ^{13}C NMR: (100.6 MHz, $CDCl_3$) δ [ppm]: 13.77 (-CH_3), 59.26(-CH_2-), 113.84, 123.27, 123.42, 128.02, 128.36, 128.60, 129.37, 129.86, 132.02, 134.89,140.83,157.42 (Ar-C and C=O),182.32 (C=O) . MS (ESI) (M+1): 353.15

Comp. No. 6e. Oxo-[2-(2-methoxy-phenylamino)-4-phenyl-thiazol-5-yl)- acetic acid ethyl ester

% Yield: 63.61, Melting point: 177-179°C, Rf: 0.62 (Dichloromethane: Methanol-9.9:0.1), I.R. (cm $^{-1}$) 3005.10 (CH-str., Ar.), 2850.51(C-H str., sp^3), 1716.65, 1651.07 (-C=O-str.), 1558.48, 1498.69, 1458.18, 1435.04 (C=C-str.).^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 1.330-1.366 (t, 3H, CH_3CH_2OCO-, J=7.2Hz), 4.212-4.230 (m, 2H, CH_3CH_2OCO-, J=7.2Hz), 6.833-6.854 (m,2H, H-Ar), 7.081-7.126 (m, 4H, H-Ar), 7.221-7.302 (m, 3H, H-Ar), 8.831 (s, 1H, -NH) ^{13}C NMR: (100.6 MHz, $CDCl_3$) δ [ppm]: 13.79 (-CH_3), 56.07(-OCH_3) 59.26(-CH_2-), 113.80, 123.24, 123.45, 128.22, 128.46, 128.58, 129.41, 129.90, 132.00, 134.84,140.81,157.37 (Ar-C and C=O),182.38 (C=O) . MS (ESI) (M+1): 383.05

Comp. No. 6f. Oxo-(4-phenyl-2-p-tolylamino-thiazol-5-yl)- acetic acid ethyl ester

% Yield: 5611, Melting point: 187-189°C, Rf: 0.68(Dichloromethane: Methanol-9.9:0.1), I.R. (cm $^{-1}$) 2987.50(C-H str., sp^3), 1732.08 (-C=O-str.), 1558.48, 1510.26, 1471.69, 1436.97 (C=C-str.).^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 1.298-1.334 (t, 3H, CH_3CH_2OCO-, J=7.2Hz), 4.199-4.217 (m, 2H, CH_3CH_2OCO-, J=7.2Hz), 6.830-6.844 (m,2H, H-Ar), 7.086-7.136 (m, 4H, H-Ar), 7.203-7.306 (m, 3H, H-Ar), 8.252 (s, 1H, -NH) ^{13}C NMR: (100.6 MHz, $CDCl_3$) δ [ppm]: 13.86 (-CH_3), 22.07(CH_3) 59.22(-CH_2-), 113.78, 123.21, 123.46, 128.23, 128.49, 128.56, 129.44, 129.96, 132.06, 134.88,140.83,157.36 (Ar-C and C=O),182.52 (C=O) . MS (ESI) (M+1): 367.05

Comp. No. 6g. Oxo-[2-(4-bromo-phenylamino)-4-phenylamino-thiazol-5-yl]- acetic acid ethyl ester

% Yield: 59.15, Melting point: 193-195°C, Rf: 0.62(Dichloromethane: Methanol-9.9:0.1), I.R. (cm $^{-1}$) 3057.21, 3048.10 (CH-str., Ar.), 2980.23, 2956.10 (C-H str., sp^3), 1726.29 (-C=O-str.), 1595.13, 1573.91, 1525.69, 1510.26, 1465.90, 1436.92, 1419.61 (C=C-str.).

