International Journal of Researches In Biosciences, Agriculture & Technology | Feb. 2015 Special Issue-1 | ISSN No. (Online) 2347-517X

Synthesis and Pharmacological Assesment of Thiazolidinone Derivatives of Dihydropyrimidinones

Ambareen Shaikh[1], Jyotsna Meshram[1] and Pravin S. Jogi[2]
[1]Rashtrasant TukadojiMaharaj Nagpur University, Nagpur-440033, Maharashtra, India.
[2]Department of Chemistry, JanataMahavidyalaya, Chandrapur-442401

Abstract:

The present work deals with the synthesis of 4-(4-(dimethylamino)phenyl)-1,2,3,4-tetrahydro-6-methyl-N-(2-aryl-4-oxothiazolidin-3-yl)-2-oxopyrimidine-5-carboxamide **4(a-g)** derivatives. The structures of newly synthesized compounds were established on the basis of elemental analysis, FTIR and ^{1}H NMR and Mass spectral data. The synthesized compounds were evaluated for their anti-inflammatory, analgesic and anti-bacterial activity and it was found that the compounds were pharmacological activeandgave appreciable results.

Keywords: Thiazolidinone, dihydropyrimidinone, anti-inflammatory, analgesic, anti-bacterial.

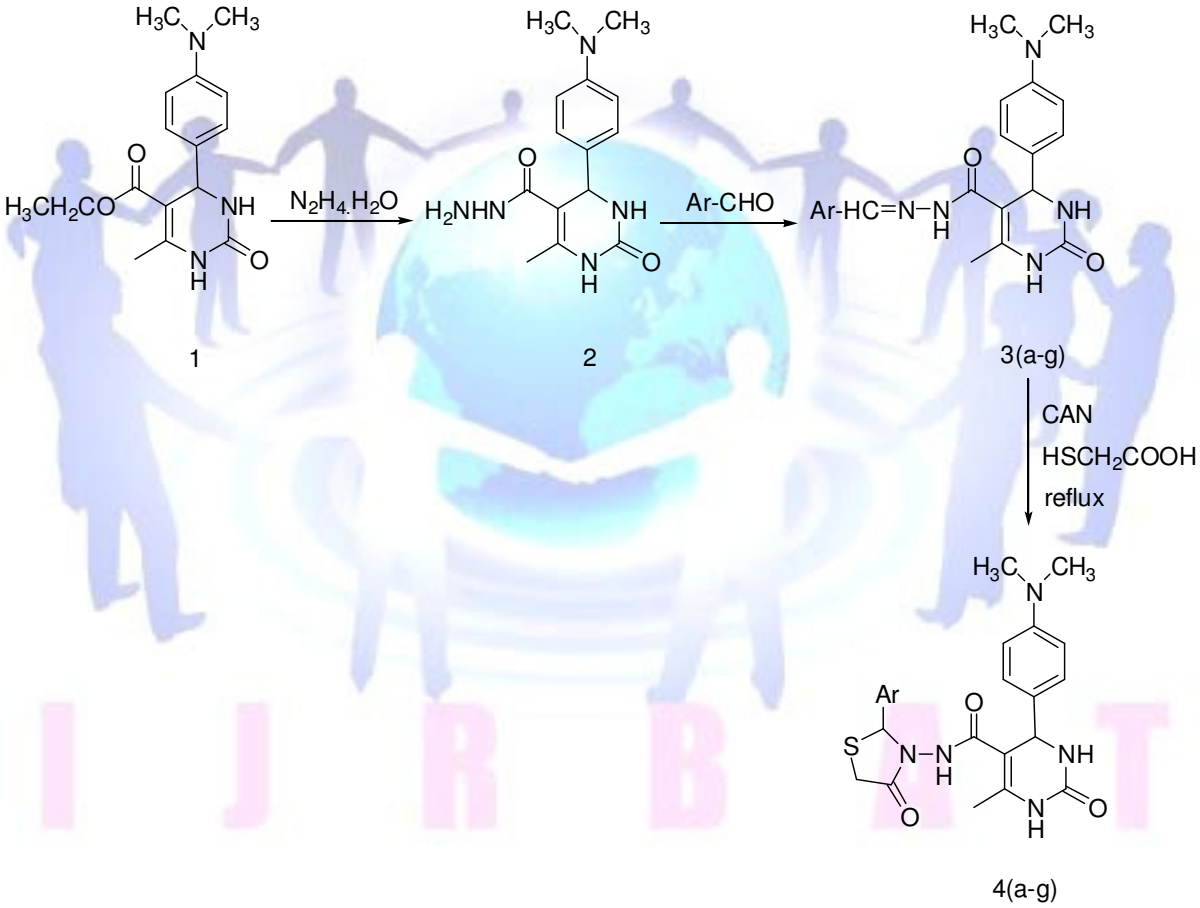
Introduction:

Thiazolidinone derivatives are a traditionally known class of biologically active compounds. Thiazolidinones and their derivatives are an important class of heterocyclic compounds because of their broad biological activities, such as COX-1 inhibition [1], anti-inflammatory [2], anti-proliferative [3,4], anti-histaminic [5] and anti-HIV activities [6,7]. In recent years, a large number of innovative drugs containing the thiazolidinone moiety have been developed, including hypoglycemic thiazolidinediones (pioglitazone and its analogs), dual COX-2/5-LOX inhibitors (darbufelon), new generation diuretics (etozolin) etc. [8]. Using modern technologies such as virtual and high-throughput screening, combinatorial chemistry, and molecular modelling, it was established that 4-thiazolidinones possess a high affinity to the PPAR-receptors family and are selective inhibitors of UDP-MurNAc/L-Ala ligase [9-13]. Numerous reports have appeared in the literature, which highlight their chemistry and use. A comprehensive review [14] has been written on thiazolidin-4-ones in 1961. Later, literatures [15-17] appeared that dealt with the use of thiazolidinone derivatives as stabilizers for polymeric materials. In recent years, several new methods for the preparation of thiazolidinone derivatives and reactions have been reported in the literature. However, these synthetic approaches suffer from the drawbacks such as low availability of starting materials, harsh reaction conditions, high temperatures, unsatisfactory yields. The discovery of new green and more efficient synthetic protocols for the preparation of industrial and biologically active organo-sulfur compounds *via* C-S bond formation have attracted a great deal of attention [20]. The environmentally benign synthesis of organic compounds without using hazardous reaction conditions has become several steps closer in recent years. Strict environmental legislations have forced chemists all over the world to develop alternatives for the synthesis of biologically and synthetically important compounds. In view of the potential biological activity of sulfur-nitrogen containing compounds and substantial reduction in reaction period under greener techniques, it was of interest to us to devise an environment friendly

method for the synthesis of some thiazolidinonederivatives and evaluation of their biological activity as potential anti-inflammatory, analgesic, anti-bacterial agents.

Materials and Methods:

All common reagents and solvents were of analytical grade and used directly. Melting points of the synthesized compounds were taken by one end open capillary tube melting point apparatus and are uncorrected. Infra Red (IR) spectra were recorded on Shimadzu FTIR 8400S spectrophotometer (KBr) and ^{1}H NMR spectra were recorded on Bruker-Avance (400 MHz) spectrophotometer with tetramethylsilane (TMS) as an internal standard. Mass spectra were recorded on *WatersMicromassQ-ToF Micro Mass Spectrometer. T*hin layer chromatography (TLC) was performed using Silica gel G obtained from Merck and the spots were visualized under iodine vapours.



Scheme 1

whereAr = C_6H_5, 2-$NO_2C_6H_4$, 3-$NO_2C_6H_4$, 2-OHC_6H_4, 4-OHC_6H_4, 4-$OCH_3C_6H_4$, 4-ClC_6H_4.

Synthesis of ethyl 6-methyl-2-oxo-4-aryl-1,2,3,4-tetrahydropyrimidine-5-carboxylate **(1)**andcorrespondingcarbohydrazide**(2)**

The desired compounds were synthesized as reported in earlier literature [21].

Synthesis of N'-(substituted benzylidene)-1,2,3,4-tetrahydro-6-methyl-2-oxo-4-arylpyrimidine-5-carbohydrazide **3(a-g)**

0.01 M of the carbohydrazide**(2)** in absolute ethanol was warmed with 0.01 M of various aromatic aldehydes with few drops of glacial acetic acid. The reaction completion was monitored by TLC. After completion, the content was poured in ice cold water. The separated product was washed with water, dried and crystallized from ethanol.

