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Inhibition of gastric H^+, K^+-ATPase by novel thiazolidinone derivatives

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In a program to identify new anti-ulcer compounds, a series of novel substituted thiazolidinone derivatives **5(a–j)** were synthesized and screened for their *in vitro* H^+, K^+-ATPase inhibitory activity. The synthesized compounds were characterized by nuclear magnetic resonance (^{1}H-NMR), liquid chromatography-mass spectrometry (LCMS) and fourier transform infrared (FTIR) analysis. We have briefly investigated the structure–activity relation (SAR) studies and reveal that the nature of position of the fluorine atom influences the anti-ulcer activity. Among the synthesized compounds **5b**, **5c** and **5e** showed 4 and 10-fold higher H^+, K^+-ATPase activity when compared with those of other derivatives **5a**, **5f**, **5g** and **5j**, respectively. H^+, K^+-ATPase activity of **5b**, **5c** and **5e** were comparable with those of known H^+, K^+-ATPase blocker lansoprazole which is a potential anti-ulcer drug.

Keywords: thiazolidinone; 5-(3-chlorophenyl)-furfural; alkyl halides; anti-ulcer; H^+, K^+-ATPase enzyme

1. Introduction

The peptic ulcer and related diseases encompass a broad spectrum of clinical disorders ranging from intense burning and pain to severe complications such as deep ulcers, strictures, etc. The mammalian stomach is a specialized organ of the digestive tract that serves to store and process the food for absorption by the intestine. The physiological studies (*1*) regarding acid secretory pathways have proved that the proton pump, being the ultimate mediator of acid secretion, is localized in a specialized acid secreting tubulovesicular system of the parietal cells in the gastric mucosa. Upon stimulation, however, this system undergoes various morphological changes accompanying oxygen consumption, which elicit an acid secretory response. Besides histamine, which acts through H_2-receptors as the major stimulant, gastric and acetylcholine also have receptors on the parietal cells (*2*).

The interest in thiazolidin-4-ones for medical applications is increasing strongly. (−)-2-(5-Carboxypentyl)-thiazolidin-4-one (actithiazic acid) isolated from the culture broth of a strain

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of streptomyces showed highly specific *in vitro* activity against *Mycobacterium tuberculosis* (*3a,b*). Other substituted thiazolidin-4-ones exhibit diverse biological activities such as anti-consultant (*4*), anti-diarrhea (*5*), anti-arthritic (*6*), anti-platelet activating factor activity (*7a–c*), anti-histaminic (*8a–c*), anti-microbial (*9a–c*), anti-diabetic (*10a,b*), oxygenase inhibitory (*11*), K^+ channel inhibitory (*12*), calcium antagonist (*13*), cardio-protective (*14*), antischemic activity (*15a,b*) and a promising agent for treating Alzheimer's (*10b*), cancer (*16*), AIDS (*17a,b*) and hepatitis B (*17a*). Among the tetrahydro-1,3-thiazin-4-ones, 2-(4-chlorophenyl)-3-methyl-tetrahydro-1,3-thiazin-4-one-1,1-dioxide (chloromezanone) is widely used as an anticoagulant (*18*), tranquilizer and for muscle spasms (*19*). Other derivatives showed a wide range activities, such as anti-microbial (*20a,b*), anti-arthritic (*21*), anti-rheumatic (*22*) and in the treatment of cardiac arrhythmia (*12*), peptic ulcers (*23*, *24*) and ocular inflammation (*25*). Recently, Masai *et al*. (*26*) reported pyridyl-thiazolidinone-4-one as a gastric H^+, K^+-ATPase inhibitor. In the course of our research into gastric H^+, K^+-ATPase inhibitors to develop effective anti-ulcer drugs, a series of synthetic compounds **5(a–j)** were synthesized.

