academicJournals

Vol. 9(7), pp. 209-222, 22 February, 2015
DOI: 10.5897/AJPP2014. 4261
Article Number: E2973CD51240
ISSN 1996-0816

http://www.academicjournals.org/AJPP

African Journal of Pharmacy and Pharmacology

Full Length Research Paper

Synthesis, *in-vitro*, *in-vivo* evaluation and molecular docking of 2-(3-(2-(1, 3-dioxoisoindolin-2-yl) acetamido)-4-oxo-2-substituted thiazolidin-5-yl) acetic acid derivatives as anti-inflammatory agents

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Received 30 December, 2014; Accepted 21 January, 2015

A series of novel 2-(3-(2-(1,3-dioxoisoindolin-2-yl) acetamido)-4-oxo-2-phenylthiazolidin-5-yl) acetic acid (5a-l) have been synthesized by cyclocondensation of *N*-substituted benzylidene/methylene-2-(1,3-dioxo isoindolin-2-yl) acetohydrazide (4a-l) with mercapto succinic acid in dimethylformamide (DMF) as solvent and using anhydrous zinc chloride as a catalyst in microsynth microwave reactor. The synthesized compounds were evaluated for anti-inflammatory activity using *in vitro* and *in vivo* model. Furthermore, ulcerogenic toxicity study was performed for selected compounds. All the compounds have shown promising anti-inflammatory activity in both the models. Docking studies were performed to know the binding affinity towards the human serum albumin (HSA).

Key words: Thiazolidinone, microwave assisted, anti-inflammatory, protein denaturation, rat paw edema, molecular docking.

INTRODUCTION

Non steroidal anti-inflammatory drugs (NSAIDs) are one of the most commonly used therapeutically important agents for the treatment of pain, fever and inflammation (Madhukar et al., 2010). The usefulness of these agents is limited due to the side effects like gastric ulceration (Lombardino, 1985), gastro intestinal (GI) bleeding (Pilotto et al., 1997) and suppression of renal function (Pirson et al., 1986), and these side effects are related to their intrinsic mechanism of action.

From the literature survey, it was observed that both phthalimide and thiazolidinone derivatives are potentially useful as anti-inflammatory agents (Pawar and Chavan, 2012; Bhalgat et al., 2011; Bosquesi et al., 2011; Pophale and Deodhar, 2010; Machado et al., 2005; Alanazi et al., 2015; Vigorita et al., 2002; Ottana et al., 2005; Bhat and Kumar, 2008; Amin et al., 2010; Unsal et al., 2012; Hu et

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al., 2013; Singh et al., 2014; Thomas et al., 2013; Ahmed et al., 2013). Thiazolidinone scaffold is very versatile and is present in a number of clinically used drugs. They have varied applications as antimicrobial activity (Balzarini et al., 2007), anti-HIV activity (Monforte, 2001), antimalarial activity (Solomon et al., 2013), anti cancer activity (Gududuru et al., 2004) and antiarrhythmic activity (Jackson et al., 2007). Furthermore, it was observed that aryl acetic acid and α-methyl aryl acetic acid derivatives have high degree of potency as anti- inflammatory agents. In the present work, our objective was to design and synthesize a series of novel acetic acid derivatives containing thiazolidinone ring and couple this moiety with phthalimide ring (dioxoisoindoline) through the amide linkage so as to get the coupled derivatives with enhanced bioactivity. The compounds were designed such that -CH_2COOH group is at C5 position of thiazolidinone ring, various alkyl/aryl/heteryl groups at C2 position of thiazolidinone ring.

We report here the synthesis, docking studies, anti inflammatory activity and ulcerogenic toxicity of these novel thiazolidinone-5-yl acetic acid analogues. The anti-inflammatory activity was assessed, *in silico*, to know the binding and affinity towards the human serum albumin (HSA), *in vivo* by using carrageenan induced rat paw edema model, *in vitro* through protein denaturation inhibition assay using albumin.

EXPERIMENTALS

All chemicals were purchased from commercial suppliers and used without further purification. Nuclear magnetic resonance (NMR) spectra were recorded on a VARIAN MERCURY YH 300 Spectrometer at 300MHz. Chemical shifts are reported in parts per million (ppm), using TMS as an internal standard and $CDCl_3$ as a solvent. ^{13}C spectra were recorded on AVANCE spectrometer at 300 MHz using $CDCl_3$ as a solvent. Infrared (IR) spectra were recorded for the compounds on JASCO Fourier transform infrared spectroscopy (FTIR) (PS 4000) using KBr pallet, mass spectra were recorded on GC-AccuTOF GC- high resolution, EI system. The homogeneity of the compounds was monitored by ascending thin layer chromatography (TLC) on silica gel-G (Merck) coated aluminum plates, visualized by iodine vapor. Elemental analyses (C, H, and N) were undertaken with a Shimadzu's FLASHEA112 analyzer and all analyses were consistent with theoretical values (within ± 0.4%) unless indicated. Digital plethysmometer (Ugo Basil 7140, Italy) was used for evaluation of anti-inflammatory activity.

General procedure for the preparation of N-substituted benzylidene/methylene-2-(1, 3-dioxo isoindolin-2-yl) acetohydrazides (4a-l)

2-(1, 3-Dioxoisoindolin-2-yl) acetic acid 1 was obtained by the reaction of phthalic anhydride (0.05 mol) with glycine (0.05 mol) (Furniss et al., 1998). Ethyl 2-(1,3-dioxoisoindolin-2-yl) acetate 2 was synthesized by refluxing 2-(1,3-Dioxoisoindolin-2-yl) acetic acid with conc. H_2SO_4 in ethanol for 2hrs by conventional route (Amir and Shikha, 2004) in preparation of 2-(1,3-dioxoisoindolin-2-yl) acetohydrazide 3. The drawback of conventional method was lump formation upon refluxing and time required was 6 to 8 h. Therefore, to avoid lump formation, reaction was carried out at room temperature with continuous stirring and adding hydrazine hydrate to the compound 2 in ethanol. The Schiff bases were obtained by condensing aldehyde (0.03 mol) with compound 3 in ethanol for 6 to 8 h, in presence of glacial acetic acid (0.06 mol) as catalyst. Products were recrystallized with ethanol. The other compounds 4(a-l) were prepared similarly by treating with various substituted aliphatic, aromatic and heterocyclic aldehydes.

General procedure for the preparation of 2-(3-(2-(1,3-dioxoisoindolin-2-yl) acetamido)-4-oxo-2-substituted thiazolidin-5-yl) acetic acid 5(a-l)

Phthalic anhydride (2.96 g, 0.02 mol) and glycine (1.5 g, 0.02 mol) were suspended in glacial acetic acid (20 ml). The suspension was refluxed for 8 h on water bath and then cooled to room temperature. The completion of reaction was monitored by thin layer chromatography (TLC). The cooled mixture was poured into ice water (20 ml). The resulting product (1) was filtered, washed with water and dried. The solid was recrystallized from hot water. The melting point and yield were recorded. Alternatively, when mixture of phthalic anhydride (2.96 g, 0.02 mol) and glycine (1.5 g, 0.02 mol) was irradiated in Erlenmeyer flask in microwave oven for 30 min at high power, 700 W, after cooling the reaction mixture was poured in cold water to obtain 2-(1,3-Dioxoisoindoline-2-yl)acetic acid compound (1). The solid was recrystallized from hot water. The melting point and yield were recorded. Melting point (MP) is 194 to 196°C. Yield: Conventional - 89%; Microwave - 98%.

Compound (1) and Conc. H_2SO_4, both 0.01 mol, were refluxed in ethanol for 2 h. The reaction was monitored by TLC. The cooled mixture was poured into 100 ml ice water. The solid obtained was filtered, washed with saturated sodium bicarbonate solution, followed by washing with water and dried to get compound ethyl -(1,3-dioxoisoindoline-2-yl)acetate (2). It was recrystallized from ethanol and MP was recorded 121°C, yield 89%. This compound (0.01 mol) was stirred in absolute ethanol and hydrazine hydrate (0.02 mol) was added drop wise with constant stirring for 1 h at room temperature. The solid appeared is 2-(1,3-dioxoisoindolin-2-yl) acetohydrazide (3) was filtered, dried and recrystallized from rectified spirit and melting point was recorded as 176°C, yield 87%.