Synthesis of 4-(4-(dimethylamino)phenyl)-1,2,3,4-tetrahydro-6-methyl-N-(2-aryl-4-oxothiazolidin-3-yl)-2-oxopyrimidine-5-carboxamide **4(a-g)**

0.01 M of the above compound in dry benzene (25ml) was mixed with 0.012 M mercaptoacetic acid and catalytic amount of ceric ammonium nitrate (CAN). The reaction mixture was refluxed for about 1 hr at room temperature. The reaction progress was checked by TLC. After completion of reaction, excess benzene was distilled off and the resulting product was treated with 5% $NaHCO_3$ solution to remove unreacted mercaptoacetic acid. The product seperated was washed with water (2x50 ml), filtered, dried and recrystallized with DMF.

The spectral data of the corresponding compounds is as follows:

Analysis of 4-(4-(dimethylamino)phenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxo-N-(4-oxo-2-phenylthiazolidin-3-yl)pyrimidine-5-carboxamide **4a**

M.P: 154-157°C. Yield: 74%. IR (cm^{-1}): 1357 (C-S), 1556 (C-N), 1654 (C-C), 1706 (C=O), 2568 (N-N), 2955 (C-H), 3068 (Ar C-H). ^1H NMR (δ ppm): 1.62 (s, 3H, CH_3), 2.75 (s, 6H, N-CH_3), 3.24 (s, 2H, CH_2), 5.62 (s, 1H, CH), 5.92 (s, 1H, CH), 6.13 (bs, 2H, NH), 6.57-7.34 (m, 9H, Ar-H). **MS**: *m/z* 451 (M^+, 100%). Anal.Calcd. ($C_{23}H_{25}N_5O_3S$): C, 61.18; H, 5.58; N, 15.51; S, 7.10. Found: C, 61.15; H, 5.53; N, 15.53; S, 7.08.

Analysis of 4-(4-(dimethylamino)phenyl)-1,2,3,4-tetrahydro-6-methyl-N-(2-(2-nitrophenyl)-4-oxothiazolidin-3-yl)-2-oxopyrimidine-5-carboxamide **4b**

M.P: 176-179°C. Yield: 69%. IR (cm^{-1}): 1354 (C-S), 1561 (C-N), 1649 (C-C), 1718 (C=O), 2563 (N-N), 2951 (C-H), 3061 (Ar C-H). ^1H NMR (δ ppm): 1.65 (s, 3H, CH_3), 2.87 (s, 6H, N-CH_3), 3.29 (s, 1H, CH_2), 5.56 (s, 1H, CH), 5.99 (s, 1H, CH), 6.18 (bs, 2H, NH), 6.54-7.93 (m, 8H, Ar-H). **MS**: *m/z* 496 (M^+, 100%). Anal.Calcd. ($C_{23}H_{24}N_6O_5S$): C, 55.63; H, 4.87; N, 16.93; S, 6.46. Found: C, 55.61; H, 4.85; N, 16.90; S, 6.45.

Analysis of 4-(4-(dimethylamino)phenyl)-1,2,3,4-tetrahydro-6-methyl-N-(2-(3-nitrophenyl)-4-oxothiazolidin-3-yl)-2-oxopyrimidine-5-carboxamide **4c**

M.P: 123-126°C. Yield: 55%. IR (cm^{-1}): 1325 (C-S), 1568 (C-N), 1661 (C-C), 1710 (C=O), 2556 (N-N), 2942 (C-H), 3079 (Ar C-H). ^1H NMR (δ ppm): 1.65 (s, 3H, CH_3), 2.68 (s, 6H, N-CH_3), 3.24 (s, 1H, CH_2), 5.55 (s, 1H, CH), 5.83 (s, 1H, CH), 6.15 (bs, 2H, NH), 6.60-8.11(m, 8H, Ar-H). **MS**: *m/z* 496 (M^+, 100%). Anal.Calcd. ($C_{23}H_{24}N_6O_5S$): C, 55.63; H, 4.87; N, 16.93; S, 6.46. Found: C, 55.60; H, 4.88; N, 16.91; S, 6.44.