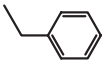
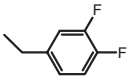
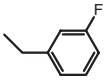
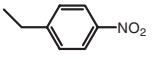
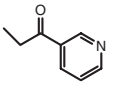
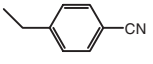
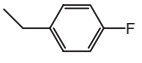
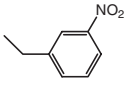
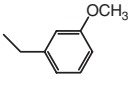
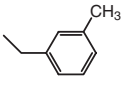
2. Results and discussion

We have determined the inhibition of H^+, K^+-ATPase by individual thiazolidinone derivatives **5(a–j)** that potentially inhibit the enzyme. Synthesized derivatives **5(a–j)** showed the maximum inhibitory effect in **5b** ($IC_{50} = 17.4 \pm 2.1\,\mu g/ml$), **5c** ($IC_{50} = 29.0 \pm 3.2\,\mu g/ml$), and **5e** ($IC_{50} = 18.3 \pm 2.9\,\mu g/ml$), followed by **5a** ($IC_{50} = 104.2 \pm 7.6\,\mu g/ml$), **5f** ($IC_{50} = 116.2 \pm 10.2\,\mu g/ml$), **5g** ($IC_{50} = 138.8 \pm 10.9\,\mu g/ml$) and **5j** ($IC_{50} = 300.0 \pm 22.5\,\mu g/ml$) (Table 1).

The H^+, K^+-ATPase enzyme, a prime component of the gastric proton pump responsible for acid secretion in the stomach, is located in the gastric membrane vesicle and catalyzes the electroneutral exchange of intracellular H^+ and extra cellular K^+ coupled with the hydrolysis of the cytoplasm ATP (*28*). Hyper-secretion of this enzyme in the stomach leads to acidity and ulcers. Therefore, this regulatory enzyme was found to be a pharmacological target for many anti-ulcer drugs. Synthesized thiazolidinone derivatives **5(a–j)** are known to inhibit gastric H^+, K^+-ATPase activity in a concentration-dependent manner (*26*). In the current study, we compared the H^+, K^+-ATPase activity of synthesised thiazolidinone derivatives **5(a–j)** with that of Lansoprazole. The concentration required to inhibit 50% of H^+, K^+-ATPase activity (IC_{50}), as calculated for **5b, 5c** and **5e**, showed a potential H^+, K^+-ATPase blocking activity with IC_{50} values of 17.3, 29.0 and 18.3 $\mu g/ml$, respectively, and the activity was compared with Lansoprazole (IC_{50} of $19.3 \pm 2.2\,\mu g/ml$), the known proton pump inhibitor. Some of the new derivatives **5a**, **5f** and **5g** showed 4-fold lower activity and compound **5a** showed a 10-fold reduction in activity when compared with **5b–e**. Derivatives **5d**, **5h** and **5i** did not show any activity. Thus, the thiazolidinone derivatives **5b**, **5c** and **5e** were determined to be good inhibitors of the enzyme. The inhibition could be due to the electron-withdrawing fluorine groups at the third and fourth positions in **5b**, electron-withdrawing fluorine groups at the third position in **5c** and a pyridine moiety attached to thiazolidinone in **5e** upon binding to the ATPase enzyme. In contrast, an electron-deficient heterocycle such as pyridine (**5e**) maintains interesting levels of anti-ulcer activity. However, electron-donating groups such as methoxy or methyl on the phenyl ring of thiazolidinone derivatives **5i** and **5j** reduces the activity.

Close inspections of the results reveal some interesting facts with respect to SAR studies. Introduction of an electron-deficient acetylpyridine group at the N-position in **5e** led to a more active compound. Shifting the fluorine group at the *meta* position of **5c** to the *para* position of **5g** completely suppressed the activity. On the contrary, introduction of an additional fluorine group at *meta* and *para* positions in **5b** had the most potent anti-ulcer activity when compared with monosubstituted **5c** and **5g** compounds. Replacing electron-withdrawing groups such as cyano (**5f**) and nitro (**5h**) resulted in a great reduction in the activity. Finally, replacing the

Table 1. Chemical structure, yield and melting point of the synthesized compounds **5(a–j)**.