Equimolar quantities of (3) and various aliphatic/and aromatic aldehyde (0.01 mol) were refluxed in absolute ethanol (25 ml) for 6 to 8 h, in presence of few drops of glacial acetic acid as a catalyst. The completion of reaction was monitored by TLC. The reaction mixture was concentrated and poured into ice cold water. The obtained solid was filtered and washed with saturated solution of sodium meta bisulphate to remove any traces of un reacted aldehyde, then washed with water and dried and the compound (4) thus obtained was recrystallized by ethanol. Similarly, other derivatives of *N*-substituted benzylidene/methylene-2-(1,3-dioxoisoindolin-2-yl) acetohydrazide 4(a-l) were prepared. The data for yield and melting point for these compounds were as follows: 4a- 72%, 226°C, 4b- 76%, 232°C, 4c- 89% 218°C, 4d- 80%, 210°C, 4e- 72%, 237°C, 4f- 85%, 296°C, 4g- 87%, 224°C, 4h- 87%, 200°C, 4i- 83%, 254°C, 4j- 85%, 240°C, 4k- 79%, 192°C , 4l- 85%, 274°C.

The final derivatives, 2-(3-(2-(1,3-dioxoisoindolin- 2-yl) acetamido)-4-oxo-2-substituted thiazolidin-5-yl) acetic acid 5(a-l) were obtained under microwave irradiation by cyclo-condensation of *N*-substituted benzylidene/methylene-2-(1,3-dioxoisoindolin-2-yl) acetohydrazide (4) taken 0.01 mol with mercapto succinic acid (0.015 mol) in 20 ml DMF as solvent and anhydrous zinc chloride, as catalyst in Microsynth microwave reactor for about 14 to 17 min (700 W) at 80°C. After completion of reaction (monitored by TLC), the mixture was poured into ice cold water. The solid product formed was filtered, dried and recrystallized by ethanol. The yield and melting point were recorded.

2-(3-(2-(1, 3-Dioxoisoindolin-2-yl)acetamido)-2-methyl-4-oxothiazolidin-5-yl)acetic acid (5a)

IR (KBr): *v*/cm^{-1}, 3500 (OH of carboxyl), 3251 (NH of amide), 3021 (C-H of aromatic), 2975 (C-H of alkyl), 1768 (C=O of thiazolidinone), 1725-1728 (C=O of Phthalimide),1716(C=O of carboxyl), 1664(C=O of Amide),746 (C-S).1H NMR (CDCl3, 300 MHz) δ ppm: 10 (s, 1H, OH), 8.0-8.2(s, 1H, NH), 7.2-7.4 (m, 4H Ar-H), 5.0(s, 2H, -CH_2), 4.3-4.6(quar, 1H, -CH), 3.4-3.6(t, 1H,-CH), 2.6-2.8(d, 2H, -CH_2), 1.5 (s, 3H, CH_3). ^{13}CNMR (CDCl3, 300 MHz) δ ppm: 175.3 (carboxyl group), 173.0 (carbonyl of thiazolidinone ring), 170.3 (carbonyl of amide), 168.2 (two peaks carbonyl carbons of phthalimide ring),132.2, 132.0, 123.7 (aromatic ring carbon), 50.2 (-CH of thiazolidinone ring) 50.1 (-CH_2 near amide group) 39.2 (-CH_2 attached to carboxyl), 25.2 (-CH_3 of thiazolidinone ring).MS m/z %: M+ 377 100%, M+1 378 19.6%, 362 M-CH_3, 303, 203, 161(base peak). Anal. Calcd. for $C_{16}H_{15}N_3O_6$ S: C, 50.92; H, 4.01; N, 11.13, Found: C, 50.96 H, 4.04 N, 11.17.

2-(3-(2-(1,3-Dioxoisoindolin-2-yl)acetamido)-2-ethyl-4-oxothiazolidin-5-yl)acetic acid (5b)

IR (KBr): *v*/cm^{-1}, 3498 (OH of carboxyl), 3341(NH of amide), 3021 (C-H of aromatic),2901(C-H of alkyl) 1788(C=O of thiazolidinone), 1728(C=O of carboxyl)1724,1720 (C=O of Phthalimide), 1656 (C=O of Amide),749(C-S).1H NMR (CDCl3, 300 MHz) δ ppm: 10.1 (s, 1H, OH), 7.2-7.6(m, 4H, Ar-H), 7.68(s, 1H,-NH), 5.2(t, 1H,), 4.7(t, 1H, thiazolidinone ring), 4.3(s, 2H), 2.6-2.45 (d, 2H), 1.92(q, 2H, CH_2), 0.95(t, 3H, CH_3). ^{13}CNMR (CDCl3, 300 MHz) δ ppm: 175.3 (carboxyl group),173.0(carbonyl of thiazolidinone ring), 170.3(carbonyl of amide), 168.2(two peaks carbonyl carbons of phthalimide ring),132.2, 132.0, 123.7 (aromatic ring carbon), 61.0 , 47.6 (-CH of thiazolidinone ring) 50.1 (-CH_2 near amide group) 39.2 (-CH_2 attached to carboxyl), 28.6, 7.6 (-CH_2CH_3 of thiazolidinone ring).MS m/z: 391.08 100%, M+1:392.09 18.2%, 393.08 4.7%, 161. Anal. Calcd. for $C_{17}H_{17}N_3O_6$: S C, 52.17; H, 4.38; N, 10.74; Found: C, 52.13;H,4.34; N,10.71.

2-(3-(2-(1,3-Dioxoisoindolin-2-yl)acetamido)-4-oxo-2-phenylthiazolidin-5-yl)acetic acid (5c)

IR (KBr): *v*/cm^{-1}, 3528(OH of carboxyl), 3128 (NH of amide), 3011(C-H of aromatic) 2985(C-H of alkyl), 1760(C=O of thiazolidinone), 1733-1721 (C=O of Phthalimide), 1723(C=O of carboxyl), 1685(C=O of Amide), 737(C-S). 1H NMR (CDCl3, 300 MHz) δ ppm: 10.12 (s, 1H, OH), 8.17 (s, 1H -NH), 7.81 - 7.71 (m, 4H, Ar-H), 7.36-7.33 (m, 5H, Ar-H), 6.26 (d, 1H, -CH), 4.64 (s, 2H, -CH_2), 4.31 (t,1H, -CH), 2.27 (d, 1H, -CH). ^{13}CNMR (CDCl3, 300 MHz) δ ppm: 175.3 (carboxyl group),173.0(carbonyl of thiazolidinone ring), 170.3(carbonyl of amide), 168.2(two peaks carbonyl carbons of phthalimide ring), 138.2,132.2, 132.0,128.6,127.1,126.9, 123.7 (two aromatic rings carbon), 61.8 , 47.6 (-CH of thiazolidinone ring) 50.1 (-CH_2 near amide group) 39.2 (-CH_2 attached to carboxyl). MS m/z: 439.08 100%, 440.09 23.1%, 439,161. Anal. Calcd. for $C_{21}H_{17}N_3O_6$ S: C, 57.40; H, 3.90; N, 9.56; Found: C, 57.45; H, 3.93;N, 9.59.

2-(3-(2-(1,3-Dioxoisoindolin-2-yl)acetamido)-2-(4-hydroxyphenyl)-4-oxothiazolidin-5-yl)acetic acid (5d)

IR (KBr): *v*/cm^{-1}, 3540(OH of carboxyl), 3410(-OH group) 3281(NH of amide),, 3025(C-H of aromatic), 2912(C-H of alkyl), 1756 (C=O of thiazolidinone), 1724(C=O of carboxyl),1722,1715 (C=O of Phthalimide), 1666(C=O of Amide), 723(C-S).1H NMR (CDCl3, 300 MHz) δ ppm: 10.2(s, 1H, -OH carboxylic), 8.2(s, 1H, -NH), 7.2-7.4(m, 4H, Ar-H),6.7-7.7 (m, 4H, aromatic ring), 5.7(s, 1H, -OH phenolic), 5.0(s, 2H, -CH of thiazolidinone ring) , 4.9(s, 1H, -CH_2 near amide group), 3.8-4(t, 1H, -CH of thiazolidinone ring), 2.2-2.8(d, 2H,CH_2), ^{13}CNMR (CDCl3, 300 MHz) δ ppm: 175.3 (carboxyl group),173.0(carbonyl of thiazolidinone ring), 170.3(carbonyl of amide), 168.2(two peaks carbonyl carbons of phthalimide ring),

156.9,132.2, 132.0,131.8, 130.1, 115.8,127.1,126.9, 123.7 (two aromatic rings carbon), 61.8 , 47.6 (-CH of thiazolidinone ring) 50.1 (-CH_2 near amide group) 39.2 (-CH_2 attached to carboxyl). MS m/z: M+455.08 100% M+1456.08 25.1%, 439 M-OH, 363 M-PhOH, 304, 203, 161 (base peak). Anal. Calcd. for $C_{21}H_{17}N_3O_7$ S: C, 55.38; H, 3.76; N, 9.23; Found: C,55.41; H, 3.81;N 9.28.