Biological Evaluation

Assay of Human Red Blood cell membrane stabilizing activity [7, 8, 9, 10]

The membrane stabilizing activity assay was carried out using 2% (v/v) human erythrocyte suspension while Diclofenac was used as standard drug. The assay mixtures consisted of 2 ml of hyposaline (0.25% w/v sodium chloride), 1.0 ml of 0.15 M sodium phosphate buffer, pH 7.4, 0.5 ml of 2% (v/v) Human erythrocyte suspension, 0.0 - 1.0 ml of drugs (standard, synthesized compounds in DMSO) and final reaction mixtures were made up to 4.5 ml with isosaline. Drugs were omitted in the blood control, while the drug control did not contain the erythrocyte suspension. The reaction mixtures were incubated at room temperature for 10 min, followed by centrifugation at 5000 rpm on Remi Centrifuge CM-12 for 10 min at room temperature. The absorbance of the released heamoglobin was read at 560 nm. The percentage membrane stability was estimated using the expression:

100 - {Abs of test drug-Abs of drug control} / {Abs of blood control} × 100

Where, the blood control represents 100% lysis or zero percent stability.

Carrageenin induced rat paw edema[11, 12, 13]

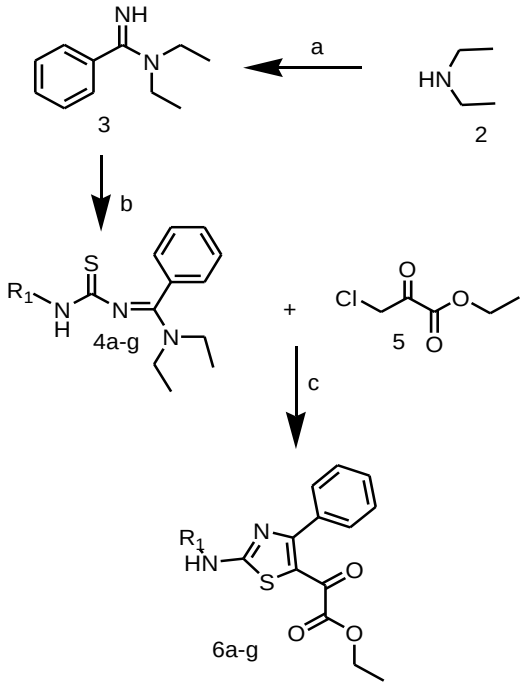
Wistar (male/female) rats weighing 150–250g were used for the edema test. Animals were divided into six rats per group. Rats were put on fast for 18h prior to the experiment. The standard drug, Diclofenac (5mg/kg body weight) and the test drugs (100mg/kg body weight) were given orally as a suspension, in 0.1% sodium CMC as vehicle. One hour later, 0.1ml of 1% carrageenan solution in saline was injected in the sub plantar region of the right hind paw of each rat. After 3h of the carrageenan injection, the reduction in the paw volume compared to vehicle control was measured using plethysmometer. The institutional ethics committee, constituted by the Ministry of Social Justice and Empowerment, Government of India, approved the experimental protocol.

RESULT AND DISCUSSION

Chemistry

The thiazole derivative were prepared according to the reported procedure. [14, 15] Diethylamine (2) was reacted with benzonitrile in the presence of aluminum chloride to form N, N diethyl benzamidine (3) (Scheme 1)[16]. Reaction of (3) with the appropriate isothiocyanate in acetone gave 4a–g.The final products, thiazole derivatives 6a–g, were prepared from 4a to 4g according to a protocol described by Rajappa et al [14]. The ethyl 3-chloro-2-oxo-propanoate were treated with 4a–g in acetonitrile to yield the desired Oxo-[2-(arylamino)-4-phenyl-thiazol-5-yl]-acetic acid ethyl esters 6a-g (Scheme 1) after reaction times of a few hours. the precipitated product was thus obtained.

