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[UCI]I804:24011-200000240206

2010 年 8月
博士學位論文

Synthesis and structure activity relationship of thiazolidinedione derivatives as 15-PGDH inhibitors for drug design

朝鮮大學校 大學院

高分子工學科

武　营

약물설계를 위한
thiazolidinedione계 15-PGDH 억제제
합성 및 구조 활성 분석

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이 論文을 工學博士學位申請 論文으로 提出함.

2010 年 4 月

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2010 年　**6** 月

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Abbreviations

AA: Arachidonic acid

ADP: Adenosine diphosphate

cAMP: Cyclic adenosine monophosphate

COX: Cyclooxygenase

DEAD: Diethyl azodicarboxylate

DMF: N,N-Dimethylformamide

DMSO: Dimethylsulfoxide

DTT: Dithiothretitol

EDTA: Ethylenediamine-N,N,N',N'-tetraacetic acid

EFAS: Essential fatty acids

EP: Prostaglandin E receptor

GPCR: G protein–coupled receptor

IL: Interleukin

MAPEG: Membrane- associated proteins in eicosanoid and glutathione

NSAID: Non-steroidal anti-inflammatory drug

15-PGDH: 15-Hydroxyprostaglandin dehydrogenase

PGE_2: Prostaglandin E_2

PGHS: Prostaglandin H synthase

mPGES: Microsomal PGE synthase

PGT: Prostaglandin transporter

PLA: Poly lactic acid

PPh3: Triphenylphosphine

SAR: Structure activity relationship

SDS: Sodium dodecylsulfate

TXs: Thromboxanes

THF: Tetrahydrofuran

TLC: Thin layer chromatography

TDs: Thiazolidinediones

VEGF: Vascular endothelial growth factor

국문초록

약물설계를 위한 thiazolidinedione계15-PGDH 억제제 합성 및 구조 활성 분석

무 영

지도교수: 조훈

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Prostaglandins (PGs)은 prostaglandin endoperoxide를 거쳐 archidonic acid로 부터 합성되어진다. Prostaglandin E_2 (PGE_2)는 생리 및 병리학 측면에서 광범위하게 관여하고 있으며, 특히 PGE_2는 생체 내에서 reproductives, gastromtestinal, nevroendocrine 및 면역시스템을 조절하는 중요한 역할을 담당하고 있다. 하지만 prostaglandin은 생체에서 15-hydroxyprostaglandin dehydrogenase (15-PGDH)에 의해 분해됨으로써 짧은 활성을 갖는다. Cytosolic 효소인 15-PGDH는 prostaglandin의 15-hydroxyl group을 ketone으로 변환시킴으로써 prostaglandin이 갖고 잇는 생리활성을 잃게 하는 기능을 갖고 있다. 따라서 이 효소의 활성을 억제하는 것은 PGE_2 부족으로부터 유발되는 여러 가지 질병 치료에 사용이 가능할 것이다.

Thiazolidinedione 유도체인 **5-(4-(2-cyclohexylethoxy)benzylidene)thiazolidine-2,4-dione（CT-8）**은 전에 발표된 15-PGDH 억제제 중 하나이다. 구조-활성 분석결과 thiazolidine-2,4-dione의 아민 그룹에 methyl 그룹을 도입하게 되면 15-PGDH 억제효과를 잃게 되며, ethylhydroxyl 그룹을 도입할 경우에는 여전히 억제 효과를 가지고 있음을 보였다. Thiazolidinedione 유도체의 구조와 억제효과에 대한 상관관계 분석으로부터 보다 선택적인 화합물을 합성하기 위해 phenyl ring에 다양한 치환체를 도입 하였으며, 유도체에 대한 억제 활성을 평가하였다. **CT-8** 의 cyclohexylethyl group을 hetero five-member ring으로 치환할

경우여 활성이 증가하였다. 하지만 cyclohexylethyl group을 hetero six-member ring으로 치환할 경우에는 반대로 억제효능이 현저히 감소함을 보였다. 또한 phenyl ring에 $–CH_3$, $-OCH_3$, -OEt, $-NO_2$, $-CF_3$, -F, -Cl, -Br과 같은 그룹을 도입할 경우 15-PGDH에 대한 좋은 억제효과를 보였다. 그 중에서도 phenyl ring에 –Cl group을 포함하고 있는 **43b** 5-(3-chloro-4-(2-cyclohexylethoxy)benzylidene)thiazolidine-2,4-dione 화합물이 nanomalar 범위에서 가장 강력한 억제효과를 보였다.

ABSTRACT

Synthesis and structure activity relationship of thiazolidinedione derivatives as 15-PGDH for drug design

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Prostaglandins (PGs) are derived from arachidonic acid through the prostaglandin endoperoxide synthase pathway. Prostaglandins have been implicated in a wide varity of physiological and pathological processes, Especially prostaglandin E_2 (PGE_2) regulated key responses in the major human systems including reproductives, gastrointestinal, neuroendocrine and immune systems. A cytosolic enzyme, NAD^+-dependent 15-hydroxyprostaglandin dehydrogenase (15-PGDH) catalyzes the oxidation of 15-(*S*) hydroxyl group of prostaglandins to 15-ketone, resulting in the biological inactivation of prostaglandins and a short life *in vivo*. Inhibitors of this enzyme will be valuable for the therapeutic management of many diseases.

Previously, 5-(4-(2-cyclohexylethoxy)benzylidene)thiazolidine-2,4-dione **(CT-8)**, a thiazolidinedione analogue, was found to be a potent inhibitor of 15-PGDH. Structure-activity analysis indicated that the *N*-methylation of thiazolidine-2,4-dione of **CT-8**, abolished its inhibitory activity, whereas the introduction of an ethyl hydroxyl group at amine in **CT-8** improved its inhibitory effect. Based on the structures of the thiazolidinedione analogues and inhibitory activities, a variety of benzylidene thiazolidinedione derivatives were synthesized with different substituents on the phenyl ring and then their inhibitory activities were evaluated. Replacement of the

cyclohexylethyl group of **CT-8** with the hetero five-member ring increased the inhibitory potency and cyclohexylethyl group was replaced with a hetero six-member ring was decreased the inhibitory potency significantly. Furthermore, compounds with substituents such as $–CH_3$, $-OCH_3$, -OEt, $-NO_2$, $-CF_3$, -F, -Cl and -Br on the phenyl ring were good inhibitors of 15-PGDH. It was found that the most active 15-PGDH inhibitors contain a -Cl group in the phenyl ring and compound **43b** 5-(3-chloro-4-(2-cyclohexylethoxy)benzylidene)thiazolidine-2,4-dione is the most effective potent inhibitor.

1. Introduction

1.1. Prostaglandins

1.1.1. Basic definitions

Prostaglandins are members of a group of lipid compounds that are derived enzymatically from essential fatty acids (EFAs) and have important functions in the animal body. Every prostaglandin contains 20 carbon atoms, including a 5-carbon ring. Prostaglandin name derives from the prostate gland. When prostaglandins were first isolated from seminal fluid in 1935 by the Swedish physiologist Ulf von Euler and independently by M.W. Goldblatt, it was believed to be part of the prostatic secretions. Later it was shown that many other tissues secrete prostaglandins for various functions. Prostaglandin E_2 (PGE_2) is a founding member of the prostaglandins, a class of mediators that belongs to the still growing family of bioactive autacoids known as the eicosanoids. The chemical structure of PGE_2 was shown in **Fig. 1.**

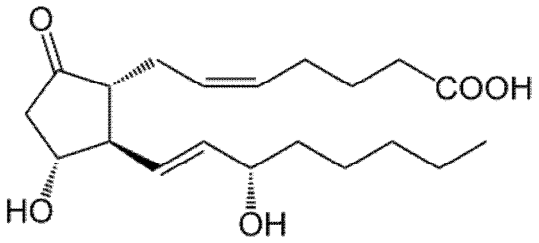


Fig. 1. Chemical structure of Prostaglandin E_2.