Compound	R_1	Yield (%)	MP (°C)	IC_{50} (μg/ml)
5a		74	172–174	104.2 ± 7.6
5b		79	166–168	17.4 ± 2.1
5c		83	174–176	29.0 ± 3.2
5d		88	198–200	[a]
5e		76	154–156	18.3 ± 2.9
5f		82	130–132	116.2 ± 10.2
5g		76	168–170	138.8 ± 10.9
5h		73	161–163	[a]
5i		80	169–171	[a]
5j		77	163–165	300 ± 22.5
Lansoprazole	–	–	–	19.3 ± 2.2

Note: [a]No significant activity.

electron-withdrawing (**5b**,**c**) by electron donating groups (**5i**, **5j**) on to the phenyl ring decreased the activity.

Preeti *et al*. (*29*) discussed 3D quantitative SAR (QSAR) studies, which led to the identification of essential structural features for gastric proton pump inhibitory activity in terms of the physicochemical properties and their spatial dispositions, and that the carbonyl oxygen atoms and the nitrogen atom of compounds in proper spatial disposition are essential and crucial for the activity of compounds. Thiazolidinone derivatives **5b**, **5c** and **5e** possess these two carbonyl oxygen and nitrogen atoms and showed potent H^+, K^+-ATPase inhibitory activity.

3. Conclusion

The aim of the present research work was to synthesize some novel substituted thiazolidinones and to evaluate their H^+, K^+-ATPase inhibitory properties. Successful arrangements of functional groups are responsible for bioactivity. Synthesis of 10 novel thiazolidinones **5(a–j)**, bearing an aryl substitution at N-position, in addition to the generation of closely related structures enable us to identify precisely the structure function activity of the H^+, K^+-ATPase enzyme. SAR studies, with various chemical groups, reveal that the position and nature of the substitution

on the phenyl ring of thiazolidinones are crucial for H^+, K^+-ATPase inhibition. It is possible that the generated compounds may involve different routes in ulcer inhibition. Hence, there is a need for further investigation to clarify the underlying mechanism of these potential anti-ulcer properties.

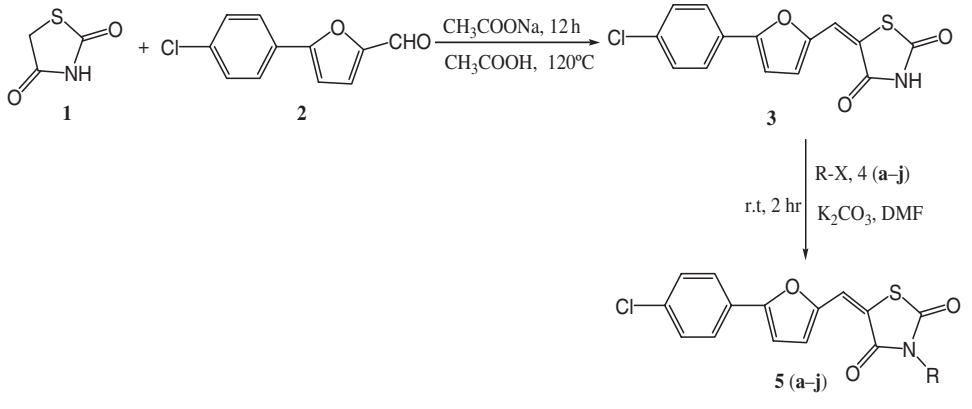
4. Experimental

Melting points were determined using SELACO-650 hot stage melting point apparatus and were uncorrected. Infrared (IR) spectra were recorded using a Jusco FTIR-4100 series. ^{1}H-NMR spectra were recorded on a Shimadzu AMX 400-Bruker, 400 MHz spectrometer using DMSO-d_6 as a solvent and TMS as the internal standard (chemical shift in δ ppm). Spin multiples are given as s (singlet), d (doublet), t (triplet) and m (multiplet). Mass and purity were recorded on a LC-MSD-Trap-XCT. Silica gel column chromatography was performed using Merck 7734 silica gel (60-120 mesh) and Merck-made TLC plates.