Analysis of 4-(4-(dimethylamino)phenyl)-1,2,3,4-tetrahydro-N-(2-(2-hydroxyphenyl)-4-oxothiazolidin-3-yl)-6-methyl-2-oxopyrimidine-5-carboxamide **4d**

M.P: 185-188°C. Yield: 72%. IR (cm^{-1}): 1336 (C-S), 1572 (C-N), 1637 (C-C), 1723 (C=O), 2571 (N-N), 2948 (C-H), 3071 (Ar C-H). ^1H NMR (δ ppm): 1.69 (s, 3H, CH_3), 2.79 (s, 6H, N-CH_3), 3.28 (s, 1H, CH_2), 5.59 (s, 1H, CH), 5.96 (s, 1H, CH), 6.18 (bs, 2H, NH), 6.63-7.28 (m, 8H, Ar-H). **MS**: *m/z* 467 (M^+, 100%). Anal.Calcd. ($C_{23}H_{25}N_5O_4S$): C, 59.08; H, 5.39; N, 14.98; S, 6.86. Found: C, 59.04; H, 5.36; N, 14.95; S, 6.84.

Analysis of 4-(4-(dimethylamino)phenyl)-1,2,3,4-tetrahydro-N-(2-(4-hydroxyphenyl)-4-oxothiazolidin-3-yl)-6-methyl-2-oxopyrimidine-5-carboxamide **4e**

M.P: 128-130°C. Yield: 57%. IR (cm^{-1}): 1321 (C-S), 1565 (C-N), 1647 (C-C), 1727 (C=O), 2569 (N-N), 2954 (C-H), 3065 (Ar C-H). ^1H NMR (δ ppm): 1.62 (s, 3H, CH_3), 2.73 (s, 6H, N-CH_3), 3.31 (s, 1H, CH_2), 5.67 (s, 1H, CH), 5.93 (s, 1H, CH), 6.10 (bs, 2H, NH), 6.43-7.11 (m, 8H, Ar-H). **MS**: *m/z* 467 (M^+, 100%). Anal.Calcd. ($C_{23}H_{25}N_5O_4S$): C, 59.08; H, 5.39; N, 14.98; S, 6.86. Found: C, 59.10; H, 5.36; N, 14.95; S, 6.84.

Analysis of 4-(4-(dimethylamino)phenyl)-1,2,3,4-tetrahydro-N-(2-(4-methoxyphenyl)-4-oxothiazolidin-3-yl)-6-methyl-2-oxopyrimidine-5-carboxamide **4f**

M.P: 141-142°C. Yield: 69%. IR (cm^{-1}): 1348 (C-S), 1555 (C-N), 1669 (C-C), 1717 (C=O), 2561 (N-N), 2949 (C-H), 3068 (Ar C-H). ^1H NMR (δ ppm): 1.73 (s, 3H, CH_3), 2.68 (s, 6H, N-CH_3), 3.27 (s, 1H, CH_2), 3.81 (s, 3H, OCH_3), 5.62 (s, 1H, CH), 5.91 (s, 1H, CH), 6.14 (bs, 2H, NH), 6.37-7.21 (m, 8H, Ar-H). **MS**: *m/z* 481 (M^+, 100%). Anal.Calcd. ($C_{24}H_{27}N_5O_4S$): C, 59.86; H, 5.65; N, 14.54; S, 6.66. Found: C, 59.89; H, 5.62; N, 14.55; S, 6.64.

Analysis of N-(2-(4-chlorophenyl)-4-oxothiazolidin-3-yl)-4-(4-(dimethylamino)phenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide **4g**

M.P: 149-153°C. Yield: 66%. IR (cm^{-1}): 1332 (C-S), 1563 (C-N), 1658 (C-C), 1708 (C=O), 2559 (N-N), 2943 (C-H), 3062 (Ar C-H). ^1H NMR (δ ppm): 1.64 (s, 3H, CH_3), 2.77 (s, 6H, N-CH_3), 3.33 (s, 1H, CH_2), 5.65 (s, 1H, CH), 5.89 (s, 1H, CH), 6.12 (bs, 2H, NH), 6.40-7.51 (m, 8H, Ar-H). **MS**: *m/z* 485 (M^+, 100%). Anal.Calcd. ($C_{23}H_{24}ClN_5O_3S$): C, 56.84; H, 4.98; Cl, 7.30; N, 14.41; S, 6.60. Found: C, 56.85; H, 4.95; Cl, 7.28; N, 14.45; S, 6.62.