2-(3-(2-(1,3-Dioxoisoindolin-2-yl)acetamido)-2-(3-hydroxyphenyl)-4-oxothiazolidin-5-yl)acetic acid (5e)

IR (KBr): *v*/cm^{-1}, 3457 (OH of carboxyl), 3346 (NH of amide), 3151 (C-H of aromatic), 2976 (C-H of alkyl), 1768 (C=O of thiazolidinone), 1730 (C=O of carboxyl) 1728, 1713 (C=O of Phthalimide), 1640 (C=O of amide), 716 (C-S). 1H NMR (CDCl3, 300 MHz) δ ppm: 10.2(s, 1H, -OH, carboxyl), 7.8-8.8 (m, 4H, Ar-H), 6.7-7.7 (m, 4H, aromatic ring), 7.33 (s, 1H, -NH), 6.52(s, 1H, -CH), 4.65(s, 2H, -CH_2) 4.31(t, 1H, -CH), 2.63(d, 2H,CH_2), ^{13}CNMR (CDCl3, 300 MHz) δ ppm: 175.3 (carboxyl group),173.0(carbonyl of thiazolidinone ring), 170.3(carbonyl of amide), 168.2(two peaks carbonyl carbons of phthalimide ring), 156.9,140.6, 132.2, 132.0,131.8, 130.1, 119.5, 123.7 114.4,114.3(two aromatic rings carbon), 62.1 , 47.6 (-CH of thiazolidinone ring) 50.1 (-CH_2 near amide group) 39.2 (-CH_2 attached to carboxyl). MS m/z: M+455.08 100% M+1456.08 25.1%, 439 M-OH, 363 M-PhOH, 304, 203, 161 (base peak). Anal. Calcd. for $C_{21}H_{17}N_3O_7$ S: C, 55.38; H, 3.76; N, 9.23; Found:C,55.34 H, 3.81;N,9.28.

2-(3-(2-(1, 3-Dioxoisoindolin-2-yl)acetamido)-2-(4-methoxyphenyl)-4-oxothiazolidin-5-yl)acetic acid (5f)

IR (KBr): *v*/cm^{-1}, 3596(OH of carboxyl), 3214(NH of amide), 3025(C-H of aromatic), 2894(C-H of alkyl) 1754(C=O of thiazolidinone), 1725(C=O of carboxyl), 1715,1713 (C=O of Phthalimide), 1663(C=O of amide), 742(C-S).1H NMR (CDCl3, 300 MHz) δ ppm: 10.23(s, 1H, -OH), 8.48.(s, 1H, -NH), 7.16-7.81 (m, 4H, Ar-H), 6.8-7.8(m, 4H, aromatic ring), 6.36(s, 1H, -CH, thiazolidinone ring), 4.65 (s, 2H, -CH_2 near amide group), 4.32(t, 1H, -CH, thiazolidinone ring), 3.8 (s, 3H, -OCH_3), 2.9-2.6(d, 2H,CH_2), ^{13}CNMR (CDCl3, 300 MHz) δ ppm: 175.3 (carboxyl group),173.0(carbonyl of thiazolidinone ring), 170.3(carbonyl of amide), 168.2(two peaks carbonyl carbons of phthalimide ring), 159.0, 132.2, 132.0,131.8, 131.5, 130.1, 129.7, 123.7 114.2, (two aromatic rings carbon), 61.8 , 47.6 (-CH of thiazolidinone ring), 55.8(-OCH_3), 50.1 (-CH_2 near amide group) 39.2 (-CH_2 attached to carboxyl). MS m/z: M+ 469.01 100%, M+1 470.10 24.3%, M-OCH_3 439, M-PhOCH_3 363,304, 203, 161 base peak. Anal. Calcd.for $C_{22}H_{19}N_3O_7$ S: C, 56.28; H, 4.08; N, 8.95; Found: C, 56.30;H, 4.06;N,8.91.

2-(2-(4-Chlorophenyl)-3-(2-(1,3-Dioxoisoindolin-2-yl)acetamido)-4-oxothiazolidin-5-yl)acetic acid (5g)

IR (KBr): *v*/cm^{-1}, 3540(OH of carboxyl), 3215(NH of amide), 3010 (C-H of aromatic), 2980(C-H of alkyl), 1755(C=O of thiazolidinone)1722(C=O of carboxyl), 1712, 1702 (C=O of Phthalimide), 1645(C=O of amide), 825(C-Cl),756(C-S). 1H NMR (CDCl3, 300 MHz) δ ppm: 10.23(s, 1H, -OH carboxyl), 8.48.(s, 1H, -NH), 7.16-7.81 (m, 8H, Ar-H), 6.36(s, 1H, -CH), 4.65 (s, 2H, -CH_2 near amide group),4.32(t, 1H, -CH), 2.61(d, 2H,CH_2), ^{13}CNMR (CDCl3, 300 MHz) δ ppm: 175.3 (carboxyl group),173.0(carbonyl of thiazolidinone ring), 170.3(carbonyl of amide), 168.2(two peaks carbonyl carbons of phthalimide ring), 137.3, 132.7, 132.0,131.8, 131.5, 130.1, 128.7, 123.7, (two aromatic rings carbon), 61.8 , 47.6 (-CH of thiazolidinone ring), 50.1 (-CH_2 near amide group) 39.2 (-CH_2 attached to carboxyl). MS m/z: M+ 473.04 100.0%, M+2 475.04 36.5%, M+1 474.05 23.1%, 161 base peak. Anal. Calcd. for $C_{21}H_{16}ClN_3O_6$ S: C, 53.22; H, 3.40; N, 8.87;Found: C, H, 3.43;N,8.91.

2-(3-(2-(1,3-Dioxoisoindolin-2-yl)acetamido)-2-(4-fluorophenyl)-4-oxothiazolidin-5-yl)acetic acid (5h)

IR (KBr): *v*/cm^{-1}, 3459(OH of carboxyl), 3314(NH of amide), 3042(C-H of aromatic),2890(C-H of alkyl),1758(C=O of thiazolidinone) 1735(C=O of carboxyl), 1712, 1710 (C=O of Phthalimide), 1680 (C=O of amide), 1329 (Ar-F), 736 (C-S).1H NMR (CDCl3, 300 MHz):.10.18(s, 1H, -OH carboxyl), 8.40.(s, 1H, -NH), 7.18-7.81 (m, 8H, Ar-H), 6.32(s, 1H, -CH thiazolodinone ring), 4.25(t, 1H, -CH thiazolodinone ring), 2.41(d, 2H,CH_2), ^{13}CNMR(CDCl3, 300 MHz) δ ppm: 175.3 (carboxyl group),173.0(carbonyl of thiazolidinone ring), 170.3(carbonyl of amide), 168.2(two peaks carbonyl carbons of phthalimide ring), 161.3, 134.8, 132.0,131.8, 131.5, 130.3, 128.7, 123.7, 115.4 (two aromatic rings carbon), 61.8 , 47.6 (-CH of thiazolidinone ring), 50.1 (-CH_2 near amide group) 39.2 (-CH_2 attached to carboxyl).MS m/z: M= 457.07 100.0%, M+1: 458.08 23.1%, 459.07 4.8%, 161 base peak .Anal. Calcd. for $C_{21}H_{16}FN_3O_6$ S: C, 55.14; H, 3.53; N, 9.19; Found: C,55.11;H,3.58; N,9.16.