1.1.2. Biosynthesis of prostaglandins

PGs are formed by most cells in our bodies and act as autocrine and paracrine lipid mediators (i.e., they signal at or immediately adjacent to their site of synthesis). They are not stored but are synthesized de novo from membrane-released arachidonic acid (AA) [1]. When cells are activated by mechanical trauma or by specific cytokine growth factor, and other stimuli [e.g., collagen and

adenosine diphosphate (ADP) in platelets, bradykinin and thrombin in endothelium]. A host of enzymes exquisitely regulate cellular levels of AA, keeping it esterified until mobilized by phospholipases (PLA_2). The control of AA release from membranes has undergone several paradigm shifts in recent years with the continuing identification of new PLA_2 members [2]. Despite this, type IV cytosolic PLA_2 ($cPLA_2$) remains the key player for eicosanoid production because cells lacking $cPLA_2$ are generally devoid of eicosanoid synthesis.

Cell-specific and agonist-dependent events coordinate translocation of $cPLA_2$ to the nuclear envelope, endoplasmic reticulum (ER), and Golgi apparatus [3]. At the ER and nuclear membrane, AA released by $cPLA_2$ is presented to prostaglandin H synthase (PGHS; referred to colloquially as COX for cyclooxygenase) and is converted to prostanoids, including the PGs and the thromboxanes (TXs), via the reaction of cyclooxygenase (COX), which results in the formation of an unstable endoperoxide intermediate, prostaglandin H_2 (PGH_2) **(Fig. 2).** PGHS exists as two isoforms referred to as PGHS-1 (COX-1) and PGHS-2 (COX-2) [4]. In simplistic terms, COX-1 is the enzyme responsible for basal, constitutive prostaglandin synthesis, whereas COX-2 is important in various inflammatory and "induced" settings. COX-2 is induced by cytokines, growth factors, tumor promoters or other agents. There are notable exceptions to this oversimplification, but in general this classification has aided the rapid advancement in this field since the discovery of COX-2. The COX enzymes are monotopically inserted in the ER and nuclear membrane with the substrate binding pocket precisely orientated to take up released AA. The crystal structures of COX-1 and COX-2 are remarkably similar, with one notable amino acid difference that leads to a larger "side-pocket" for substrate access in COX-2 [4]. Then the endoperoxide intermediate, PGH_2 is metabolized to prostaglandin D_2 (PGD_2), prostaglandin (PGE_2), prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), prostaglandin I_2 (PGI_2) and thromboxane-2 (TXA_2) by downstream enzymes is intricatelyorchestrated in a cell-specific fashion.

Thromboxane synthase is found in platelets and macrophages, prostacyclin synthase is found in endothelial cells and prostaglandin F synthase in uterus, and two types of prostaglandin D synthase are found in brain and mast cells. Microsomal PGE synthase (mPGES), a member of the MAPEG (membrane- associated proteins in eicosanoid and glutathione metabolism) family, is responsible

for PGE_2 synthesis [5]. Coordinate induction of multiple enzymes in the prostanoid pathway, in particular mPGES and COX-2, in inflammatory settings is a current concept being developed [6].

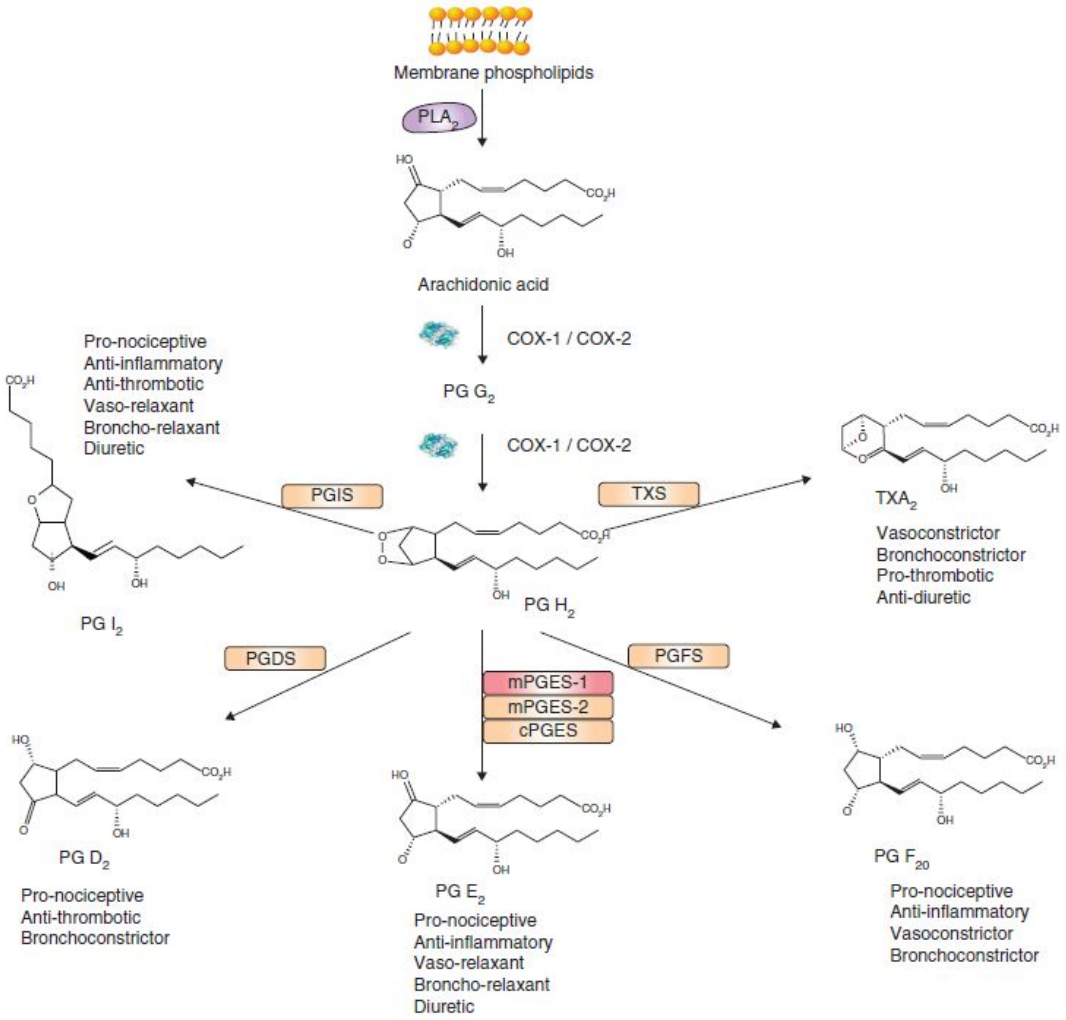


Fig. 2. Biosynthesis of prostaglandins [7].