Pharmacological appraisal

Anti-inflammatory activity:

The *in vivo* anti-inflammatory activity for the synthesized compounds was evaluated by the carrageenan induced hind paw edema method [22]. Wistar albino rats both male and female weighing around 150-200 g were used for this study. The experimental protocol for anti-inflammatory activity was approved by the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Ministry of Social Justice and Empowerment, Government of India **(SPCP/2013/595-2)**. The rats were divided into 9 groups of 4 animals each. The rats belonging to Group I, which was kept as the control, were given only 0.5% w/v carboxymethyl cellulose (CMC) whereas those of Group II were given standard drug

Diclofenac (10 mg/kg). The synthesized test compounds (40 mg/ kg) were administered orally to the rats of Group III and the other groups respectively. After 1hr of drug administration, all the rats were injected with freshly prepared 0.1 ml of 1% carrageenan solution in normal saline in the subplantaraponeurosis of left hind paw so as to induce inflammation. The volume of injected paw was measured using plethysmometer immediately (at 0 hr) and then at an interval of 1hr up to 3 hr (Table 1).The average paw volume in a group of treated rats was compared with control group and the percentage inhibition of edema was calculated by using the formula:

Percent inhibition = (1-Vt/Vc) x 100

Where;

Vt is the mean paw volume of the test and drug treated rats and

Vc is the mean paw volume of the control.

The results obtained are expressed as mean ± S.E.M. (standard error of mean) of four rats. Statistical differences of control and test groups were carried out using the Analysis of Variance (ANOVA) followed by Dunnett's test**.** The difference in results was considered significant when $P < 0.05$.

Analgesic activity:

Wistar albino rats both male and female weighing around 150-200 g were used for this study. The animals were divided into 9 groups each of 4 rats. One group was kept as a control and another group received the standard drug Indomethacin (at a dose of 10 mg/kg body weight). The tested compounds were administrated orally at a dose of 10 mg/kg and Indomethacin was used as a reference drug (10 mg/kg). The analgesic activity of the synthesized compounds was evaluated by applying the Hot plate method [23] where the painful stimulus is represented by a hot plate. The temperature of the plate was maintained at 55 ± 1°C. Rats were placed on the hot plate and the time required by them for flicking their tail or jumping off the plate was recorded (Table 2). The analgesic activity was measured at 30 min, 60 min, 90 min and 120 min time intervals after drug administration. The results obtained are expressed as mean ± S.E.M. (standard error of mean) of six rats. Statistical differences of control and test groups were carried out using the Analysis of Variance (ANOVA) followed by Dunnett's test**.** The difference in results was considered significant when $P < 0.05$.

Anti-bacterial activity:

The *in vitro*anti-bacterial activity of the newly synthesized compounds was estimated bythe well diffusion method using Hi-Media agar medium against some gram positive *(Staphylococcusaureus, Bacillussubtilis)* and gram negative *(Escherichia coli, Klebsiellapneumoniae)* strains of bacteria. In the method herein, the Petri plates of agar medium were prepared by pouring melted agar inoculated with above mentioned strains of bacteria. Wells were scooped out of the agar medium contained in these Petri plates.Each test compound (1 mg) was dissolved in ethanol (1 ml, 1000 µg/ml), which was used as sample solution. Sample size for

all the compounds was fixed at 0.1 ml. The test compound solution (0.1 ml) was added in the wells and the Petri plates were subsequently incubated at 37°C for 24 hr.Ampicillin and Streptomycin were used as reference drugs and ethanol as the negative control. The zones of inhibition thus produced by each compound were measured and compared with the control and the consequent results are depicted in Table 3.

Results and Discussion:

Chemistry:

A series of thiazolidinone derivatives bearing the dihydropyrimidinone skeleton **4(a-g)**was synthesized using CAN under good yield. The synthesis was carried out following the synthetic route outlined in **Scheme 1**.Reaction progress was duly monitored by TLC. The structures of various synthesized compounds were assigned on the basis of elemental and spectral studies. The melting points and corresponding % yields (physical data) of all the synthesized compounds **4(a-g)** along with the IR, ^{1}H NMR and Mass spectral data are represented in the experimental protocols.