Scheme 1



a) Bemzonitrile, $AlCl_3$, 0-8°C

b) R_1NCS, Acetone, 0°C

c) Acetonitrile (ACN), RT, ethyl 3-chloro-2-oxo-propanoate

Biological Evaluation

All of the 7 compounds synthesized were evaluated for their anti-inflammatory activity using *in vitro* Human Red Blood Cells (HRBC) Membrane stabilizing activity and *in vivo* model of acute inflammation, carrageenan induced rat paw edema test. Out of the 7 synthesized compounds 4 compounds exhibited significant ($p<0.001$) Human Red Blood Cells (HRBC) Membrane stabilizing activity at 100µg/ml and 200µg/ml concentration. These compounds exhibited significant protective activity in the carrageenan induced rat paw edema model as well (*in vivo*, 100 mg/kg, p.o.) in comparison to the existing anti-inflammatory drug Diclofenac (Table 1). On the basis of the biological activity exhibited by the designed series we can classify this set of compounds into two classes. (1) Compounds which showed significant activity both in, *in vitro* HRBC membrane stabilizing activity and *in vivo* carrageenan induced rat paw edema test, like 6a, 6b and 6f (Table 1). (2) Compounds like 6e (Table 1) which showed only HRBC membrane stabilizing activity and no activity in carrageenan induced rat paw edema test, and (3) Compounds which showed no activity both in, *in vitro* HRBC membrane stabilizing activity and *in vivo* carrageenan induced rat paw edema test, like 6c, 6d and 6g (Table 1).

The substituent selected for the synthesis of various compounds consisted of electron donating and electron withdrawing moieties. It is found that the compounds with substitution at the para position of phenylamino exhibited good anti-inflammatory activity, compounds 6a and 6b with para methoxy and 6f showed significant activity in both the *in vitro* and *in vivo* anti-inflammatory models, whereas compound 6c and 6e with ortho methyl and ortho methoxy substitution respectively showed no significant activity and the unsubstituted and compound with para bromo substitution, 6d and 6g respectively showed no activity at all. The results suggest that the electron donating group para methoxy and para methyl on the phenylamino at 2nd position of thiazole is important for the biological activity, whereas absence of this and electron withdrawing substituent gives a mild or less active agents.

Table 1: Effect of synthesized compounds (6a-6g) on Human Red Blood Cells (HRBC) Membrane stabilizing activity and carageenan induced rat paw edema

Compound	R_1	Paw volume (% Protection)[a] 100 mg/ kg)	% Stability[b] 100µg/ml	200µg/ml
6a	(p-OCH_3) C_6H_4CO-	1.51±0.02*(38.67)	22.58±0.62*	38.71±1.64*
6b	(p-OCH_3) C_6H_4	1.48±0.02*(40.16)	32.97±5.21*	46.95±5.21*
6c	(o-CH_3) C_6H_4	2.41±0.01(2.37)	7.89±4.23	4.30±1.86
6d	phenyl	2.43±0.02(1.35)	8.96±3.42	3.94±0.36
6e	(o-OCH_3) C_6H_4	2.18±0.01 (11.76)	29.39±4.40*	45.16±0.62*
6f	(p-CH_3) C_6H_4	1.63±0.02*(34.08)	32.62±2.93*	43.01±4.48*
6g	(p-Br) C_6H_4	2.43±0.01(1.35)	6.45±1.24	2.87±0.95
Diclofenac		1.22±0.01*(50.37)	63.41±1.31*	74.28±2.02 *

[a] Paw volume expressed in ml ± standard deviation (anti-inflammatory activity expressed as % protection).

b Human Red Blood Cells Membrane Stabilizing acitivity

*$p<0.001$ ANOVA

CONCLUSION

A new series of substituted thiazole analogues were designed, synthesized and characterized. The synthesized compounds 6a-6g were evaluated for their anti-inflammatory activity in HRBC membrane stabilizing activity and carrageenan-induced rat hind paw edema model. As the synthesized compounds have the structural features of TNF α inhibitors and the p38 MAP kinase inhibitor; the anti-inflammatory activity exhibited by the experimental candidates may be due to blocking of more than one rate limiting steps in the inflammatory cascade. In search of the optimum structural requirements for the anti-inflammatory activity around the thiazole scaffold it was possible to find, on the basis of SAR studies of target compounds, the electron donating substitution at the para position of phenyl of 2-phenylamino of thiazole which has showed a significant anti-inflammatory activity in both the models studied. The thiazole ring substituted by substituted arylamino at 2 position, phenyl at 3 position and Oxo acetic acid ethyl ester at the 5 position are the potential candidates for the anti-inflammatory activity. Though the relationship between the activities shown by these compounds in, *in vivo* and *in vitro* model is still to be established, these results suggest the suitability of the designed molecular framework as a potential anti-inflammatory lead. This will be worth studying further to explore its complete potential particularly in chronic inflammatory conditions.

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