2-(3-(2-(1,3-Dioxoisoindolin-2-yl)acetamido)-2-(3-nitrophenyl)-4-oxothiazolidin-5-yl)acetic acid (5i)

IR (KBr): *v*/cm^{-1}, 3546 (OH of carboxyl),), 3445(NH of amide), 3055 (CH of aromatic), 2936 (CH of alkyl), 1761(C=O of thiazolidinone), 1728, 1723 (C=O of Phthalimide), 1724(C=O of carboxyl) 1681 (C=O of amide), 1515(-NO_2), 737 (C-S), 1H NMR ($DMSOd_6$, 300 MHz):.11.1(s, 1H, -OH carboxyl), 8.42 (s, 1H, NH), 7.81 -

7.89(m, 4H, Ar- H), 6.23(s, 1H, -CH, thiazolidinone ring), 4.54 (s, 2H, -CH_2 near amide group) 4.35(t, 1H, -CH thiazolidinone ring), 2.81(d, 2H,CH_2),), ^{13}CNMR(CDCl3, 300 MHz) δ ppm: 175.3 (carboxyl group),173.0(carbonyl of thiazolidinone ring), 170.3(carbonyl of amide), 168.2(two peaks carbonyl carbons of phthalimide ring), 147.8, 140.1, 133.0, 132.2 132.0, 125.1, 123.7, 122.3 (two aromatic rings carbon), 60.8 , 47.6 (-CH of thiazolidinone ring), 50.1 (-CH_2 near amide group) 39.2 (-CH_2 attached to carboxyl).MS m/z::484.07 100.0%, 485.07 25.3%, 486.06 4.5 %, 161 base peak. Anal. Calcd. for $C_{21}H_{16}N_4O_8$ S: C, 52.07; H, 3.33; N, 11.57;Found: C, 52.03; H,3.30; N, 11.54.

2-(3-(2-(1, 3-Dioxoisoindolin-2-yl) acetamido)-2-(furan-2-yl)-4-oxothiazolidin-5-yl) acetic acid (5j)

IR (KBr): *v*/cm^{-1}, 3516 (OH of carboxyl), 3435(NH of amide), 3068 (CH of aromatic), 2945 (CH of alkyl), 1764(C=O of thiazolidinone), 1728, 1725 (C=O of Phthalimide), 1724(C=O of carboxyl) 1681 (C=O of amide), 737 (C-S), 1H NMR (CDCl3, 300 MHz): 11.1(s, 1H, -OHcarboxyl), 9.56 (s, 1H,NH), 7.81-7.89 (m, 4H, Ar-H), 6.07-7.09 (m, 3H, furan ring) 6.32(s, 1H, -CH), 4.61 (s, 2H, -CH_2) 4.25(t, 1H, -CH), 2.41(d, 2H,CH_2, ^{13}CNMR (CDCl3, 300 MHz) δ ppm: 175.3 (carboxyl group),173.0(carbonyl of thiazolidinone ring), 170.3(carbonyl of amide), 168.2(two peaks carbonyl carbons of phthalimide ring), 151.5, 142.1,132.2 132.0, 123.7,110.6, 107.0 (aromatic rings carbon and furan ring carbon), 61.5 , 45.1 (-CH of thiazolidinone ring), 50.1 (-CH_2 near amide group) 39.2 (-CH_2 attached to carboxyl).MS m/z: M+: 429.06 100%, M+1 430.07 21.0% 431.06 4.8%, 161 base peak . Anal. Calcd. for $C_{19}H_{15}N_3O_7S$: C, 53.14; H, 3.52; N, 9.79; Found: C,53.11; H, 3.56;N,9.75.

2-(3-(2-(1, 3-Dioxoisoindolin-2-yl) acetamido)-4-oxo-2-(thiophen-2-yl)thiazolidin-5-yl)acetic acid (5k)

IR (KBr): *v*/cm^{-1}, 3563(OH of carboxyl), 3325 (NH of amide), 3108 (CH of aromatic), 2852 (CH of alkyl), 1780 (C=O of thiazolidinone), 1735(C=O of carboxyl)1733,1721 (C=O of Phthalimide), 1688(C=O of amide), 785, 737 (C-S) 1H NMR (CDCl3, 300 MHz): 11.1(s, 1H, -OH), 7.81-7.89 (m, 4H, Ar-H), 7.36(s, 1H,NH), 6.07-7.09 (m, 3H,thiphene ring) 6.32(s, 1H, -CH thiazolidinone ring), 4.58 (s, 2H, -CH_2 near amide group) 4.25(t, 1H, -CH thiazolidinone ring), 2.81(d, 2H,CH_2), ^{13}CNMR(CDCl3, 300 MHz) δ ppm: 175.3 (carboxyl group),173.0(carbonyl of thiazolidinone ring), 170.3(carbonyl of amide), 168.2(two peaks carbonyl carbons of phthalimide ring), 139.4, 132.2 132.0, 127.0, 126.7, 125.5123.7, (aromatic rings carbon and thiphene ring carbon), 61.0 , 47.5 (-CH of thiazolidinone ring), 50.1 (-CH_2 near amide group) 39.2 (-CH_2 attached to carboxyl). MS m/z: M+ 445.04 100%, 446.04 23.5%, 447.04 10.9%,161 base peak . Anal. Calcd. for $C_{19}H_{15}N_3O_6S$: C, 51.23; H, 3.39; N, 9.43;Found:C, 51.20;H,3.36;N,9.39.

2-(3-(2-(1,3-Dioxoisoindolin-2-yl)acetamido)-2-(1H-indol-2-yl)-4-oxothiazolidin-5-yl)acetic acid (5l)

IR (KBr): *v*/cm^{-1}, 3540 (OH of carboxyl), 3396 (NH of indole), 3209 (NH of amide), 3015 (CH of aromatic), 2867 (CH of alkyl), 1768 (C=O of thiazolidinone), 1724, 1721 (C=O of Phthalimide), 1724(C=O of carboxyl) 1680 (C=O of amide), 732 (C-S). 1H NMR (CDCl3, 300 MHz): 11.1(s, 1H, -OH), 9.56 (s, 1H,NH),8.7(s, 1H, NH of indole) 7.81-7.89 (m, 4H, Ar-H), 6.07-7.09 (m, 4H, aromatic ring) 6.32(s, 1H, -CH), 4.61 (s, 2H, -CH_2) 4.25(t, 1H, -CH), 2.41(d, 2H,CH_2), ^{13}CNMR (CDCl3, 300 MHz) δ ppm: 175.3 (carboxyl group),173.0(carbonyl of thiazolidinone ring), 170.3(carbonyl of amide), 168.2(two peaks carbonyl carbons of phthalimide ring),136.6, 136.5, 132.2 132.0, 128.1, 123.7,121.7, 120.7, 119.8, 111.1 (aromatic rings carbon and indolyl ring carbon), 61.5 , 47.5 (-CH of thiazolidinone ring), 50.1 (-CH_2 near amide group) 39.2 (-CH_2 attached to carboxyl). MS m/z: M+ 478.09 100%, 479.10 25.3%, 480.10 4.9%, 161 base peak. Anal. Calcd. for $C_{23}H_{17}N_4O_6$ S: C, 57.73; H, 3.79; N, 11.71; Found: C, 57.76;H,3.75;N,11.68.

Biological activity

In our present study we have performed *in vitro* biological activity by protein denaturation method and *in vivo* activity by carrageenan induced rat paw edema method, using diclofenac as standard.

In vitro anti-inflammatory activity

The synthesized compounds were screened for anti inflammatory activity by using inhibition of albumin denaturation technique. The standard drug and test compounds were dissolved 10 mg compound in DMF and diluted with phosphate buffer saline (pH 7.4) in such a way that concentration of DMF in all solutions was less than 2.5%. Test solution (1 ml, 100 µg/ml) was mixed with 1 ml of 1% albumin solution in phosphate buffer saline and incubated at 27 ± 1°C in an incubator for 15 min. Denaturation was induced by keeping the reaction mixture at 60± 1°C in a water bath for 10 min. After cooling, the turbidity was measured at 660 nm with UV visible spectrophotometer. Percentage of inhibition of denaturation was calculated from control where no drug was added. Each experiment was done in triplicate and average is taken. The diclofenac sodium was used as standard drug. The percentage of inhibition was calculated using the following formula:

$$\% \text{ Inhibition of denaturation} = [(Vt/Vc) - 1] \times 100$$

Where, Vt = mean absorption of test compound, Vc = mean absorption of control.

In vivo anti-inflammatory activity

The animals were procured under the CPCSEA number CPCSEA/IAEC/Pharm.Chem/19/2012-13/77 approved by Institutional Animal Ethics Committee (IAEC). Swiss Albino rats (150 to 200 g) were supplied by Wockhardt Ltd Aurangabad. The animals were housed in stainless steel cages, divided into groups of five animals each and deprived of food but not water 24 h before the experiment. The anti-inflammatory activity of the compounds under investigation was studied using carrageenan-induced rat paw oedema.

