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# Development of Efficient Manufacturing Process for Active Pharmaceutical Ingredient Epalrestat and its Derivatives in Continuous Flow Synthesis

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An effective method for synthesis of the active pharmaceutical ingredient epalrestat in continuous or tubular flow circumstances with a high yield and a quick reaction time (10 min) has been reported. The reaction conditions for the aldol condensation reaction under tubular continuous flow technology by controlling light-sensitive degradation impurities was optimized. The developed method was more efficient, environmentally benign, time-economic, energy-saving, cost-efficient and also gives a reduction in process mass intensity in comparison with batch process.

**Keywords: Aldol condensation, Process intensification, Continuous flow, Epalrestat.**

## INTRODUCTION

Epalrestat is a reversible and non-competitive aldose reductase inhibitor (ARI) used to treat diabetes problems such as cataract, nephropathy, retinopathy and diabetic neuropathy [1]. Epalrestat works by blocking the enzyme aldose reductase and is the only carboxylic acid ARI, which has been approved for use as a medicinal medication for diabetic complications [2]. Epalrestat can be prepared *via* the construction of two structurally distinct units: phenylacrylaldehyde and thioxothiazolidine acetic acid. Ever since the first synthesis of epalrestat (**1**) by Ono pharmaceuticals [3] in 1984, various optimization trials have been developed.

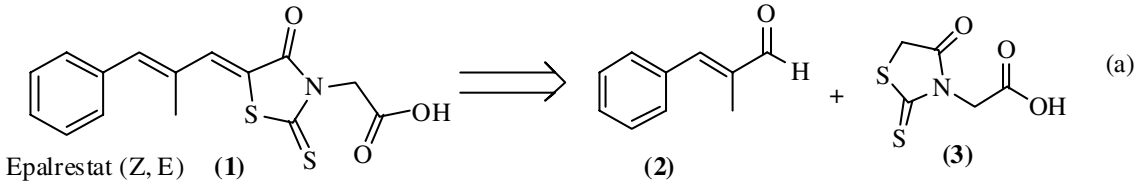
One of the most practical methods for the preparation of epalrestat (**1**) is the aldol condensation between phenylacrylaldehyde (**2**) and thioxothiazolidine acetic acid (**3**) (**a, Scheme-I**). Previously, a reaction time of 8 h was required to achieve the desired product conversion and a high purity product with a higher yield was difficult to obtain due to the high level of impurities formation (**b, Scheme-I**). A large quantity of reagents and process solvents (acetic acid and ethanol) are also required, which leads to high manufacturing costs and environmental hazards. Thus, the development of efficient, green and cost-saving method for the synthesis of epalrestat is demanding and most-indeed in pharmaceutical industry.

In recent studies, tubular flow process has become one of the most emerging technologies that can substantially affect the manufacturing process [4-9]. This tubular flow technology is symbolized with safe process, precise control of reaction variables, occurrence of process condition under high pressure and high temperature (process intensification), high reproducibility, automation, compliance of production scale, line of purification, smaller size of manufacturing area. Many cases, the tubular flow technology has successfully been applied in several active pharmaceuticals manufactures, like ciprofloxacin [10], betahistine [11], prexasertib [12] and edoxaban [13]. Utilizing the dominance of tubular flow process, herein, we report a continuous flow synthesis process of eplarestat with various advantages, which substantially reduced the reaction time and improved the product conversion, subsequently enhancing the yield (d, **Scheme-I**). This flow condition is expected to give a shorter period of reaction time, cost economical, reproducible, reliable, reduction in process mass intensity and green process for the synthesis of eplarestat.