4.1. *Synthesis*

4.1.1. *Synthesis of compound 5-((5-(4-chlorophenyl)furan-2-yl)methylene) thiazolidine-2,4-dione **3***

A mixture of thiazolidine-2,4-dione **1** (1.0 g, 8.5 mmol), 5-(3-chloro phenyl)-furfural **2** (1.75 g, 8.5 mmol) and anhydrous sodium acetate (2.1 g, 25.6 mmol) were taken in 10 ml of glacial acetic acid. The reaction mixture was heated to 120 °C in an oil bath for 12 h. The progress of the reaction was monitored by thin-layer chromatography (TLC). Then the reaction mixture was cooled, filtered and washed with ether to finally get a reddish solid compound (2.10 g, 81%). The absence of $-$CHO and $-CH_2$ proton peak and the presence of $-$CH proton peak confirms the formation of compound **3**. The schematic representation of the synthesized compound is shown in Scheme 1. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 12.56 (bs, 1H, $-$NH), 7.92 (s, 1H, =CH), 7.60 (d, 2H, $J = 8.2$ Hz, Ar-H), 7.55 (d, 2H, $J = 8.1$ Hz, Ar-H), 7.35 (d, 1H, $J = 8.2$ Hz, Ar-H), 6.83 (d, 1H, $J = 8.1$ Hz, Ar-H). IR (KBr, cm^{-1}): 3318, 1636, 1609, 1329, 1207, 806.



Scheme 1. Synthesis of 5-((5-(4-chlorophenyl)furan-2-yl)methylene)thiazolidine-2,4-dione derivatives.

4.1.2. *General procedure for synthesis of 5-((5-(4-chlorophenyl)furan-2-yl)methylene) thiazolidine-2,4-dione derivatives **5(a–j)***

A solution of 5-((5-(4-chlorophenyl)furan-2-yl)methylene)thiazolidine-2,4-dione **3** (1.0 eq) in dry DMF was taken and cooled to 0–5 °C in an ice bath. Anhydrous potassium carbonate (3 eq) was added to the cold mixture and stirred for 10 min. Different alkyl halides (1.1 eq) were added, and the mixture was stirred at room temperature for 2 h. The progress of the reaction was monitored by TLC. When the reaction was completed, water was added to the reaction mixture and extracted with ethyl acetate. The organic layer was washed with water and dried with anhydrous sodium sulfate. The solvent was evaporated and the crude product obtained was purified by column chromatography over silica gel (60–120 mesh) using hexane: ethyl acetate (8:2) as an eluent. The absence of –CO-NH and the presence of $=N-CH_2-$ proton peak in synthesized derivatives **5(a–j)** in ^{1}H-NMR and IR spectra confirm the identity of the products. The chemical structures and physical data of all the synthesized compounds are given in Table 1.

4.1.3. *Synthesis of 3-benzyl-5-((5-(4-chlorophenyl)furan-2-yl)methylene) thiazolidine-2,4-dione **5a***

The product obtained was a pale yellow solid from 5-((5-(4-chlorophenyl)furan-2-yl) methylene)thiazolidine-2,4-dione **3** (0.1 g, 0.32 mmol), benzyl bromide **4a** (0.06 g, 0.35 mmol) and K_2CO_3 (0.132 g, 0.98 mmol). ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 7.95 (s, 1H, =CH), 7.82 (dd, 4H, $J = 8.2$ Hz, Ar-H), 7.60 (m, 5H, Ar-H), 7.01 (d, 1H, $J = 8.1$ Hz, Ar-H), 6.65 (d, 1H, $J = 8.0$ Hz, Ar-H), 5.14 (s, 2H, $-CH_2$). MS (ESI) m/z: 396.04 ($M + H^+$). IR (KBr, cm^{-1}): 1605, 1335, 1253, 1190, 1056, 1030, 778.