A suspension of the test compounds 5 (a-l) and standard drug diclofenac in carboxy methyl cellulose (CMC) solution (0.5% w/v in water) was administered intraperitoneally in a dose level of 10 mg/kg. Control animals were treated similarly with CMC solution (0.5% w/v in water). After 1 h, 0.1 ml of freshly prepared 1% carrageenan solution was injected into the sub plantar region of the left hind paw of rats according to the method of Winter et al. (1962). The volume was measured before and after carrageenan treatment at 1, 2, 3, 6 h with the help of digital plethysmometer (Ugo Basil 7140, Italy). Paw edema volume was compared with vehicle control group and percent reduction was calculated by formula:

$$\text{Paw enema} = (Vc - Vt / Vc) \times 100$$

Where Vc = paw volume of control group, Vt = paw volume of test group

Ulcerogenic toxicity study

Ulcerogenic toxicity study was performed with Wistar albino rats as per the protocol (Susan et al. 1993; Shoman et al., 2009). Adult Wistar albino rats were divided into different groups each containing five animals. Animals were deprived of food with no water 24 h before experiment. Ulcerogenic activity was evaluated after oral administration of suspension of standard drug and test compounds in carboxy methyl cellulose solution (0.5% w/v in water) in dose level of 100 mg/kg.

Control animals were treated similarly with carboxy methyl cellulose solution (0.5% w/v in water). After 5 h, rats were scarified by decapitation, the stomach were removed, collected, opened along the greater curvature, washed with water, and cleaned gently in saline solution. The stomach was stretched on a piece of foam core mat and the numbers of severity score were recorded.

Severity score: 0 = Normal colored stomach, 0.5 = Red coloration, 1 = Spot ulcer, 1.5 = Hemorrhagic streaks, 2 = Ulcers ≥ 3 but ≤ 5, 3 = ulcers > 5. Calculation:

$$UI = UN + US + UP \times 10^{-1}$$

Where, UI = ulcer index, UN = average of number of ulcers per animal, US = average of severity score, UP = percentage of animals with ulcer.

RESULTS AND DISCUSSION

Chemistry

The synthetic protocol employed for the synthesis of 2-(3-(2-(1, 3-dioxoisoindolin-2-yl) acetamido)-4-oxo-2-substituted thiazolidin-5-yl) acetic acid derivatives 5(a-l) is presented in Figure 1. In the first step, 2-(1, 3-dioxoisoindolin-2-yl) acetic acid 1 was synthesized by refluxing phthalic anhydride and glycine in glacial acetic acid. Ethyl 2-(1, 3-dioxoisoindolin-2-yl) acetate 2 was synthesized by refluxing 1 with conc. H_2SO_4 in ethanol for 2 h. 2-(1, 3-Dioxoisoindolin-2-yl) acetohydrazide, 3 was synthesized by stirring ethyl 2-(1,3-dioxoisoindolin-2-yl) acetate 2 with hydrazine hydrate at room temperature for about 1 h. The compounds N-substituted benzylidene/methylene-2-(1,3-dioxoisoindolin-2-yl) acetohydrazides 4(a-l) were synthesized by refluxing 2-(1,3-dioxoisoindolin-2-yl) acetohydrazide and aromatic/heterocyclic aldehydes in absolute ethanol in presence of catalytic amount of glacial acetic acid.

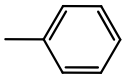
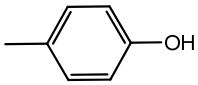
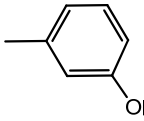
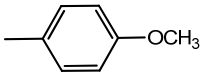
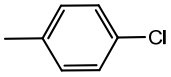
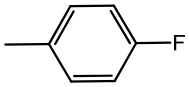
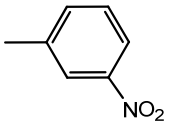
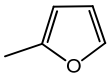
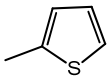
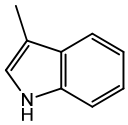
The title compounds 2-(3-(2-(1,3-dioxoisoindolin-2-yl) acetamido)-4-oxo-2-substituted thiazolidin-5-yl) acetic acid 5(a-l) were obtained by cyclo-condensation of *N*-substitutedbenzylidene/methylene-2-(1,3-dioxoisoindolin-2-yl)acetohydrazide with mercapto succinic acid in dimethylformamide (DMF) as solvent in presence of catalytic amount of anhydrous zinc chloride, under microwave irradiation for about 14 to 17 min (700 W) at 80°C. The reactions were carried out in microwave so as to reduce the longer reaction time of 6-8hrs refluxing in benzene, required in conventional synthesis of thiazolindinone derivatives to have better yields and to have neat and clean reactions. In the present synthesis of thiazolidinone derivatives the carcinogenic solvent benzene is replaced by DMF. The characterization data of synthesized derivatives is given in Table 1.

Biological activity

The synthesized derivatives 5(a-l) were evaluated for anti inflammatory activity using *in vitro* activity by protein denaturation method and *in vivo* activity was performed by using carageenan induced paw edema method. Diclofenac was used as the standard reference compound for both *in vivo* and *in vitro* evaluation.

The *in vivo* biological activity was performed according to Winter et al. (1962) and it has been observed that the new series of 2-(3-(2-(1,3-dioxoisoindolin-2-yl) acetamido)-4-oxo-2-substituted thiazolidin-5-yl) acetic acid derivatives exhibited the significant anti-inflammatory

Table 1. Physical data 2-(3-(2-(1,3-dioxoisoindolin-2-yl) acetamido)-4-oxo-2-substituted thiazolidin-5-yl)acetic acid.

Code	R/Ar	Molecular formula	Molecular weight	% Yield	MP (°C)	R_f value
5a	—CH_3	$C_{16}H_{15}N_3O_6$ S	377	89	280-284	0.63
5b	—CH_2CH_3	$C_{17}H_{17}N_3O_6$ S	391	93	298-302	0.56
5c		$C_{21}H_{17}N_3O_6$ S	439	98	310-312	0.56
5d		$C_{21}H_{17}N_3O_7$ S	455	90	300-302	0.61
5e		$C_{21}H_{17}N_3O_7$ S	455	85	320-322	0.48
5f		$C_{22}H_{19}N_3O_7$ S	469	95	270-273	0.45
5g		$C_{21}H_{16}ClN_3O_6$ S	473	94	312-316	0.61
5h		$C_{21}H_{16}FN_3O_6$ S	457	93	273-276	0.53
5i		$C_{21}H_{16}N_4O_8$ S	484	89	298-300	0.52
5j		$C_{19}H_{15}N_3O_7S$	429	88	304-306	0.49
5k		$C_{19}H_{15}N_3O_6S$	445	98	284-288	0.39
5l		$C_{23}H_{17}N_4O_6$ S	478	90	312-318	0.67

*Melting points are uncorrected

Table 2. Mean paw volume (ml) and % inhibition of compounds (5a-l).

No.	Mean paw volume in ml ± SEM					% inhibition				
	1 h	2 h	3 h	4 h	6 h	1 h	2 h	3 h	4 h	6 h
Control	1.34±0.15	1.53±0.017	1.926±0.15	1.776±0.061	1.856±0.053	-	-	-	-	-
5a	0.7±0.30**	0.91±0.069*	0.846±0.037	1.243±0.098	1.433±0.19	47.76	87.58	50.07	30.01	22.79
5b	1.023±0.038	0.88±0.017	0.97±0.011	1.153±0.075	1.33±0.050	23.65	42.48	49.63	35.07	28.34
5c	1.29±0.084	0.96±0.04	1.09±0.005**	1.243±0.035	1.19±0.078	3.7	37.25	43.40	30.01	35.88
5d	1.26±0.072	1.216±0.029	1.42±0.14**	1.43±0.12*	1.286±0.10	5.9	20.52	26.27	19.48	30.71
5e	0.91±0.07	1.06±0.060	1.296±0.046	1.13±0.047	1.346±0.069	32.08	30.71	32.71	36.37	27.47
5f	1.29±0.04	1.253±0.089	1.12±0.10**	1.61±0.065	1.4±0.061	3.7	18.10	41.84	9.34	24.56
5g	0.96±0.037	1.22±0.058	1.34±0.14*	1.003±0.093**	1.06±0.06	28.35	20.26	30.42	43.52	42.88
5h	1.223±0.017	1.013±0.080*	1.43±0.052*	1.123±0.035**	1.583±03031	8.73	33.79	25.75	36.76	14.70
5i	1.143±0.086	1.11±0.055	1.333±0.071**	1.38±0.127	1.113±0.014	14.70	64.26	30.94	22.29	40.03
5j	0.896±0.031	1.366±0.023	1.1±0.10**	1.206±0.053	1.22±0.11	33.13	10.71	42.88	32.09	32.26
5k	1.22±0.035	1.29±0.036	1.496±0.139	1.256±0.089	1.486±0.069	8.95	15.66	22.32	29.27	19.93
5l	1.25±0.075	1.33±0.75	1.556±0.15	1.273±0.72	1.643±0.68	6.7	13.07	19.21	28.32	11.47
Diclofenac	1.123±0.16	1.056±0.99	1.156±0.098**	1.133±0.021**	1.36±0.033	16.19	30.98	39.97	36.20	26.72