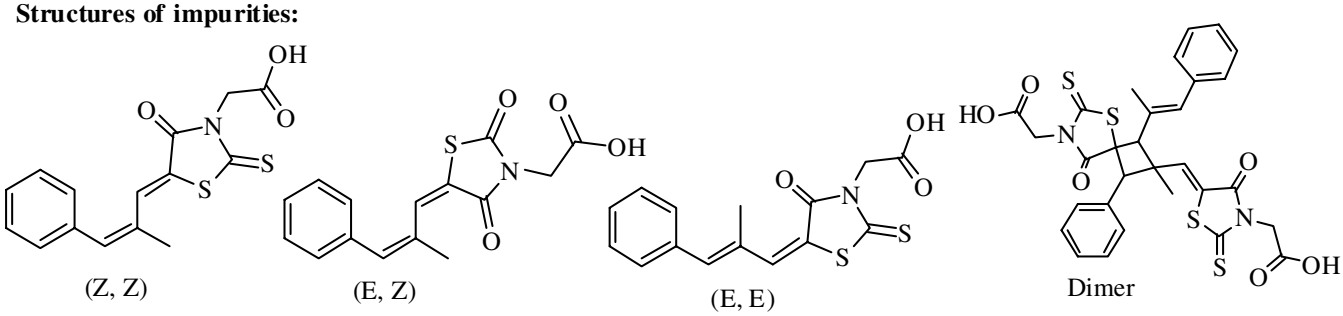
## EXPERIMENTAL

The chemicals used for this research were brought from Sigma-Aldrich, USA. The TLC plates ($60F_{254}$) were used to monitor the reaction progress under short and long UV light.

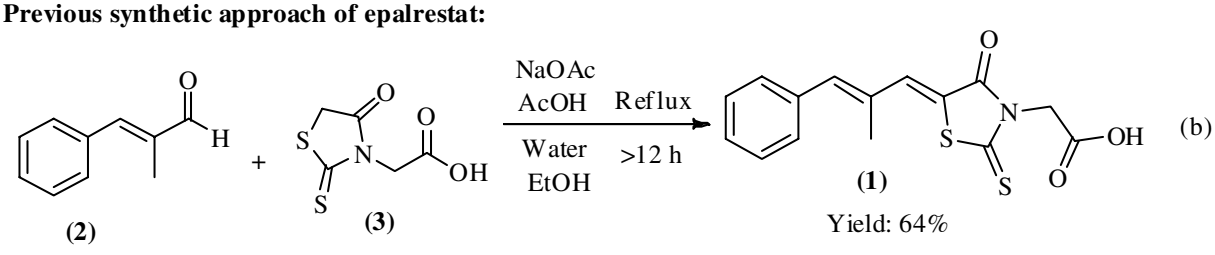
**Retro synthetic approach of epalrestat:**