1.1.3. Metabolism of PGE_2

The eicosanoids are made in a burst of enzymatic activity in cells, following a specific stimulus. Further more, these molecules transmit the information of cellular activation to cells in the immediate vicinity. Thus, it is felt that some means for rapid inactivation is important for regulation of their actions. The major route of inactivation of eicosanoids is through metabolic conversion into

inactive products. A large number of enzymes are involved in the eicosanoid deactivation process. One of the most widely distributed enzymes involved in the metabolic inactivation of eicosanoids is 15-hydroxyprostaglandin dehydrogenase, which has been purified to homogeneity from various sources [8]. This cytosolic enzyme appears to be present in two different types, requiring either oxidized nicotinamide-adenine dinucleotide (NAD^+) for activity or, as a second type found in kidney, brain, and erythrocytes, which uses oxidized nicotinamide-adenine dinucleotide phosphate ($NADP^+$) as a cofactor. This enzyme converts the 15-hydroxy group in prostaglandins into a conjugated α，β-unsaturated ketone at the 15 position. Another enzyme, prostaglandin 13, 14 reductase, then reduces the double bond at these positions of the 15-keto-prostaglandin metabolite to yield the corresponding 13, 14-dihydro-15-keto-prostaglandin metabolites. This enzyme has been partially purified and requires reduced NAD (NADH) for activity [9]. For PGE_2, the metabolite 15-keto-13, 14-dihydro-PGE_2 can be cyclyzed *in vitro* or *in vivo* to yield the bicycle-PGE_2 metabolite illustrated **in Fig. 3**.

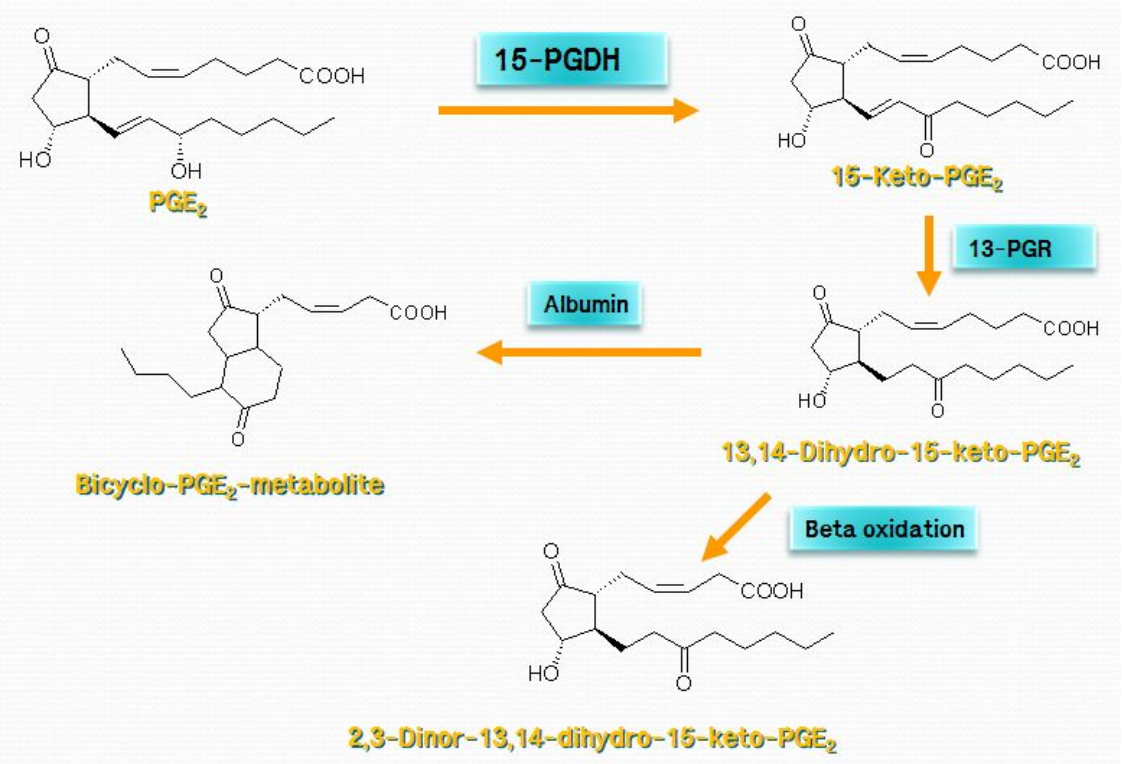


Fig. 3. Summary of the chemical structures involved in the transformations of PGE_2 into its major

urinary metabolite.

This metabolite can be measured in blood or urine as an index of the production of PGE_2 *in vivo* [10]. In addition, extensive metabolic transformations also occur with the 15-keto-13, 14-dihydro-PGE_2 metabolite following omega-oxidation of C20 terminus to the omega carboxy group and formation of CoA ester at C1 carboxy terminus followed by one or two cycles of betaoxidation. It has been recently suggested that the peroxisomes in the hepatocyte may be responsible for much of the beta-oxidation of prostaglandins [11]. This latter route of metabolic conversion leads to the metabolites of dinor and tetranor series. A dinor metabolite PGE_2 is illustrated in **Fig. 3.**

1.2. 15-Hydroxyprostaglandin dehydrogenase (15-PGDH)

1.2.1. Basic definitions

NAD^+-dependent 15-PGDH is ubiquitously present in mammalian tissues and has been purified to apparent homogeneity from several mammalian tissues. The enzyme is believed to be a dimer composed of identical subunits with a molecular weight of 29 kDa, although it has also been proposed that the monomeric enzyme might be active [12]. 15-PGDH can use a wide variety of prostaglandins as substrates with K_m values in the μM range for PGE_1, PGE_2, $PGF_{1\alpha}$, $PGF_{2\alpha}$, PGI_2, and 6-keto-$PGF_{1\alpha}$. PGB_2, PGD_2, and TXB_2 are poor substrates of 15-PGDH. In addition to prostaglandins, some other eicosanoids are also excellent substrates for 15-PGDH. These include 12-HHT; 15-HETE; 5, 15-diHETE; 8, 15-diHETE; and lipoxin A_4 [13]. It appears that a cyclopentane ring of the prostaglandins is not required for the compound to be oxidized by 15-PGDH. The enzyme is NAD^+ specific and is a B-side specific dehydrogenase [14].

There are two different types of 15-PGDH. Type I is NAD^+ specific, while Type II is $NADP^+$ preferred. Type I is more prostaglandin specific and exhibits a low K_m for prostaglandins, whereas Type II has a much broader substrate specificity and shows a high K_m for prostaglandins [15]. Indeed, Type II was later found to be identical to carbonyl reductase [16]. Therefore, Type I is considered to be the key enzyme responsible for the biological inactivation of prostaglandins. Studies on the prostaglandin catabolism have focused on the Type I enzyme (hereafter referred to as 15-PGDH).

1.2.2. Function of 15-PGDH

15-PGDH catalyzes reversible oxidation/reduction of prostaglandins at C-15. The oxidation rate is maximal at pH 9.0, whereas the reduction is favored at pH 5.5 [17]. In addition to 15-ketoprostaglandins, a variety of non-prostanoid polycyclic aromatic hydrocarbons such as 9,10-phenanthrenequinone can be reduced by this enzyme in the presence of NADH [18]. This suggests that 15-PGDH may have substrate specificity much broader than previously recognized. It may function like other known oxidoreductases [19] to carry out oxidation and reduction of compounds of physiological as well as of pathological interest including procarcinogens and carcinogens. Kinetic analysis of the enzyme using initial velocity, production inhibition and dead-end inhibition studies have indicated that the enzyme exhibits an ordered Bi–Bi mechanism in which NAD^+ binds first to the enzyme followed by the prostaglandin, and then the 15-ketoprostaglandin is released followed by NADH [20].