The observations are mean ± SEM, n= 5, $^{**}P < 0.01$, $^{*}P < 0.05$, test compounds = 10 mg/kg. Reference standard, Diclofenac = 10 mg/kg. Statistical analysis were done by one way ANOVA followed by Dunnett's test

action to all the compounds except 5b , 5k and 5l, when compared with control. Some of the synthesized derivatives have shown the enhanced anti-inflammatory activity than diclofenac as shown in Table 2. The most significant ($^{**}P < 0.01$) anti-inflammatory activity is foundat 3 h and gradually reduces at subsequent hours. The compound with highest percent inhibition is 5a and is found to be most significant at 1 h. From the overall percent inhibition the compound 5c, 5f and 5j have shown to posses the enhanced and significant anti-inflammatory activity. Moreover, the other derivatives are also significant but less or equipotent with the standard drug, diclofenac.

The synthesized compound were subjected to *in vitro* anti inflammatory activity using albumin inhibition of albumin denaturation technique according to (Mizushima and Kobayashi. 1968), and with slight modification according to Bhalgat et al. 2011. Amongst all the synthesized compounds 5a, 5b and 5e have shown more inhibition as compared to diclofenac. It was observed in *in-vivo* activities, that lower aliphatic groups such as–CH_3, -C_2H_5 attached to C2 of thiazolidinone ring show the highest anti-inflammatory activity. All the compounds have resulted in decrease in rat paw edema and hence showed excellent anti-inflammatory activity. Compound 5c in which the phenyl ring is without any substituent attached at C2 of thiazolidinone ring exhibited significant and enhanced anti-inflammatory activity. Other derivatives possessing 4-nitro phenyl, 4-fluro phenyl, 4-chloro phenyl, 3- hydroxy phenyl, 4-hydroxy phenyl group on C2 of thiazolidinone ring ie. 5i, 5h, 5g, 5e, 5d, respectively are less active than diclofenac but show significant activity. The bulky derivatives such as indole and thiophene rings at C2 of thiazolidinone ring like 5k and 5l have exhibited very less anti-inflammatory activity when compared to the standard drug, diclofenac. The anti-inflammatory activity data is presented in Table 3. The ulcerogenic toxicity was performed for selected compounds having shown better anti-inflammatory activity, such as, compound 5a, 5b, 5c, 5f & 5j. As shown in Table 4, it was observed that all the compounds exhibited lesser ulcerogenic index than diclofenac. Thus the synthesized derivatives have shown minimum toxicity effects.

Docking methodology

Molecular docking studies were performed by using Glide, V 5.5 (Schrödinger. LLC, New York, NY 2009). The coordinates for HSA were taken from RCSB Protein Data Bank (PDB Id. 2BXQ) (Ghuman et al., 2005) and prepared for docking using protein preparation wizard. Water molecules in the structure were removed. The bond order and formal charges were added for hetero groups and the hydrogens were added to all atoms in the structure. Side chains that were not close to the binding cavity were removed. After preparation, the structures were refined to optimize the hydrogen bond network using OPLs_2005 force field which helps in the orientation of side chain hydroxyl group. The minimization was terminated when the energy converged to root-mean-square deviation (RMSD) reached a maximum cutoff of 0.30A°. Grids were then defined around refined structure by centering on ligand using default box size. The standard precision (SP) docking mode for compounds, optimized earlier by Ligprep, was performed on generated grid of protein structure.

Table 3. Mean absorbance± SEM and % inhibition of compounds (5a-5l).

Compound	Mean Absorbance	SEM	% Inhibition
Control	0.1023	0.060	-
5a	0.1890	0.026	84.75
5b	0.1784	0.014	74.38
5c	0.1501	0.03	46.72
5d	0.1212	0.02	18.96
5e	0.1697	0.020	65.88
5f	0.1091	0.015	6.64
5g	0.1276	0.015	24.73
5h	0.1289	0.014	26.00
5i	0.1346	0.30	31.57
5j	0.1566	0.15	53.07
5k	0.1493	0.2	45.94
5l	0.1176	0.026	14.95
Std (diclofenac sodium)	0.1673	0.019	63.53

Table 4. Ulcerogenic potential in rat stomach.

Group	Dose mg/kg	Ulcer index
Control	0.5% sodium CMC	0
Diclofenac	100	11.4 ± 0.2082
5a	100	3.348 ± 0.0833
5b	100	7.21 ± 0.02887
5c	100	4.13 ± 0.04410
5f	100	4.66 ± 0.0333
5j	100	6.15 ± 0.05774

The observations are mean ± SEM, n= 6, $^{**}P < 0.01$, $^{*}P < 0.05$. Test compounds = 100 mg/kg. Reference standard, Diclofenac = 100 mg/kg. Statistical analysis were done by one way ANOVA followed by Dunnett's test.

Docking results

While performing docking study the hydrogen bonding with ARG114 was selected as constraints for the specificity of binding of compounds in activity site of enzyme as reported in literature and as detected in Ligplot (Pawar et al., 2010). The docking pose of synthesized compounds showing higher inhibition compared with that of standard. In present docking study both the standard drug Indomethacin shows the binding with Arg114 (Figure 2) and diclofenac shows the binding with Arg 117, as found in Figure 3. The compound 5a and 5b shows binding with ARG114 and ARG117, as shown in Figure 4 and Figure 5, respectively. Moreover the compound 5a showed the highest G score of -7.731, it was observed in the docking pose of 5a that –C=O of carboxyl group formed hydrogen bonding with –-NH group of Arg186 and –NH of amide group formed hydrogen bonding with –C=O of Arg114. This indicates the importance of carboxyl group for anti-inflammatory activity and also confirms the importance of amide group in the structure of the synthesized derivatives. The docking results have shown that all the synthesized compounds have better anti inflammatory effect compared to Indomethacin and diclofenac. Molecular modeling helps to realize the mechanism of their actions, which could be their interactions with the same residues of ARG114 and ARG117, as shown by indomethacin and diclofenac.

Conclusion

The present study describes eco-friendly synthesis of twelve final derivatives 5(a-l) in Milestone's Microsynth microwave. All the compounds were obtained in good yield and in shorter reaction times, i.e. 14 to 17 min.