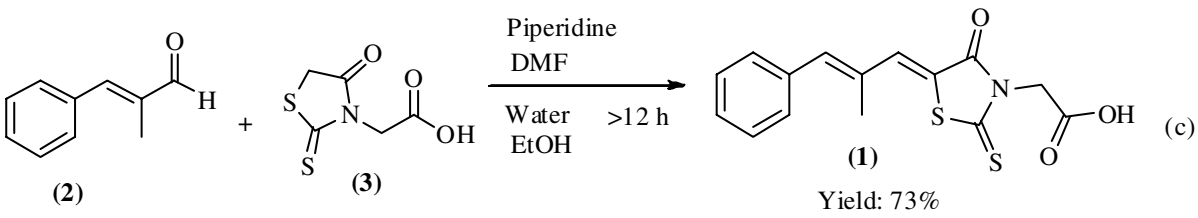



**Structures of impurities:**

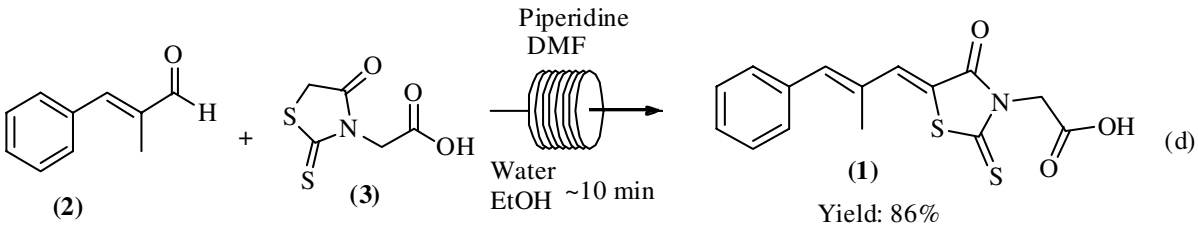



**Previous synthetic approach of epalrestat:**




**Current flow approach of epalrestat:**




**Scheme-I:** Schematic for the preparation of epalrestat

Continuous flow experiments were conducted with the HPLC pumps of JASCO Corporation and parts of Chromatopak Analytical Instrumentation (India) Pvt. Ltd. Melting points were recorded using Mettler Toledo MP70 model and were corrected. $^{1}H$ & $^{13}C$ NMR spectra were recorded using 400 MHz on Bruker Avance spectrometer with tetramethylsilane (TMS) as a standard. Identification by mass was carried out on a Waters UPLC H-Class connected to Xevo-G2 XS Q-TOF detector (high resolution mass spectrophotometer) by using Acquity UPLC BEH C18 (50 × 2.1) mm, 1.7 µm column as stationary phase at 40 ºC column oven temperature, mixture of 0.1% formic acid in water:acetonitrile (20:80) v/v mixture as mobile phase at flow rate of 0.3 mL/min and run-time up to 5 min. For mass detector ionization source ESI negative mode with Source temperature 150 ºC, capillary voltage 2.1 kV, cone voltage 20 V, desolvation gas flow 800 L/h, Cone gas flow at 20 L/h and desolvation temperature set at 450 ºC.

Purity by HPLC analysis was carried out on a Waters e2645 HPLC system with UV/Visible detector by using C18 stationary phase (Make: Inertsil ODS-3V (150 × 4.6) mm, 5 µm) column as stationary phase at 25 ºC column oven temperature and to 0.05 mol/L potasium dihydrogen phosphate added

0.05 mol/L disodium hydrogen phosphate (pH 6.50). To a 2 volumes of this mixture added, 1 volume of acetonitrile used as mobile phase at flow rate 1.0 mL/min, recorded UV absorbance at 280 nm, isocratic elution mode at run time of 40 min.

**Synthesis of (5*Z*)-5-[(2*E*)-2-Methyl-3-phenyl-2-propen-1-ylidene]-4-oxo-2-thioxo-3-thiazolidine acetic acid/epalrestat in batch process**: Phenylacrylaldehyde (**2**) (1.0 g, 6.84 mmol), thioxothiazolidine acetic acid (**3**) (1.31 g, 6.84 mmol), piperidine (0.58 g, 6.84 mmol) in DMF (13 mL) solvent were charged into the round bottom flask. The reaction mass was warmed to 50-55 ºC and stirred for 8 h. Upon reaction completion, the reaction was cooled to 20-30 ºC, 10 N HCl (1 mL) was added, the mixture was stirred for 1 h and then obtained solid was filtered. The wet filter cake was washed with ethanol (12 mL) and then dried under reduced pressure to obtain pure 1.43 g of epalrestat (**1**).

**General flow procedure for the synthesis of epalrestat and its intermediates in a continuous flow reactor (5a-k):** A continuous flow reactor set-up contains two pumps, a micro mixer (T-shaped tee, OD 1/163) and stainless steel tubular reactor. The oil bath was used to control reaction temperature. The reaction mixture was heated to 100 ºC in the stainless steel tubular flow reactor and in a short stainless steel tubular reactor cooled to 25-30 ºC, 0-5.2 bar sustainable range of pressures adjustable back pressure regulator (BPR) was placed at the outlet of the tubular reactor. The flow reaction set up is shown in Fig. 1.