It is known that 15-PGDH is sensitive to sulfhydryl inhibitors such as *N*-ethyl maleimide [21] and to metal ions such as Cu^{2+} [22] indicating that a cysteine residue is essential for activity. The enzyme is also inhibited by a variety of pharmacological agents including non-steroidal anti-inflammatory drugs such as indomethacin [23], anti-platelet aggregatory drugs such as panaxynol [24], anti-allergic drugs such as flavinoid baicalein [25], anti-ulcer drug such as plaunotol [26], anti-colitic drugs such as sulfasalazine analogs [26, 27], obstetric drugs such as methylergometrine maleate [28], acrolein [29], papaverine [30], and fatty acids [31]. Among these pharmacological agents, 2-hydroxy-5-(3, 5-dimethoxycarbonyl-benzoyl)-benzene acetic acid, a sulfasalazine analog, was found to be the most potent inhibitor of 15-PGDH (IC_{50} = 28 nM) [32]. Inhibition appears to be non-competitive with respect to both $PGF_{2\alpha}$ and NAD^+. It is interesting to note that anti-psychotic drugs such as chlorpromazine and obstetric drugs such as isoxsuprine activate the enzyme in an uncompetitive manner with respect to both PGE_2 and NAD^+ [28, 32].

The primary structure of the human 15-PGDH was independently elucidated by classical peptide sequencing [33] and by cDNA cloning [34]. Subsequently, the cDNAs encoding the enzyme were cloned from mouse [35], rat [36], guinea pig [37], and bovine [38] sources. These cDNAs code for

a protein of 266 amino acids with a calculated molecular weight of 28,975 Da for the human enzyme. It appears that the sequences are largely homologous among different species except for two regions, the C-terminal domain and the region from residue 205 to 224. The genomic DNA of the mouse 15-PGDH gene [39] and the promoter region of the human 15-PGDH gene [40] have also been cloned. The human gene is localized to 4q34–q35 [41]. The mouse gene is approximately 11.3 kb in length and contains seven exons and six introns. Two truncated forms of the human 15-PGDH have been reported [42 , 43]. One lacks the sixth exon and the other in missing fifth and sixth exons (assuming the human gene has the same gene structure as the mouse). Neither of these forms is likely to have enzyme activity since the deleted portions contain the catalytically essential Tyr 151 and Lys 155 [44, 45].

1.2. 3. Three-dimensional structure of 15-PGDH

Comparison of the primary structure of 15-PGDH with those of short-chain dehydrogenases (SDRs) reveals an overall homology of around 20% [46]. Sequence comparisons of these SDR sequences indicate that six amino acid residues are strictly conserved in these oxidoreductases corresponding to three glycines at positions 12, 18, and 131, Asp 64, Tyr 151 and Lys 155 in 15-PGDH. There are also nine residues that are highly conserved among SDRs. These residues are Thr 11, Gly 16, Asp 86, Ala 92, Gly 93, Asn 107, Ser 138, Pro 183, and Thr 188 of the human 15-PGDH. Gly 12, 16, and 18 are found in the putative coenzyme binding site having a "Rossmann fold" structure with a conserved glycine pattern (GlyXaaXaaXaaGlyXaaGly). It appears that the N-terminal portion is involved in NAD^+ binding as demonstrated by photoaffinity labeling studies of 15-PGDH with [α-^{32}P]-2-azido-NAD^+ [47] and homology modeling based on the structure of another dehydrogenase [48]. Tyr 151 and Lys 155 located in the motif of TyrXaaXaaXaaLys near to the central part of the SDRs appear to be essential for catalytic activity [49].

Structure characterization, transcriptional regulation and biological function of this enzyme have been investigated. Molecular modeling corroborated with site-directed mutagenesis has identified key residues and domains involved in coenzyme and substrate binding site. The three-dimensional structural model of a ternary complex of 15-PGDH-NAD^+-PGE_2 is shown in **Fig. 4.** The model

consists of a core domain that includes most of the polypeptide and a small lobe that produces from the core. A deep cleft is recognized between the core domain and small lobe, which is presumed to be the binding site for PGE_2. In the center of core domain is a seven stranded parallel β-sheet, flanked on each side by α-helices, which constitutes the "Rossmann fold" topology. The core structure is highly conserved among the SDR family member, despite relatively low residue identity between these enzymes (about 30% identify) [49, 51]. The small lobe of this model is also very similar to each oyher, although the structure of this region is highly variable among SDR family member for which a few crystal structure are know. As seen in **Fig. 4**, NAD^+ is located at the bottom of the cleft between the core domain and the small lobe.

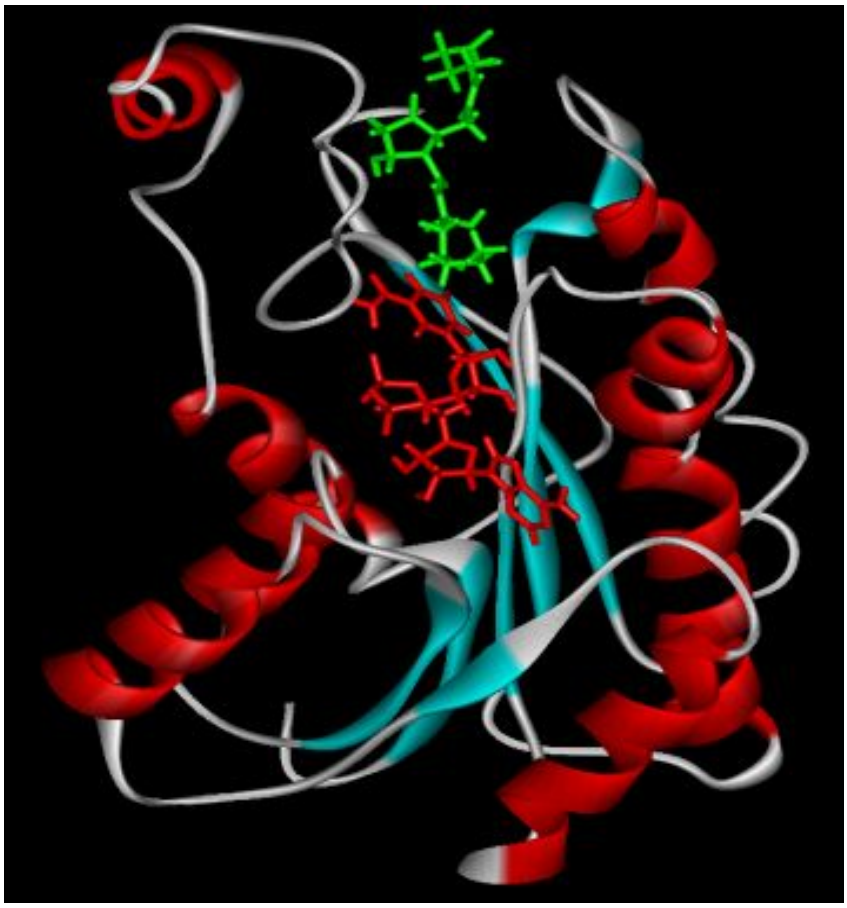


Fig. 4. A stereoview of 3D structure of 15-PGDH-NAD^+-PGE_2 complex. The green molecular is

substrate PGE_2, the red molecular is cofactor NAD^+ [50].