4.1.4. *Synthesis of 3-(3,4-difluorobenzyl)-5-((5-(4-chlorophenyl)furan-2-yl)methylene) thiazolidine-2,4-dione **5b***

The product obtained was a pale yellow solid from 5-((5-(4-chlorophenyl)furan-2-yl) methylene)thiazolidine-2,4-dione **3** (0.1 g, 0.32 mmol), 3,4-difluoro benzyl bromide **4b** (0.074 g, 0.35 mmol) and K_2CO_3 (0.132 g, 0.98 mmol). ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 8.01 (s, 1H, =CH), 7.75 (dd, 4H, $J = 8.3$ Hz, Ar-H), 7.65 (m, 3H, Ar-H), 7.10 (d, 1H, $J = 8.0$ Hz, Ar-H), 6.65 (d, 1H, $J = 8.1$ Hz, Ar-H), 5.50 (s, 2H, $-CH_2$). MS (ESI) m/z: 432.04 ($M + H^+$). IR (KBr, cm^{-1}): 1615, 1607, 1331, 1190, 1030, 753, 593.

4.1.5. *Synthesis of 3-(3-fluorobenzyl)-5-((5-(4-chlorophenyl)furan-2-yl)methylene) thiazolidine-2,4-dione **5c***

The product obtained was a pale yellow solid from 5-((5-(4-chlorophenyl)furan-2-yl) methylene)thiazolidine-2,4-dione **3** (0.1 g, 0.32 mmol), 3-fluoro benzyl chloride **4c** (0.052 g, 0.35 mmol) and K_2CO_3 (0.132 g, 0.98 mmol). ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 7.95 (s, 1H, =CH), 7.73 (dd, 4H, $J = 8$ Hz, Ar-H), 7.60 (m, 4H, Ar-H), 7.03 (d, 1H, $J = 8.1$ Hz, Ar-H), 6.62 (d, 1H, $J = 8.0$ Hz, Ar-H), 5.32 (s, 2H, $=CH_2$). MS (ESI) m/z: 414.03 ($M + H^+$). IR (KBr, cm^{-1}): 1657, 1611, 1502, 1329, 1209, 754, 682.

4.1.6. *Synthesis of 3-(4-nitrobenzyl)-5-((5-(4-chlorophenyl)furan-2-yl)methylene) thiazolidine-2,4-dione **5d***

The product obtained was a pale yellow solid from 5-((5-(4-chlorophenyl)furan-2-yl) methylene)thiazolidine-2,4-dione **3** (0.1 g, 0.32 mmol), 4-nitro benzyl chloride **4d** (0.06 g,

0.35 mmol) and K_2CO_3 (0.132 g, 0.98 mmol). ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 8.11 (s, 1H, =CH), 7.83 (dd, 4H, J = 8.1 Hz, Ar-H), 7.61 (d, 2H, J = 8.0 Hz, Ar-H), 7.45 (d, 2H, J = 8.1 Hz, Ar-H), 7.1 (d, 1H, J = 8.0 Hz, Ar-H), 6.7 (d, 1H, J = 8.1 Hz, Ar-H), 5.5 (s, 2H, $-CH_2$). MS (ESI) m/z: 441.02 ($M + H^+$). IR (KBr, cm^{-1}): 1657, 1608, 1547, 1317, 1201, 753, 667.