A solution of thioxothiazolidine acetic acid (**3**) (1.0 g, 5.23 mmol), piperidine (0.44 g, 5.23 mmol) mixture in DMF (5 mL), (0.5 mL $min^{-1}$, flow rate) and a solution of aldehyde derivative (2) (1.0 eq, 5.23 mmol) in DMF (5 mL) (0.5 mL $min^{-1}$, flow rate) were sent into the micro mixer by a HPLC pump (PA, PB). The combined solution introduced in the stainless steel reactor coil (1/163 ID, V = 8.0 mL, 100 ºC, t = 8 min) through the adjustable BPR, fractions were collected to the batch reactor, then the reaction mixture was acidified with 10 N HCl (1 mL). The product was filtered and washed with ethanol (12 mL), the wet cake dried under reduced pressure to obtain pure epalrestat (**1**), the resulting product was used for analysis.

**(5*Z*)-5-[(2*E*)-2-Methyl-3-phenyl-2-propen-1-ylidene]-4-oxo-2-thioxo-3-thiazolidine acetic acid (5a):** Yellow colour solid, yield: 86%, m.p.: 210-212 ºC; $^1$H NMR (400 MHz; $CDCl_3$) δ ppm: 13.43 (1H, s), 7.63 (1H, m), 7.46 (4H, m), 7.38 (2H, m), 4.73 (2H, s), 2.23 (3H, s); $^{13}$C NMR (100 MHz; $CDCl_3$) δ ppm: 16.0, 45.1, 120.5, 128.8, 128.9, 129.8, 133.2, 136.0, 140.2, 144.8, 166.6, 167.5, 193.4; Purity by HPLC: 99.93 (area %), HRMS (ESI) calcd. for $C_{15}H_{13}NO_3S_2$, [M-H] exact mass 318.0264 Da, found 318.0267 Da.

**(*Z*)-2-(5-(4-Ethoxybenzylidene)-4-oxo-2-thioxothiazolidin-3-yl)acetic acid (5b):** Pale yellow solid, yield: 81%; $^1$H NMR (400 MHz; $CDCl_3$) δ ppm: 13.39 (1H, s), 7.84 (1H, s), 7.64-7.61 (2H, d), 7.12-7.10 (2H, d), 4.72 (2H, s), 4.15-4.10 (2H, m), 1.36-1.32 (3H, t); HRMS (ESI) calcd. for $C_{14}H_{12}NO_4S_2$: [M-H] exact mass 322.0213 Da, found 322.0401 Da.

**(*Z*)-2-(5-(2-Methoxybenzylidene)-4-oxo-2-thioxothiazolidin-3-yl)acetic acid (5c):** Pale yellow solid, yield: 81%, $^1$H NMR (400 MHz, DMSO) δ ppm: 13.40 (1H, s), 7.98 (1H, s), 7.55-7.47 (2H, m), 7.19-7.10 (2H, m), 4.72 (2H, s), 3.92 (3H, m); HRMS (ESI) calcd. for $C_{13}H_{10}NO_4S_2$: [M-H] exact mass 308.0057 Da, found 308.0231 Da.

**(*Z*)-2-(5-(4-Methylbenzylidene)-4-oxo-2-thioxothiazolidin-3-yl)acetic acid (5d):** Pale yellow solid, yield: 68 %, $^1$H NMR (400 MHz, $CDCl_3$) δ ppm: 13.41 (1H, s), 7.85 (1H, s), 7.55-7.57 (2H, m), 7.39-7.37 (2H, m), 4.73 (2H, s), 2.36 (3H, s); HRMS (ESI) calcd. for $C_{13}H_{10}NO_3S_2$: [M-H] exact mass 292.0108 Da, found 292.0276 Da.

**(*Z*)-2-(5-(3,4-Dimethoxybenzylidene)-4-oxo-2-thioxothiazolidin-3-yl)acetic acid (5e):** Pale yellow solid, yield: 83%; $^1$H NMR (400 MHz, $CDCl_3$) δ ppm: 13.38 (1H, s), 7.84 (1H, s), 7.28-7.24 (2H, m), 7.15-7.17 (1H, m), 4.73 (2H, s), 3.84 (3H, m), 3.83 (3H, m); HRMS (ESI) calcd. for $C_{14}H_{12}NO_5S_2$: [M-H] exact mass 338.0162 Da, found 338.0348 Da.