1.2.4. Reaction mechanism for 15-PGDH

By examining the high-resolution crystal structures of the apo form, binary and ternary complexes and biochemical data gathered from many SDR family members, we can propose a reaction mechanism for 15-PGDH [51-55]. At present, the "Ser-Tyr-Lys catalytic triad" is considered to be important in SDR catalysis, whereby the side-chain oxygen of tyrosine residue functions as an acid-base catalyst for proton transfer. These conserved residues are in fact located around the hydroxyl group of PGE_2 in the ternary complex of 15-PGDH, and the side-chain oxygen of Tyr-151 residue points toward the face of cofactor nicotinamide ring. The finding indicates that the Gln-148 also has important role in catalytic oxidation of PGE_2 **(Fig. 5).** This structural conservation clearly indicates that the reaction mechanism common to the SDR family also operates in 15-PGDH, namely, the concerted transfer of a proton from the C-15 hydroxyl group to the Tyl-151 residue and a proton from PGE_2 to the NAD^+, respectively. Tyl-15 should be able to act as a general acid/base catalyst in the 15-PGDH active site. Ser-138 is within hydrogen-bonging distance to the hydroxyl group of PGE_2 from the opposite direction of Tyr-151. The distance between the side chain nitrogen of Lys-155 and the side chain oxygen of Tyr-151 is 4.5 Å, and Lys-155 could reduce the pK_a of Tyr-155 by electrostatic interaction. In addition, Lys-155 is also responsible for NAD^+ binding. Once the catalytic cavity has oriented and fixed PGE_2, its hydroxyl group is placed in between oxygen atoms of side-chain of Ser-138, Gln-148 and Tyr-151. A proton can then be easily transferred from the alcohol group of PGE_2 to the unprotonated form of residue Tyr-151. This process generates a partial positive charge on the C-15 atom of PGE_2 that facilitates a hydride transfer to the C-4 position of the nicotinamide ring of NAD^+. Ser-138 and Gln-148 either orients the PGE_2 or stabilizes the transient reaction intermediate during the oxidation process, or both. Lys-155 has possibly two roles: first, to assist in the proper orientation of NAD^+ by forming hydrogen bonds with the oxygen atoms of the nicotinamide-ribose moiety and second, to lower the pK_a of the Tyr-151 residue through electrostatic interaction. The pK_a of Tyr-151 seems to be strongly influenced also by the positively charged nicotinamide ring of the NAD^+ in the binary complex.

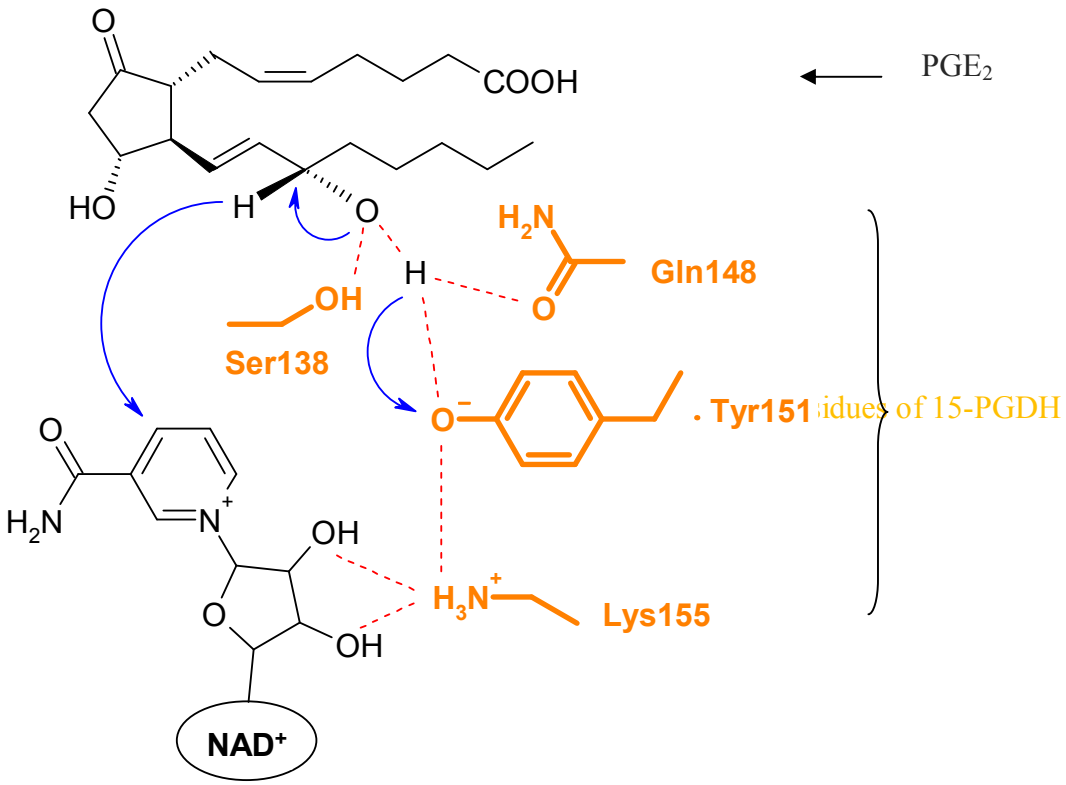


Fig. 5. Catalytic mechanism of 15-PGDH.

1.3. Thiazolidinediones (TDs)

Thiazolidinediones (TDs) have been the subject of extensive researches because of their deep involvement in the regulation of different physiological processes. TDs act by binding to PPARs (peroxisome proliferator-activated receptors), a group of receptor molecules inside the cell nucleus (Lehman et al., 1995). TD derivatives have been shown to possess potent immunostimulatory property, antiarthritic activity as well as oncostatic activity [56]. TDs such as troglitazone, pioglitazone, and rosiglitazone are potent reducer of plasma glucose level in vivo. Besides their anti-diabetic potency, these TDs have been shown to exert anti-inflammatory effects on vascular cells [57]. TDs were also found to inhibit the production of inflammatory cytokines and the expression of inducible nitric oxide syntheses in monocytes/macrophages [58, 59]. It has been shown that TDs suppress the growth of several cancer cell lines including colon, breast, and prostate [60-62]. TDs were also found to inhibit angiogenesis [63]. Some TD derivatives also

showed Cu^{2+} mediated lipid-peroxidation inhibitory activity and were found to inhibit serum aspartate aminotransferase (AST), alanine aminotransferase (ALT) as well as γ-Glutamyltranspeptidase (γ-GTP) levels significantly during treatment in patients with type 2 diabetes [64]. TDs are also potential cancer chemopreventive agents against colon, breast, tongue, and gastric carcinogenesis [63]. Previously, it was reported that ciglitazone, an antidiabetic thiazolidinedione, is a potent antagonist of the 15-PGDH enzymatic activity with an IC_{50} of 2.7 μM [65]. In addition, the inhibitory potency of ciglitazone was higher than rosiglitazone (10 times) and troglitazone (127 times). The structures of these TDs are shown in **Fig. 6.** It appears the nature of the moiety linking to benzylidenethiazolidine-2, 4-dione through an ether linkage plays an important role in its inhibitory potency [66]. Further modifications of this moiety may yield thiazolidines of greater inhibitory activity. The benzylidene thiazolidinedione **CT-8** was synthesized and was found that this compound was the most potent inhibitor. Kinetic studies revealed that inhibition by **CT-8** was noncompetitive with respect to NAD^+ and uncompetitive with respect to PGE_2, indicating that the inhibitor interacts with the enzyme at a site distinct from the substrate binding site.