4.1.7. *Synthesis of 5-((5-(4-chlorophenyl)furan-2-yl)methylene)-3-(2-oxo-2-(pyridin-3-yl) ethyl)thiazolidine-2,4-dione **5e***

The product obtained was a pale yellow solid from 5-((5-(4-chlorophenyl)furan-2-yl) methylene)thiazolidine-2,4-dione **3** (0.1 g, 0.32 mmol), 3-acetyl bromo pyridine **4e** (0.1 g, 0.35 mmol) and K_2CO_3 (0.132 g, 0.98 mmol). ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 8.05 (s, 1H, =CH), 7.83 (m, 4H, J = 8.2 Hz, Ar-H), 7.70 (dd, 4H, J = 8.0 Hz, Ar-H), 7.03 (d, 1H, J = 8.0 Hz, Ar-H), 6.65 (d, 1H, J = 8.1 Hz, Ar-H), 4.81 (s, 2H, $-CH_2$). MS (ESI) m/z: 425.03 ($M + H^+$). IR (KBr, cm^{-1}): 1633, 1413, 1330, 1191, 1023, 778.

4.1.8. *Synthesis of 4-((-5-((5-(4-chlorophenyl)furan-2-yl)methylene)-2,4-dioxothiazolidin-3-yl)methyl)benzonitrile **5f***

The product obtained was a pale yellow solid from 5-((5-(4-chlorophenyl)furan-2-yl) methylene)thiazolidine-2,4-dione **3** (0.1 g, 0.32 mmol), 4-cyano benzyl bromide **4f** (0.064 g, 0.35 mmol) and K_2CO_3 (0.132 g, 0.98 mmol). ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 7.95 (s, 1H, =CH), 7.87 (dd, 4H, J = 8.2 Hz, Ar-H), 7.75 (dd, 4H, J = 8.1 Hz, Ar-H), 7.20 (d, 1H, J = 8.0 Hz, Ar-H), 6.71 (d, 1H, J = 8.1 Hz, Ar-H), 5.23 (s, 2H, $-CH_2$). MS (ESI) m/z: 421.03 ($M + H^+$). IR (KBr, cm^{-1}): 1634, 1413, 1330, 1191, 1054, 778, 593.

4.1.9. *Synthesis of 3-(4-fluorobenzyl)-5-((5-(4-chlorophenyl)furan-2-yl)methylene) thiazolidine-2,4-dione **5g***

The product obtained was pale yellow solid from 5-((5-(4-chlorophenyl)furan-2-yl)methylene) thiazolidine-2,4-dione **3** (0.1 g, 0.32 mmol), 4-fluoro benzyl chloride **4g** (0.052 g, 0.35 mmol) and K_2CO_3 (0.132 g, 0.98 mmol). ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 7.96 (s, 1H, =CH), 7.83 (dd, 4H, J = 8.1 Hz, Ar-H), 7.75 (d, 2H, J = 8.0 Hz, Ar-H), 7.50 (d, 2H, J = 8.2 Hz, Ar-H), 7.35 (d, 1H, J = 8.1 Hz, Ar-H), 6.67 (d, 1H, J = 8.2 Hz, Ar-H), 5.54 (s, 2H, $-CH_2$). MS (ESI) m/z: 414.03 ($M + H^+$). IR (KBr, cm^{-1}): 1641, 1607, 1414, 1329, 1192, 675, 595.

4.1.10. *Synthesis of 3-(3-nitrobenzyl)-5-((5-(4-chlorophenyl)furan-2-yl)methylene) thiazolidine-2,4-dione **5h***

The product obtained was a pale yellow solid from 5-((5-(4-chlorophenyl)furan-2-yl) methylene)thiazolidine-2,4-dione **3** (0.1 g, 0.32 mmol), 3-nitro benzyl chloride **4h** (0.056 g, 0.35 mmol) and K_2CO_3 (0.132 g, 0.98 mmol). ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 8.18 (s, 1H, =CH), 7.91 (d, 2H, J = 8.3 Hz, Ar-H), 7.85 (dd, 4H, J = 8.2 Hz, Ar-H), 7.65 (m, 3H, Ar-H), 7.41 (d, 1H, J = 8.0 Hz, Ar-H), 6.70 (d, 1H, J = 8.0 Hz, Ar-H), 5.60 (s, 2H, $-CH_2$). MS (ESI) m/z: 421.02 ($M + H^+$). IR (KBr, cm^{-1}): 1615, 1562, 1513, 1246, 1028, 746, 614.