**(*Z*)-2-(5-(3-Nitrobenzylidene)-4-oxo-2-thioxothiazolidin-3-yl)acetic acid (5f):** Pale yellow solid, yield: 83%; $^1$H NMR (400 MHz, $CDCl_3$) δ ppm: 13.46 (1H, s), 8.51 (1H, s), 8.31-8.33 (1H, m), 8.05-8.07 (2H, m), 7.82-7.86 (1H, m), 4.75 (2H, s); HRMS (ESI) calcd. for $C_{12}H_8N_2O_5S_2$: [M-H] exact mass 322.9802 Da, found 322.9962 Da.

**(*Z*)-2-(5-(4-Nitrobenzylidene)-4-oxo-2-thioxothiazolidin-3-yl)acetic acid (5g):** Pale yellow solid, yield: 83%; $^1$H NMR (400 MHz, $CDCl_3$) δ ppm: 13.45 (1H, s), 8.34-8.36 (2H, m), 8.0 (1H, s), 7.92-7.94 (3H, m), 4.75 (2H, s); HRMS (ESI) calcd. for $C_{12}H_7N_2O_5S_2$: [M-H] exact mass 322.9802 Da, found 322.9964 Da.

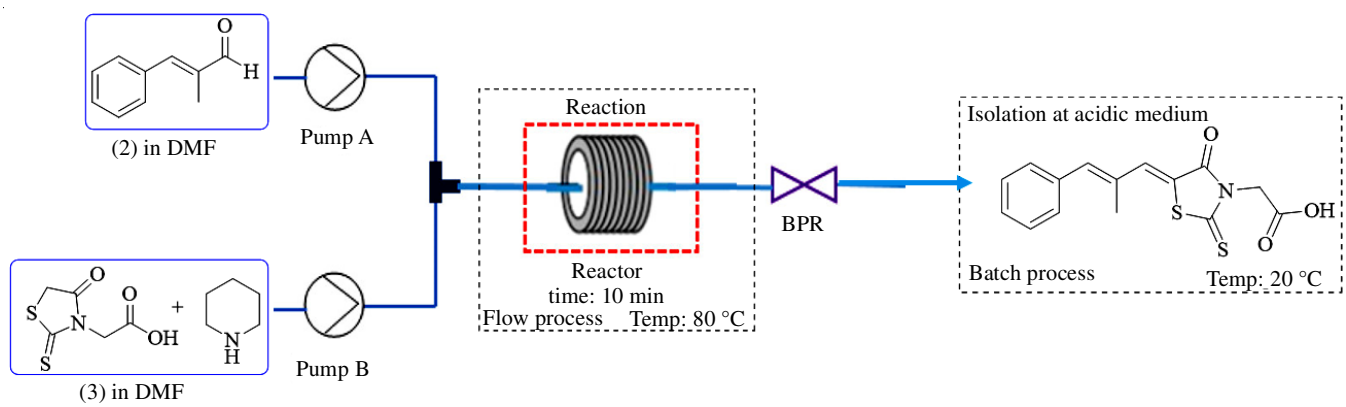



Fig. 1. Flow reaction setup for the synthesis of epalrestat

**(*Z*)-2-(5-(4-Chlorobenzylidene)-4-oxo-2-thioxothiazolidin-3-yl)acetic acid (5h):** Pale yellow solid, yield: 83%; $^1$H NMR (400 MHz, $CDCl_3$) δ ppm: 13.38 (1H, s), 7.84 (1H, s), 7.61-7.64 (2H, m), 7.10-7.12 (2H, m), 4.72 (2H, s); HRMS (ESI) calcd. for $C_{12}H_7ClNO_3S_2$: [M-H] exact mass 311.9561 Da, found 311.9678 Da.