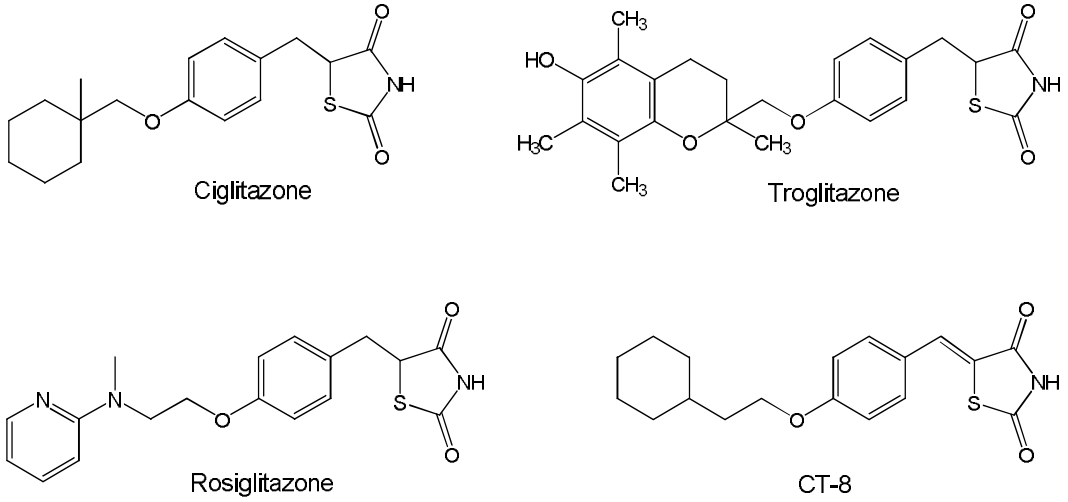


Fig. 6. Structures of ciglitazone, rosiglitazone, troglitazone and CT-8.

1.4. Necessity of 15-PGDH inhibitors

PGE_2 participates in a wide range of body functions such as the contraction and relaxation of

smooth muscle, the dilation and contraction of blood vessels, control of blood pressure, and modulation of inflammation.

Recently, clinical studies demonstrated that PGE_2 causes the growth of body hair and eyelashes in humans and animals [67]. In humans, trials carried out on the scalp have shown that PGE_2 could increase the hair density [68]. Minoxidil, a Katp channel opener initially developed to treat hypertension in human [69] are known to stimulate human hair growth. Among its pleiotropic effects, minoxidil was able to sustain prostaglandin synthesis by dermal papilla cells, and to protect the catalytic activities of the purified prostaglandin endoperoxide synthase, against its self-inactivating catalytic process [70]. Early observations reported an increase of eyelash pigmentation [71, 72] as well as hypertrichosis of eyelashes and ancillary hairs around eyelids [73]. A central question rapidly emerged in the field of androgenic alopecia about the trichogenic potential of prostaglandins [74] A report indeed described positive effects of PGE_2, the most representative prostaglandins in human and mouse skin, on hair growth and follicular melanogenesis in a murine model [75]. As far as regulation process is concerned, dihydrotestosterone-a well-known physiological androgen is involved in hair growth control [76]. Several non-steroidal anti-inflammatory drugs (NSAIDs) reported to inhibit hair growth [77] not only decreased prostaglandin synthesis but also increased 15-PGDH activity [78].

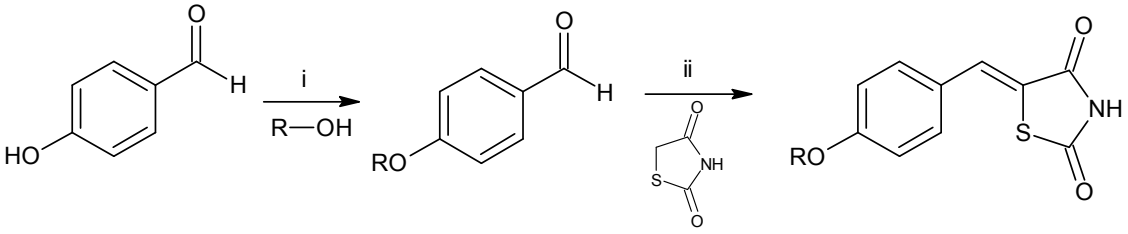
In pregnancy, PGE_2 is secreted continuously by the fetal membranes and placenta and plays an important role in the final events leading to the initiation of labor [79, 80]. It is known that PGE_2 stimulates the production of $PGF_{2\alpha}$ which in turn sensitizes the myometrium to endogenous or exogenously administered oxytocin. Although PGE_2 is capable of initiating uterine contractions and may interact with oxytocin to increase uterine contractility, the available evidence indicates that, in the concentrations found during the early part of labor, PGE_2 plays an important role in cervical ripening without affecting uterine contractions [81-83]. Therefore, inhibitors of 15-PGDH will be valuable for the therapeutic management of diseases requiring elevated PGE_2 levels.

2. Results and discussion

2.1. Chemistry

Thiazolidine-2, 4-dione derivatives were prepared from the corresponding aryl aldehydes by the procedure shown in **Scheme 2.2.1 - 2.2.4.** The substituted benzaldehyde intermediate was afforded via a Mitsunobu coupling [84] between a starting material *p*-Hydroxybenzaldehyde and various substituents in reproducible good yield. Knoevenagel condensation between the substituted benzaldehyde intermediate and thiazolidine-2, 4-dione in refluxing toluene, containing a catalytic amount of piperidine and acetic acid, gave the final TDs, which cryatallized from the reaction mixture with high purity. **Scheme 2.2.5** summarizes the synthetic routes of various of substituents on the thiazolidinedione ring. *N*-substituents of thiazolidine-2, 4-dione ring was treated with compound **CT-8** with equimolar amounts of sodium hydride and iodomethane or 2-iodoethanol to give **97** and **98** respectively**.** Toward that end we utilized a modified conjugate reduction protocol of Pfaltz [85]. A stirring mixture of $CoCl_2.H_2O$ and dimethylglyoxime in THF/H2O containing aqueous NaOH was treated with $NaBH_4$ to produce a deep blue mixture. The reducing mixture was cooled in an ice-water bath and olefin thiazolidine-2, 4-diones was added. The reaction was quenched upon the disappearance of olefin to give single bond product **(Scheme 2.2.6)**. An efficient one-step route to the thiazolidine-2, 4-dione derivatives was employed to provide compounds **107, 108** and **109 (Scheme 2.2.7).**

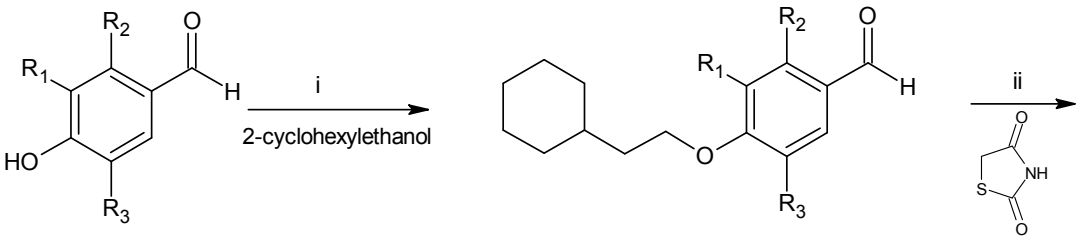
2.1.1. Synthesis of compounds (1b - 36b)



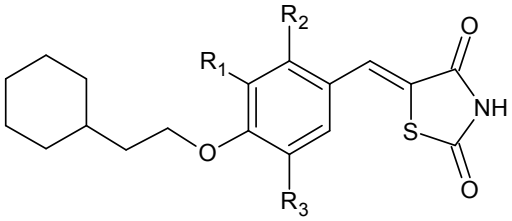
1a - 36a **1b - 36b**

Scheme 2.1.1. Reagents and conditions: (i) PPh_3, DEAD, THF, 25℃, 18h; (ii) piperidine, AcOH, reflux, 12h.