The IR spectrum of compounds **4(a-g)** reveals a characteristic aromatic stretching within 3079-3062 cm^{-1}. The spectra also showed absorption peak within 1572-1555 cm^{-1} due to C-N vibrations. Absorption peak within 1357-1321 cm^{-1} confirmed the presence of C-S bond. Spectra also cleared the information regarding the frequency ranging from 1727-1706 cm^{-1} which accounts for the presence of (C=O). The ^{1}H NMR spectra were recorded in DMSO-d_6 using TMS as internal standard.The NMR data of all compounds exhibit multiplet peak between 6.37-8.11 ppm owing to the presence of aromatic protons. Sharp singlet within 2.68-2.87 ppm range is a characteristic of the methyl protons of the para dimethyl amino group. The other signals and peaks of ^{1}H NMR and IR are in complete agreement with the assigned structures. The mass spectra of the requisite compounds displayed a molecular ion peak at appropriate m/z values, which corresponded well with the respective molecular formula. The compounds gave satisfactory results for their elemental analysis.

Pharmacological Assessment:

The synthesized compounds were screened for their *in vivo* anti-inflammatory activity by the carrageenan induced rat paw edema method. The compounds were tested at dose level of 40 mg/ kg. Observed results reveal that, all the compounds show significant anti-inflammatory activity against control at the said concentration after 3 hours.The compounds exhibited anti-inflammatory activity ranging from 28.26% to 54.34% (Table 1), when compared to standard drug Diclofenac (83.69%). Compounds **4b, 4c** and **4g** were found to be potent anti-inflammatory agents.

The *in vivo* analgesic activity of the synthesized compounds was determined by the Hot plate method. Rats administered with doses of compounds **4c, 4f** and **4g** required greater time for jumping off the hot plate and thus these compounds were considered to be active analgesic agents.

Besides, *in vitro* anti-bacterial activity for the synthesized compounds was also evaluated against some gram positive and gram negative strains of bacteria using the well diffusion method. Compounds **4b, 4c** and **4g**were found to be highly active against all the tested strains of bacteria showing the broadest spectrum of antibacterial activity against the selected pathogens. Thus, the combined observed results of the *in vivo* and *in vitro* studiesinfer thatthe synthesized compounds may be utilized as potent anti-inflammatory, analgesic and anti-bacterial agents.

Table 1: Anti-inflammatory activity of compounds**4(a-g)**

Compounds	Paw volume (ml) ± SEM				% inhibition
	0hr	1hr	2hr	3hr	after 3hr
Control	0.37±0.009	0.72±0.009	0.89±0.006	0.92±0.008	-
Diclofenac	0.34±0.011	0.27±0.009	0.21±0.006	0.15±0.010	83.69
4a	0.33±0.006	0.74±0.008	0.69±0.006	0.66±0.006	28.26
4b	0.32±0.009	0.66±0.012	0.54±0.009	0.55±0.009*	40.21
4c	0.31±0.013	0.62±0.006	0.58±0.009	0.50±0.009*	45.65
4d	0.28±0.008	0.69±0.006	0.61±0.009	0.59±0.009	35.87
4e	0.32±0.006	0.72±0.006	0.69±0.013	0.63±0.006*	31.52
4f	0.25±0.009	0.77±0.008	0.71±0.006	0.66±0.006*	28.26
4g	0.32±0.006	0.55±0.009	0.45±0.008	0.40±0.009	54.34

Data were given in mean ± SEM and analyzed by ANOVA followed by Dunnett's multiple comparison test, (n= 6). *P < 0.05 compared to standard drug.

Table 2: Analgesic activity of compounds**4(a-g)**

Compounds	Response time (min) after			
	30 min	60 min	90 min	120 min
Control	3.34±0.09	3.39 ±0.09	3.42±0.06	3.47±0.08
Indomethacin	9.67±0.11	11.55±0.09	13.32±0.06	15.15±0.10
4a	4.33±0.06	5.74±0.08*	6.69±0.06	7.66±0.06
4b	4.79±0.09	6.66±0.12	7.54±0.09	9.55±0.09*
4c	7.99±0.13*	9.02±0.06	10.58±0.09	11.50±0.09
4d	5.18±0.08	6.69±0.06	7.36±0.09*	7.99±0.09
4e	2.82±0.06	3.27±0.06	5.39±0.13	6.63±0.06*
4f	6.85±0.09	7.77±0.08	9.31±0.06	10.66±0.06
4g	8.42±0.06	10.55±0.009	11.85±0.08	12.40±0.09*

Data were given in mean ± SEM and analyzed by ANOVA followed by Dunnett's multiple comparison test, (n= 6). *P < 0.05 compared to standard drug.