**(*Z*)-2-(5-(4-Fluorobenzylidene)-4-oxo-2-thioxothiazolidin-3-yl)acetic acid (5i):** Pale yellow solid, yield: 83%; $^1$H NMR (400 MHz, $CDCl_3$) δ ppm: 13.32 (1H, s), 7.91 (1H, s), 7.73-7.77 (2H, m), 7.39-7.43 (2H, m), 4.73 (2H, s); HRMS (ESI) calcd. for $C_{12}H_7FNO_3S_2$: [M-H] exact mass 295.9857 Da, found 295.9946 Da.

**(*Z*)-2-(5-Benzylidene-4-oxo-2-thioxothiazolidin-3-yl) acetic acid (5j):** yellow solid, yield: 83%; $^1$H NMR (400 MHz, $CDCl_3$) δ ppm: 13.41 (1H, s), 7.89 (1H, s), 7.66-7.68 (2H, m), 7.53-7.59 (3H, m), 4.74 (2H, s); HRMS (ESI) calcd. for $C_{12}H_8NO_3S_2$: [M-H] exact mass 277.9951 Da, found 278.0088 Da.

**(*Z*)-2-(5-(2-Hydroxybenzylidene)-4-oxo-2-thioxothiazolidin-3-yl)acetic acid (5k):** Off Yellow colour solid, yield: 74%; $^1$H NMR (400 MHz, $CDCl_3$) δ ppm: 13.38 (1H, s), 10.78 (1H, s), 8.03 (1H, s), 7.34-7.39 (2H, m), 6.95-6.99 (3H, m), 4.72 (2H, s); HRMS (ESI) calcd. for $C_{12}H_8NO_4S_2$: [M-H] exact mass 293.9900 Da, found 294.0025 Da.

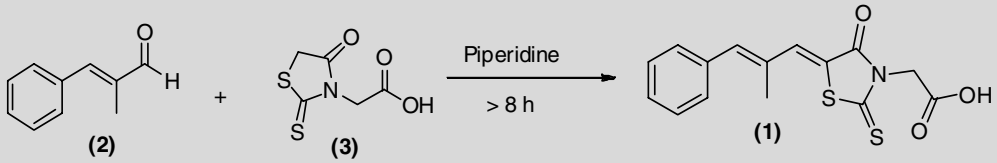
## RESULTS AND DISCUSSION

**Optimization in batch process:** A detailed optimization study was carried out in a batch process before conducting the synthesis of eplarestat in tubular flow. To avoid the generation of any solid precipitates in the background of flow process, the process solvents were tested first and avoided inorganic bases. Considering the solubility, piperidine (0.29 g, 1.0 equiv.) was chosen as the base source rather than an inorganic reagent (sodium acetate). Typically, a mixture of phenylacrylaldehyde (**2**) (0.5 g, 1.0 equiv.) and thioxothiazolidine acetic acid (**3**) (0.65 g, 1.0 equiv.) and piperidine in different process solvents like DMF, DMSO, methanol, ethanol, THF and $H_2O$ was kept at 100 ºC for 10 h in a glass seal tubes considering high-pressure condition. As shown in Table-1, solids were found in the many process solvents. Surprisingly, DMF as a process solvent given the highest conversion and yields according to the TLC analysis (Table-1, entry 4). As per the yield and conversion details, DMF is an excellent to satisfy the target of tubular flow process as it is a more soluble in presence of base. Notably, the product formation was better compared with an increase in the concentration of the starting materials (Table-1, entry 4).

**A tubular flow process for the synthesis of epalrestat:** Following the completion of the batch process optimization, we focused our investigation on the transformation to continuous flow process from the optimized batch to overcome current challenges such as longer reaction time, high impurity formation and low yield. Due to the chemicals nature, the presence of DMF and high temperature in the reaction system, the corrosion resistant stainless steel reactor was chosen.