The synthesized derivatives were evaluated for *in vitro*

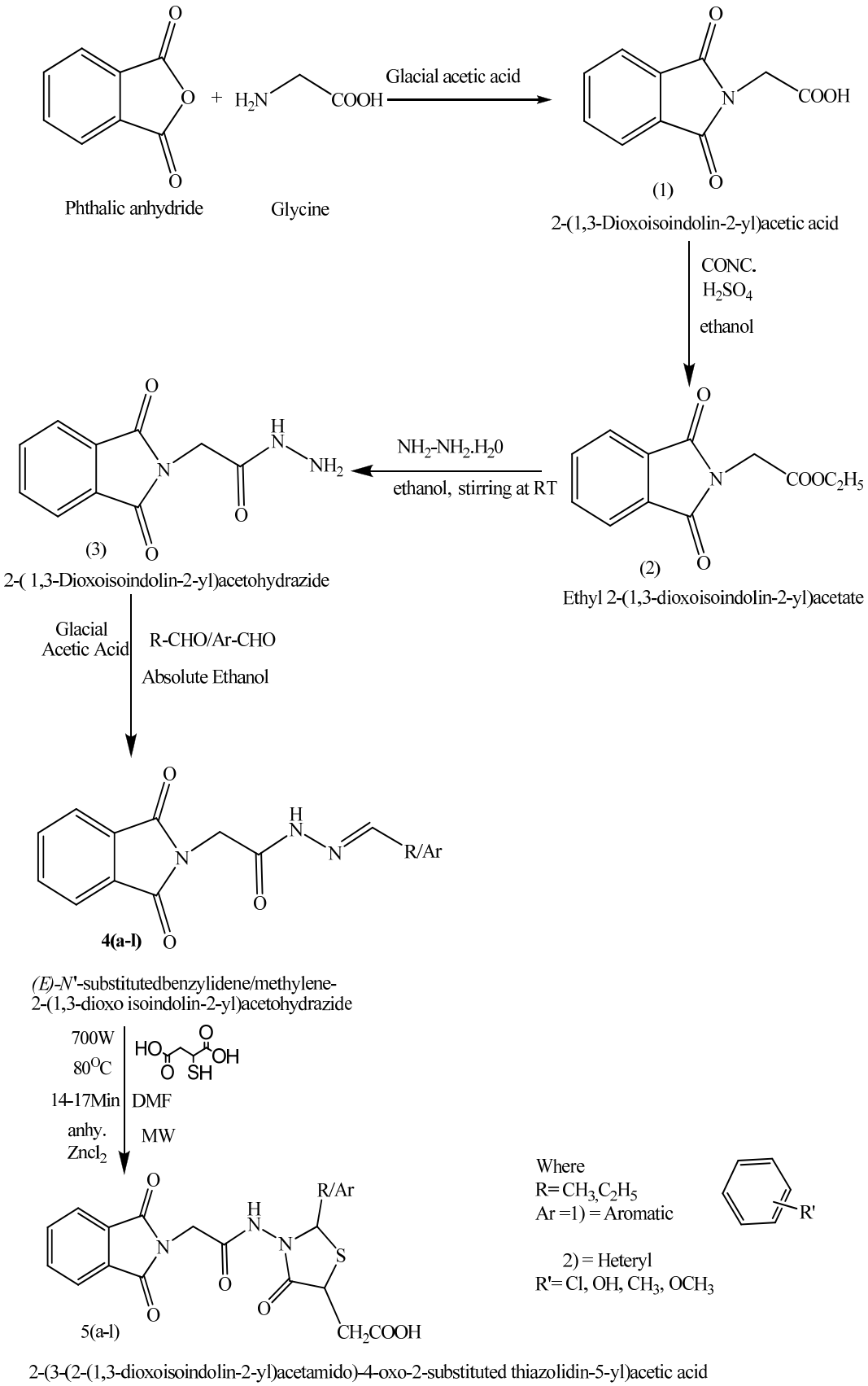


Figure 1. Scheme of synthesis of 2-(3-(2-(1,3-Dioxoisoindolin-2-yl) acetamido)-4-oxo-2-substituted thiazolidin-5-yl)acetic acid.

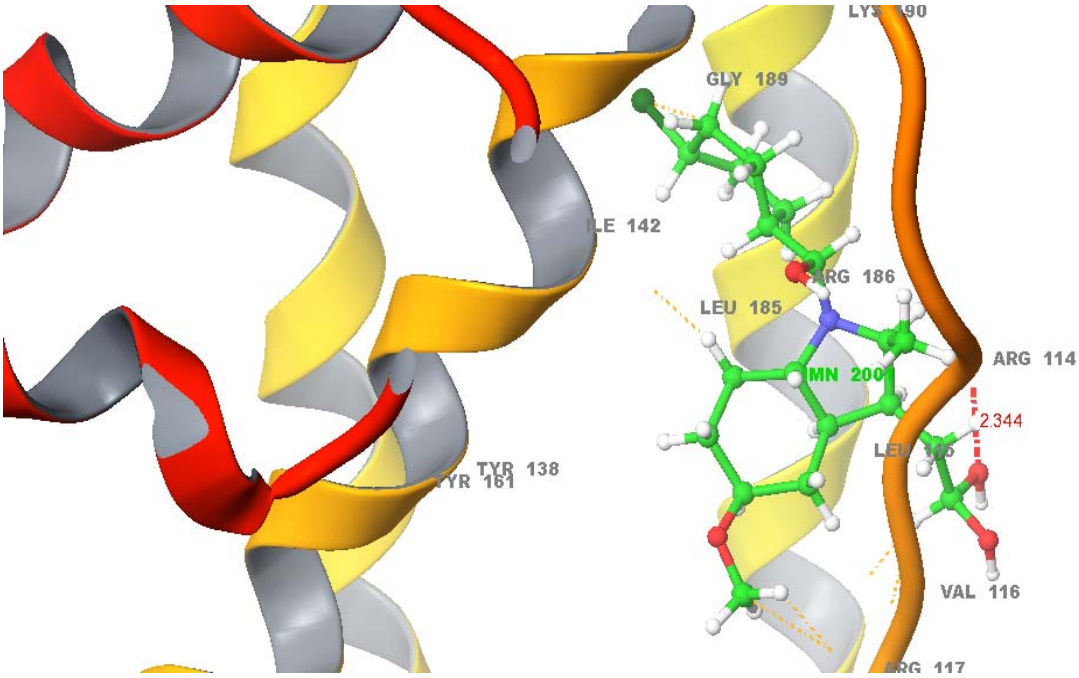


Figure 2. Docking pose of compound indomethacin at active binding site of enzyme. Visualization of hydrogen bonding of Indomethacin with Arg114 and Arg186.

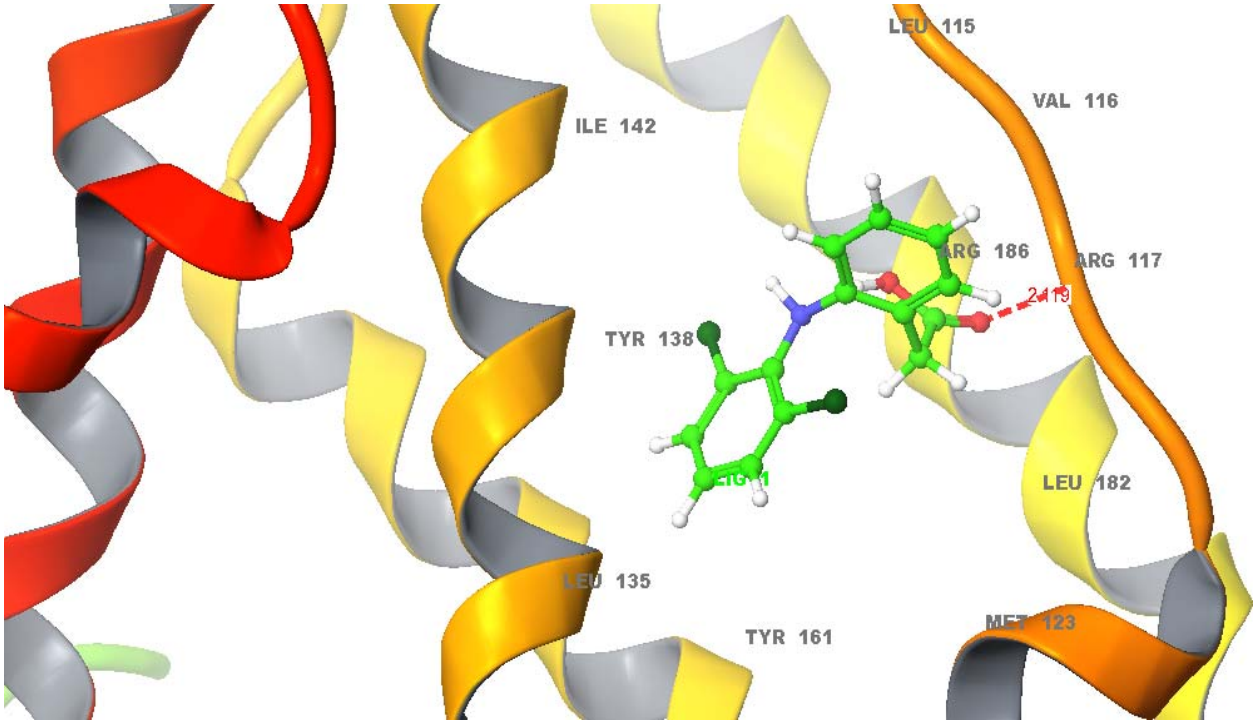


Figure 3. Docking pose of compound diclofenac at active binding site of enzyme. Visualization of hydrogen bonding of diclofenac with Arg117 (hydrogen bonding with amino acid is shown in pink dotted lines).