4.1.11. *Synthesis of 3-(3-methoxybenzyl)-5-((5-(4-chlorophenyl)furan-2-yl)methylene) thiazolidine-2,4-dione **5i***

The product obtained was a pale yellow solid from 5-((5-(4-chlorophenyl)furan-2-yl) methylene)thiazolidine-2,4-dione **3** (0.1 g, 0.32 mmol), 3-methoxy benzyl chloride **4i** (0.054 g,

0.35 mmol) and K_2CO_3 (0.132 g, 0.98 mmol). ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 7.95 (s, 1H, =CH), 7.82 (dd, 4H, $J = 8.2$ Hz, Ar-H), 7.76 (m, 3H, Ar-H), 7.65 (d, 2H, $J = 8.2$ Hz, Ar-H), 7.35 (d, 1H, $J = 8.1$ Hz, Ar-H), 6.62 (d, 1H, $J = 8.0$ Hz, Ar-H), 5.50 (s, 2H, $-CH_2$), 3.86 (s, 3H, $-OCH_3$). MS (ESI) m/z: 426.05 ($M + H^+$). IR (KBr, cm^{-1}): 1626, 1609, 1482, 1173, 847, 752.

4.1.12. *Synthesis of 3-(3-methylbenzyl)-5-((5-(4-chlorophenyl)furan-2-yl)methylene) thiazolidine-2,4-dione* ***5j***

The product obtained was a pale yellow solid from 5-((5-(4-chlorophenyl)furan-2-yl) methylene)thiazolidine-2,4-dione **3** (0.1 g, 0.32 mmol), 3-methyl benzyl chloride **4j** (0.05 g, 0.35 mmol) and K_2CO_3 (0.132 g, 0.98 mmol). ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 7.93 (s, 1H, =CH), 7.82 (dd, 4H, $J = 8.3$ Hz, Ar-H), 7.75 (m, 3H, Ar-H), 7.66 (d, 2H, $J = 8.2$ Hz, Ar-H), 7.41 (d, 1H, $J = 8.2$ Hz, Ar-H), 6.70 (d, 1H, $J = 8.0$ Hz, Ar-H), 5.55 (s, 2H, $-CH_2$), 3.55 (s, 3H, $-CH_3$). MS (ESI) m/z: 410.05 ($M + H^+$). IR (KBr, cm^{-1}): 1636, 1620, 1325, 1208, 659, 589.

4.2. *Inhibition of gastric H^+, K^+-ATPase activity*

Fresh sheep stomach was obtained from a local slaughterhouse in Mysore, India. The mucosa of gastric fundus was cut off and the inner layer was scraped for parietal cells (*27*), which were homogenized in 16 mM Tris buffer (pH 7.4) containing 10% Triton X-100 and centrifuged at 6000*g* for 10 min. The supernatant (enzyme extract) was used for the assay. Protein content was determined according to Bradford's method using BSA as the standard.

The enzyme extract (350 g/ml) was incubated with different fractions of synthesized novel substituted thiazolidinones **5**(**a**–**j**), in a reaction mixture containing 16 mM Tris buffer (pH 6.5), and the reaction was initiated by adding substrate 2 mM ATP, in addition to 2 mM $MgCl_2$ and 10 mM KCl. After 30 min of incubation at 37 °C, the reaction was stopped by the addition of assay mixture containing 4.5% ammonium molybdate and 60% perchloric acid. Inorganic phosphate formed was measured spectrophotometrically at 400 nm. Enzyme activity was calculated as micromoles of P_i released per hour at doses (10–50 μg/ml) of synthesized novel substituted thiazolidinones. The results were compared with the known anti-ulcer proton potassium ATPase inhibitor drug Lansoprazole.

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