Table-2 shows the optimization of the process conditions on the tubular flow process of epalrestat. At 100 ºC, better product formation obtained within a reaction time of 8 min (entry 1, Table-2). After that, at 100 ºC (entries 3 & 4, Table-2), the conversion and product formation was almost comparable with entry 1. At 100 ºC (entry 2, Table-2), the product formation was less comparable with entry 1. At 80 ºC (Table-2, entry 5), the conversion and product formation was less comparable with entry 1. On raising the temperature to 120 ºC under same conditions (entry 6, Table-2), the product formation decreased slightly. The maximum conversion of 86% was found at 100 ºC (entry 1, Table-2), which was better condition compared with batch. In terms of the residence time, the reactants converted completely within 8 min (entries 1 and 3, Table-2). Yields were low at lesser residence times because of the partial product conversion (entry 2, Table-2), while higher residence times also resulted to poor yields of epalrestat drug (entry 6, Table-2). Therefore, the reaction residence time was set as 8 min. As a result, on 8.0 mL reactor, the optimized conditions for the flow process of epalrestat was pump A: thioxothiazolidine acetic acid (**3**) and piperidine mixture in DMF (0.5 mL min$^{-1}$, 1.0 eq) and pump B: phenylacrylaldehyde (**2**) in DMF (0.5 mL min$^{-1}$,

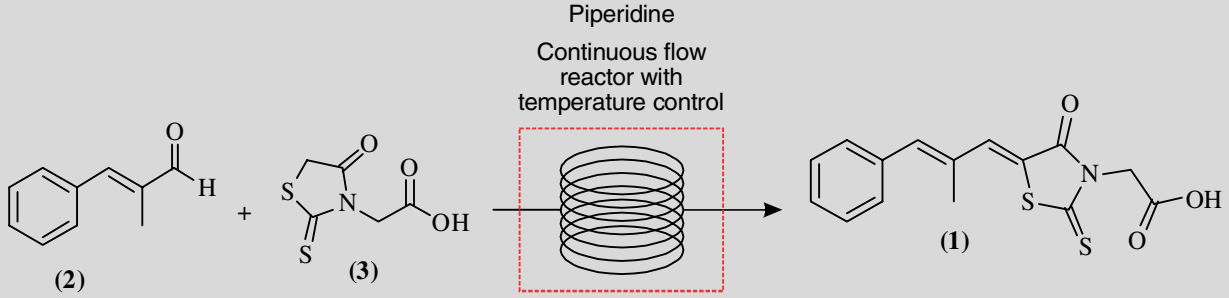
TABLE-1
SOLVENTS SCREENING FOR THE PREPARATION OF EPALRESTAT




| Entry | Solvent | mL | Yield (%) | Observation |
|---|---|---|---|---|
| 1 | Acetic acid | 10 | 46 | Not clear |
| 2 | Methanol | 10 | 52 | Not clear |
| 3 | Toluene | 10 | 50 | Not clear |
| 4 | DMF | 10 | 86 | Clear |
| 5 | Ethanol | 10 | 64 | Not clear |
| 6 | DMSO | 10 | 67 | Clear |
| 7 | THF | 10 | 55 | Clear |
| 8 | Water | 10 | – | Not clear |
| 9 | Ethyl acetate | 10 | 58 | Not clear |

Reaction progress monitored by TLC.

TABLE-2
PROCESS CONDITION FOR THE TUBULAR FLOW REACTION OF EPALRESTAT




| Entry | Residing time (min) | Temperature (°C) | Yield (%) |
|---|---|---|---|
| 1 | 8 | 100 | 86 |
| 2 | 5 | 100 | 78 |
| 3 | 10 | 100 | 84 |
| 4 | 20 | 100 | 84 |
| 5 | 8 | 80 | 73 |
| 6 | 8 | 120 | 75 |

Reaction progress monitored by TLC.

1.0 equiv.), reaction temperature at 100 ºC, time 8 min and sustainable pressure of flow system 5 bar.