and *in vivo* anti-inflammatory activity, using diclofenac as a reference standard. The selected compounds were studied for ulcerogenic toxicity and have shown good gastrointestinal safety profile. The compounds were also subjected to *in vitro* analysis by using diclofenac as standard. The compounds 5a, 5b and 5e have proved to

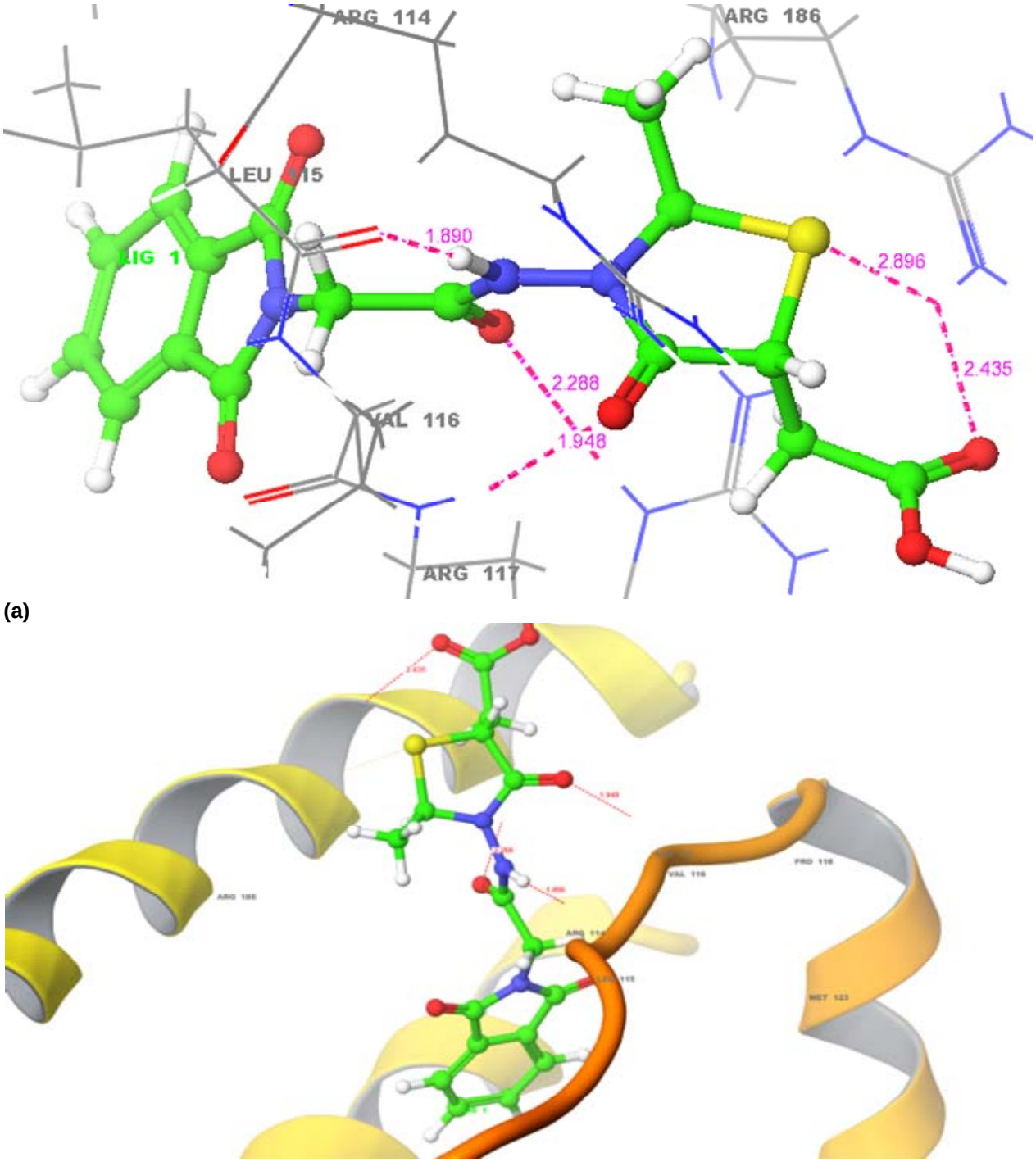


Figure 4. Docking pose of compound (5a) at active binding site of enzyme. Visualization of hydrogen bonding of (5a) with Arg114, Arg117 and Arg186. Hydrogen bonding with amino acid is shown in pink dotted lines.

be more effective than diclofenac while others have shown moderate to weak activity. All the derivatives were fitted into the same pocket of HSA where indomethacin has fitted during docking. The compounds have shown good docking results (G-score) and good fitting into the active site. Thus the synthesized compounds 2-(3-(2-(1,3-dioxoisoindolin-2-yl) acetamido)-4-oxo-2-substituted thiazolidin-5-yl) acetic acid derivatives 5(a-l) show good potential as anti-inflammatory agents and can be further evaluated for diabetic neuropathy as the structure

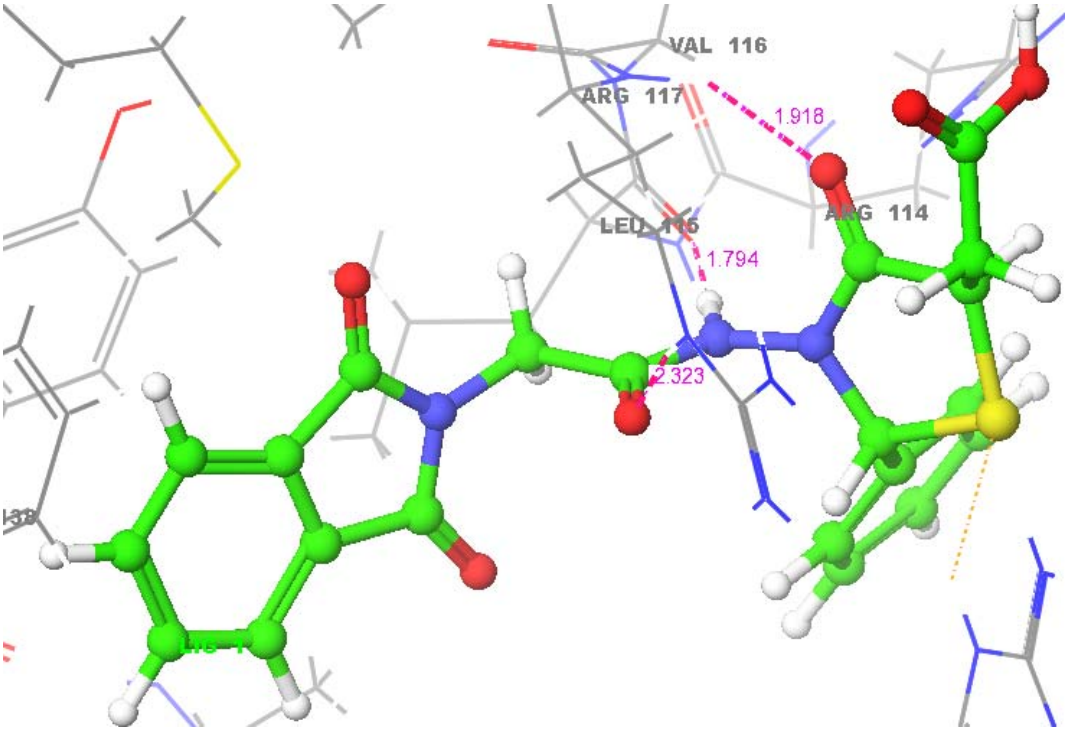


Figure 5. Docking pose of compound (5b) at active binding site of enzyme. Visualization of hydrogen bonding of (5b) with Arg114, Arg117. Hydrogen bonding with amino acid is shown in pink dotted lines.

contains thiazolidinone ring which is also present in anti-diabetic drugs such as rosiglitazone and pioglitazone.

ACKNOWLEDGMENTS

Authors are grateful to Mrs. Fatma Rafiq Zakaria, Chairman, Maulana Azad Education Trust and Principal, Y.B Chavan College of Pharmacy, Aurangabad for encouragement and support. The authors thank the Government College of Pharmacy, for assisting in pharmacological screening.

Conflict of interest

The authors declared no conflict of interest.

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