2.1.2. Synthesis of compounds (37b - 50b)



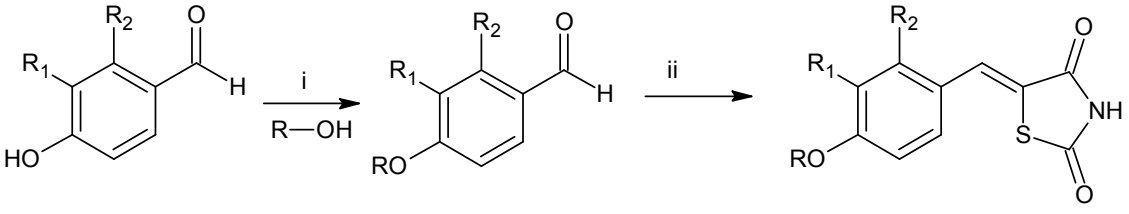
37a - 50a



37b - 50b

Scheme 2.1.2. Reagents and conditions: (i) PPh_3, DEAD, THF, 25℃, 18h; (ii) piperidine, AcOH, reflux, 12h.

2.1.3. Synthesis of compounds (51b - 77b)

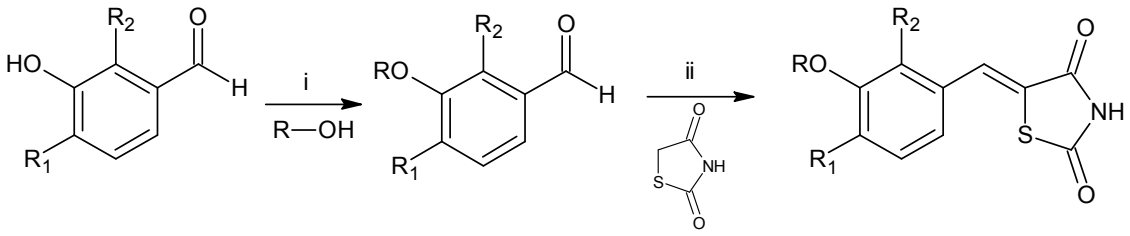


51a - 77a **51b - 77b**

Scheme 2.1.3. Reagents and conditions: (i) PPh_3, DEAD, THF, 25℃, 18h; (ii) piperidine, AcOH,

reflux, 12h.

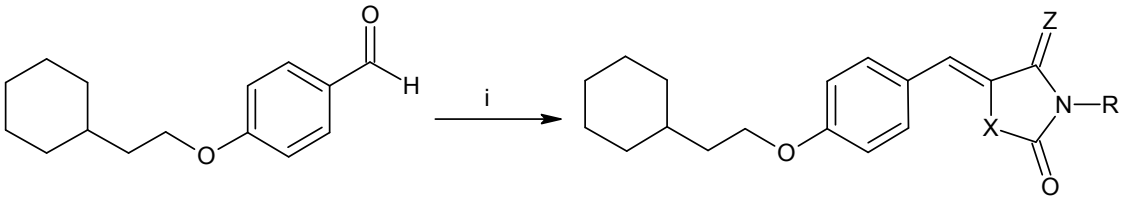
2.1.4. Synthesis of compounds (78b - 92b)



78a - 92a **78b - 92b**

Scheme 2.1.4. Reagents and conditions: (i) PPh_3, DEAD, THF, 25℃, 18 h; (ii) piperidine, AcOH, reflux, 12 h.

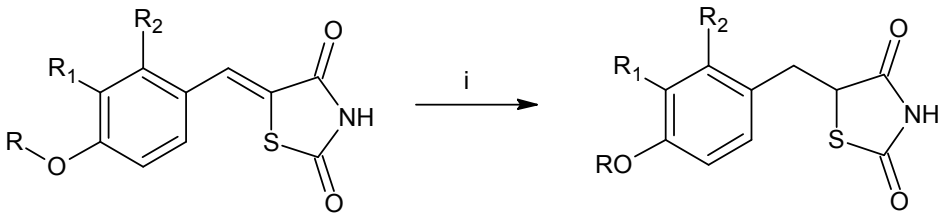
2.1.5. Synthesis of compounds (93 - 98)



3a **93 - 98**

Scheme 2.1.5. Reagents and conditions: (i) piperidine, AcOH, reflux, 12 h.

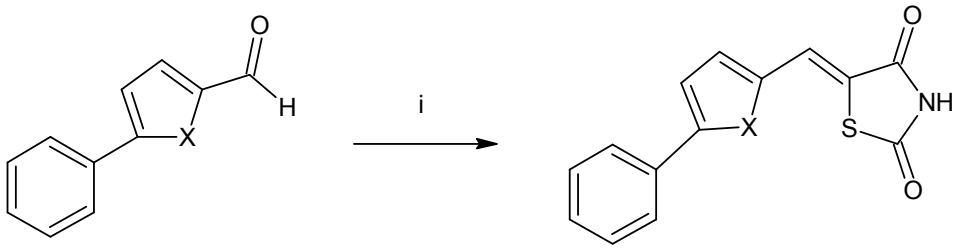
2.1. 6. Synthesis of compounds (99 - 106)



99 - 106

Scheme 2.1.6. Reagents and conditions: (i) $CoCl_2 \cdot 6H_2O$, dimethylglyoxime, $NaBH_4$, 1.0 N NaOH, 0℃.

2.1.7. Synthesis of compounds (107 - 109)



107 - 109

Scheme 2.1.7. Reagents and conditions: (i) piperidine, AcOH, reflux, 12 h.

2.2. In vitro evaluation

PGE_2 is a major inflammatory product derived from arachidonic acid through the cyclooxygenase pathway, which is involved in pain and inflammatory responses and is a key player in controlling various physiological functions. PGE2 exerts its diverse effects by binding to four different EP receptor subtypes (EP_1–EP_4) [86] **(Fig. 7)**, resulting in the activation of different intracellular signal-transduction pathways. The EP_1 receptor couples to Gq and mediates a rise in intracellular calcium concentration. PGE_2 acts through EP_1 to control the impulsive behavior associated with enhanced dopaminergic activity under stress conditions. The EP_2 and EP_4 receptors couple to Gs and mediate a rise in cyclic adenosine monophosphate (cAMP) concentration. Actions of PGE_2 via EP_2 and EP_4 have been implicated in a number of critical mech-anisms critical to arthritis. PGE_2 also regulates the production of cytokine and growth factor such as IL-6, vascular endothelial growth factor, parathy-roid hormone-related peptide, and macrophage colony stimulating factor though the activation of EP_2 and EP_4 receptors in IL-1 stimulated synovial fibroblasts [87, 88]. Both EP_2 and EP_4 also mediate PGE_2-induced bone formation via osteoblastogenesis in animal models. In contrast, The EP_3 receptor exists in multiple splice variants generated by alternative splicing of the COOH-terminal tail and triggers Gi protein-coupled

adenylate cyclase inhibition and subsequent decrease in intracellular cAMP. Transient intracellular variations of the secondary mediators cAMP or Ca^{2+} generate specific induction of cell regulation mechanisms [89].