Table 3: Anti-bacterial activity of compounds**4(a-g)**

Compounds	Gram-positive bacteria		Gram-negative bacteria	
	S. aureus	*B. subtilis*	*E. coli*	*K. pneumoniae*
4a	++	+	++	++
4b	+++	++	++	++
4c	++	+++	+++	++
4d	++	+	+	+++
4e	++	+	++	++
4f	+	++	-	+++
4g	++	++	+	++
Ampicillin	+++	++	+++	++
Streptomycin	+++	+++	+++	+++

Key to symbols: inactive = - (inhibition zone < 5 mm); slightly active = + (inhibition zone 5-10 mm);moderately active = + + (inhibition zone 10-15 mm); highly active = + + + (inhibition zone > 15 mm).

Conclusion:

A series of thiazolidinone derivatives were synthesized in appreciable yield. The compounds showed moderate to good results for theanti-inflammatory and analgesic activity analysis when compared to the standard reference drug Diclofenac and Indomethacin respectively. The compounds were also found to be the active anti-bacterial agents with reference to standard drug Ampicillin and Streptomycin. Thus these synthesized compounds can be used as anti-inflammatory, analgesic and anti-bacterial agents.

Acknowledgement:

The authors thank the Head, Department of Chemistry, RTM Nagpur University, Nagpur for providing essential laboratory facilities and Director, SAIF, Chandigarh for providing spectral data. The authors also wish to thank the Head, SharadPawar College of Pharmacy, Nagpur, India and Head, Department of Biotechnology, SindhuMahavidyalaya, Nagpur, India for the pharmacological studies.

References:

[1] **Look, G.C., Schullek, J.R., Holmes, C.P., Chinn, J.P., Gordon, E.M. and Gallop, M.A. (1996):**The identification of cyclooxygenase-1 inhibitors from 4-thiazolidinone combinatorial libraries. Bioorg. Med. Chem. Lett. **6**: Pp. 707-712.

[2] **Allen, S., Newhouse, B., Anderson, A.S., Fauber, B., Allen, A., Chantry, D., Eberhardt, C., Odingo, J., Burgess, L.E. (2004):**Discovery and SAR of trisubstitutedthiazolidinones as CCR4 antagonists. Bioorg. Med. Chem. Lett. **14**: Pp. 1619-1624.

[3] **Ottana, R., Carotti, S., Maccari, R., Landini, I., Chiricosta, G., Caciagli, B., Vigorita, M.G. and Mini, E. (2005):***In vitro antiproliferative activity against human colon cancer cell lines* of *representative 4-thiazolidinones*. Bioorg. Med. Chem. Lett. **15**: Pp. 3930-3933.

[4] **Gududuru, V., Hurh, E., Dalton, J.T. and Miller, D.D. (2004):**Synthesis and antiproliferative activity of 2-aryl-4-oxo-thiazolidin-3-yl-amides for prostate cancer. Bioorg. Med. Chem. Lett. **14**: Pp. 5289-5293.

[5] **Diurno, M.V., Mazzoni, O., Piscopo, E., Calignano, A., Giordano, F. and Bolognese, A. (1992):**Synthesis and Antihistaminic Activity of Some. Thiazolidin-4-ones. J. Med. Chem. **35**: Pp. 2910-2912.

[6] **Rawal, R.K., Tripathi, R.K., Katti, S.B., Pannecouque, C. and De Clercq, E. (2007):**Design, synthesis and evaluation of 2-aryl-3-heteroaryl-1,13-thiazolidin-4-ones as anti-HIV agents. Bioorg. Med. Chem. **15**: Pp. 1725-1731.

[7] **Solomon, V.R., Haq, W., Srivastava, K., Puri, S.K. and Katti, S.B. (2012):** Design and synthesis of 3-[(7-chloro-1-oxidoquinolin-4-ylamino)alkyl]-1,3-thiazolidin-4-ones as antimalarial agents. Enzyme Inhib Med Chem. **7**

[8] **Lesyk, R., Zimenkovsky, B., Atamanyuk ,D. and Jensen, F. (2006):**Anticancer thiopyrano[2,3-d][1,3]thiazol-2-ones with norbornane moiety. Synthesis, cytotoxicity,

physico-chemical properties, and computational studies.Bioorg. Med. Chem. 14: Pp. 5230-5240.