The reaction sequence working for the synthesis of targeted molecule is shown in **Scheme-II**. In present work, in continuous flow condition pump-A: Thioxothiazolidin acetic acid (**3**) and piperidine mixture in DMF (0.5 mL $min^{-1}$, 1.0 equiv.), pump B: aldehyde derivative (**2**) in DMF (0.5 mL $min^{-1}$, 1.0 equiv.), process temperature at 100 ºC, flow time at 8 min and flow set-up pressure at 5 bar, further the output mass of flow was treated with 10 N hydrochloric acid in at 20 ºC in batch process to give epalrestat and other derivatives (**5a-k**).

## Conclusion

In conclusion, we have designed and synthesized a library of (5-[(1*Z*,2*E*)-2-methyl-3-phenylpropenylidene]-4-oxo-2-thioxo-3-thiazolidine acetic acid derivatives (**5a-k**) in tubular flow process, which in turn utilized for the process optimization of epalrestat (**1**). The transition from a regular batch to a tubular flow technology permitted for the process intensification. The process was developed and optimized in less reaction time, highest purity (> 99.9%), high yield and reduction in process mass intensity. This flow process offers robust process and reduction in process mass intensity compared to the batch.

## ACKNOWLEDGEMENTS

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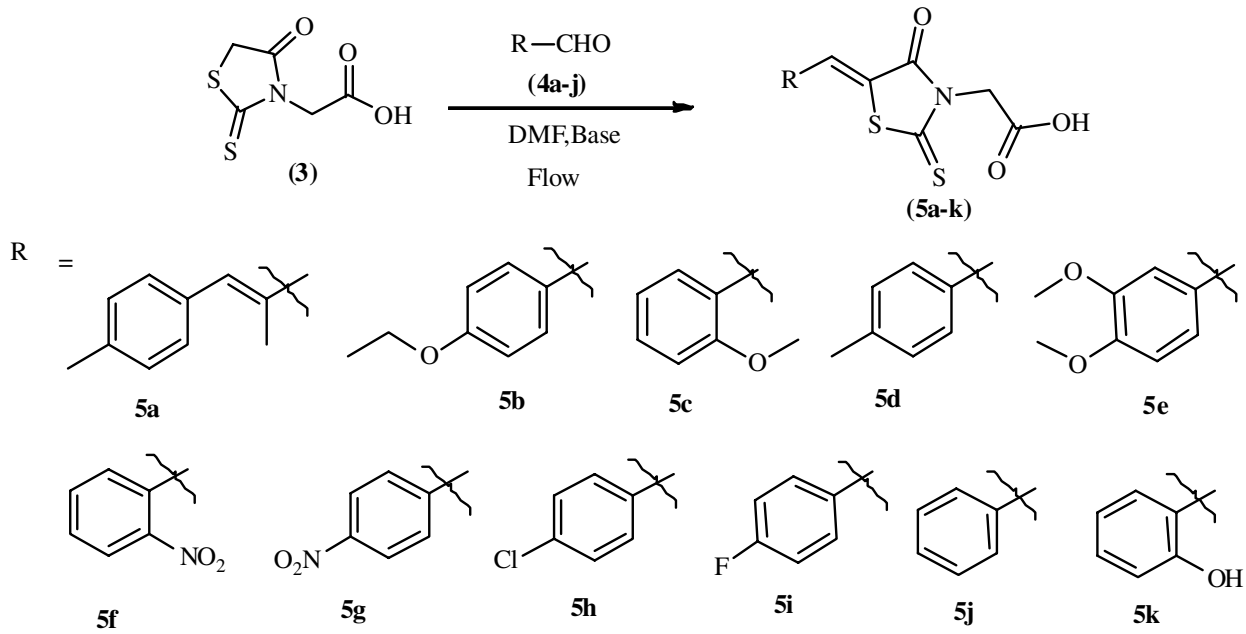


**Scheme-II:** Synthetic route of epalrestat and its derivatives (**5a-k**)

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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