[9] **Sim, M.M., Ng, S.B., Buss, A.D., Crasta, S.C., Goh, K.L. and Lee, S.K. (2002):**Benzylidenerhodanines as novel inhibitors of UDP N-acetylmuramate/L-alanine ligase. Bioorg. Med. Chem. Lett. **12**: Pp. 697-699.

[10] **Rawal, R.K., Tripathi, R., Katti, S.B., Pannecouque, C. and De Clercq, E. (2007):**Synthesis and evaluation of 2-(2,6-dihalophenyl)-3-pyrimidinyl-1,3-thiazolidin-4-one analogues as anti-HIV-1 agents.Bioorg. Med. Chem. **15**: Pp. 3134-3142.

[11] **Vishvakarma, V.K., Singh, P., Dubey, M., Kumari, K., Chandra, R. and Pandey, N.D. (2013):**Quantitative structure-activity relationship analysis of thiazolidineones: potent antidiabetic compounds. Drug Metabolism and Drug interaction.**28**: Pp. 31-47

[12] **Bailey, C.J. (2000):**Potential new treatments for type 2 diabetes. Trends Pharm. Sci.**21**: Pp. 259-265.

[13] **Murphy, G.J. and Holder, J.C. (2000):**PPAR-gamma agonists: therapeutic role in diabetes, inflammation and cancer..Trends Pharm. Sci.**21**: Pp. 469-474.

[14] **Brown, F.C. (1961):** 4-Thiazolidinones. Chem. Rev.**61**: Pp. 463-521.

[15] **Rawal, R.K., Tripathi, R.K., Katti, S.B., Pannecouque, C. and De Clercq, E. (2007):**Synthesis and biological evaluation of 2,3-diaryl substituted-1,3-thiazolidin-4-ones as anti-HIV agents. **Med Chem** 3: Pp. 355-363

[16] **Raza S, Srivastava SP, Srivastava DS, Srivastava AK, Haq W andKatti SB. (2013):**Thiazolidin-4-one and thiazinan-4-one derivatives analogous to rosiglitazone as potential antihyperglycemic and antidyslipidemic agents. Eur J Med Chem. 63: Pp. 611-620.

[17] **Rawal, R.K., Kumar, A., Siddiqi, M.I.and KattiSetu B**. (**2007):** Molecular docking studies on 4-thiazolidinones as HIV-1 RT inhibitors.Journal of Molecular Modeling (Online). 13: Pp. 155-161

[18] **Rawal, R.K., Prabhakar, Y.S. and Katti, S.B.(2007):** Molecular surface features in modeling the HIV-1 RT inhibitory activity of 2-(2,6-disubstituted phenyl)-3-(substituted pyrimidin-2-yl)-thiazolidin-4-ones. **QSAR & Combinatorial Science. 26**: Pp. 398-406

[19] **Rawal, R.K., Tripathi, R.K., Katti, S.B., Pannecouque, C. and De Clercq, E. (2007):**Synthesis and biological evaluation of 2,3-diaryl substituted-1,3-thiazolidin-4-ones as anti-HIV agents. **Med Chem. 3**: Pp. 355-363

[20] **Y. Quin, G. -Y. Ma, Y. Yang, K. Cheng, Q. -Z. Zheng, W. J. Mao, L. Shi, J. Zhao and H. L. Zhu, (2010):**Synthesis, molecular modeling and biological evaluation of dithiocarbamates as novel antitubulin agents. Bio. Org. Med. Chem. **18**: Pp. 4310-4316.

[21] **Shaikh, A. and Meshram, J. (2013):**Synthesis and pharmacological activity evaluation of oxadiazoles containing substituted dihydropyrimidinone and chloroquinoline moieties. Int. J. Pharm. Sci. Res.**4** (12): Pp. 4607-4614.

[22] **Winter, C.A., Risley, E.A. and Nuss, G.W. (1962):**Carrageenan-induced edema in hind paws of the rat as an assay for anti-inflammatory drugs. Proc. Soc. Exp. Biol. Med. **111**: Pp. 544-547.

[23] **Turner, R.A. (1965):***Screening Methods in Pharmacology*, Academic Press: London. Pp. 100-116.


I J R B A T