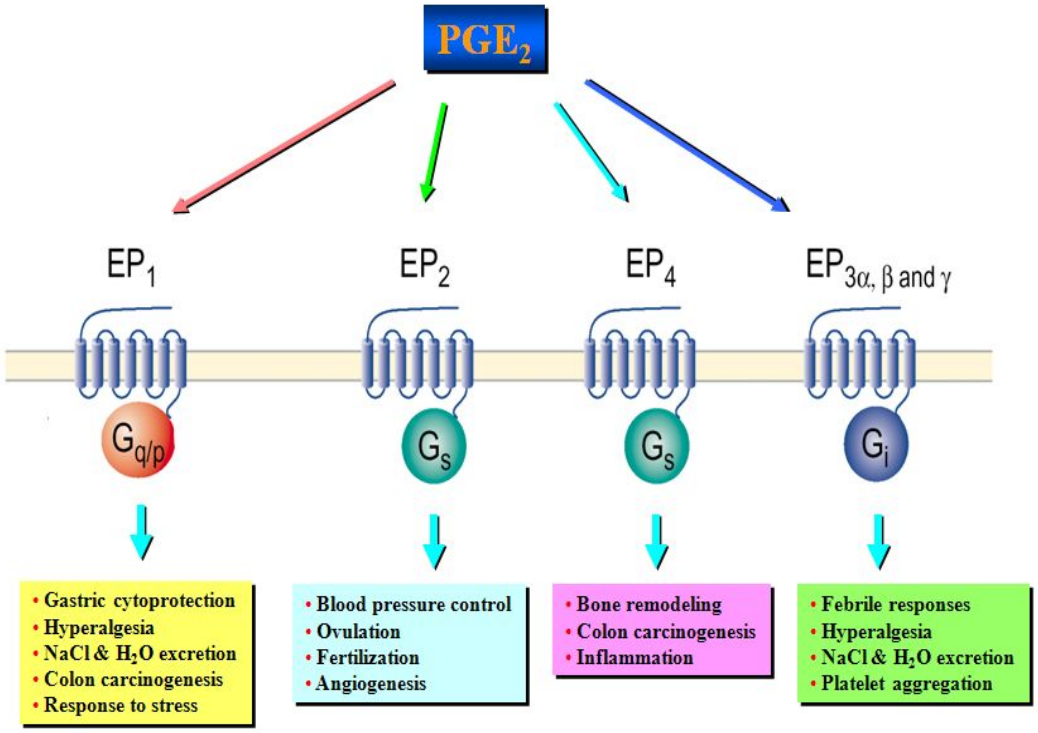


Fig.7. Actions of PGE_2 with EP receptors.

PGE_2 has been also identified as an important mediator of gastric ulcer healing. [90-97] and dermal wound healing [98-103] with specific effects on fibroblast behavior. Hatazawa et al. [104] reported that endogenous PGE_2 plays a role in the healing of NSAID-induced intestinal ulcers through the EP_4 receptors. They also reported that the healing-promoting action of PGE_2 is associated with an increase in angiogenesis by up-regulating vascular endothelial growth factor (VEGF) expression in the fibroblasts of the gastric ulcer bed or margin by activating the EP4 receptors [90]. Numerous *In vivo* studies have also identified PGE_2 as a potent anabolic agent that stimulates both modeling (i.e. formation drift on quiescent surface) [105-110] and remodeling-

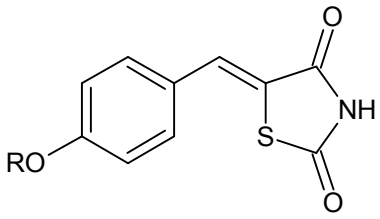
dependent (i.e. positive basic multi-cellular unit bone balance) bone gain when delivered intermittently by daily subcutaneous injections [110-118]. PGs, including PGE_1, PGE_2 and $PGF_{2\alpha}$, have been demonstrated to stimulate both bone resorption and bone formation but tend to favor bone formation, thereby increasing bone mass and bone strength [108, 109]. Endogenous PGE_2 increases locally after fracture and the inhibition of PGE_2 production impairs bone healing [119, 120]. In contrast, the local administration of PGE_2 stimulates bone formation and callus development in animal models.

15-PGDH catalyzes the NAD^+ dependent oxidation of the 15(S)-hydroxyl group of prostaglandins and is considered to be a key enzyme in the biological inactivation of prostaglandins. Therefore, inhibitors of 15-PGDH will be valuable for the therapeutic management of diseases requiring elevated PGE_2 levels.

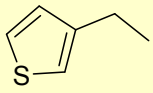
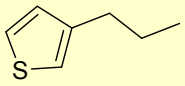
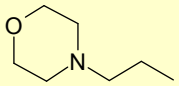
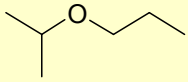
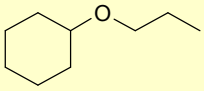
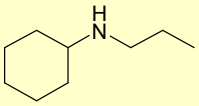
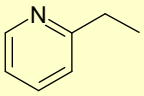
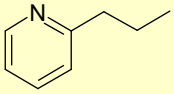
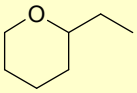
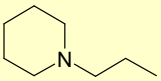
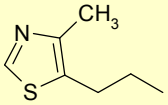
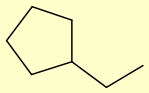
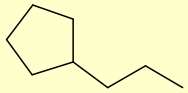
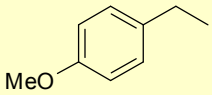
Many studies have reported that the local administration of PGE_2 accelerates the healing of gastric ulcers and wounds, increases bone formation and callus development in animal models. However, local administration of PGE_2 is an unacceptable therapeutic option for human diseases due to the limited knowledge of the potential changes caused by it on the tissue and cellular level as well as the biological instability of PGE_2. Therefore, inhibitors of 15-PGDH will be valuable for the therapeutic management of diseases requiring elevated prostaglandin levels.

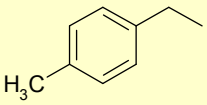
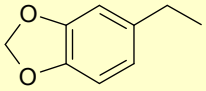
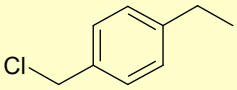
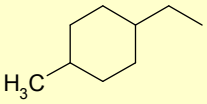
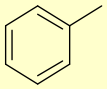
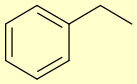
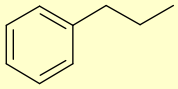
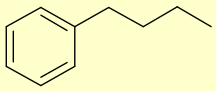
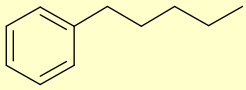
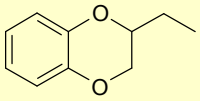
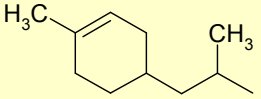
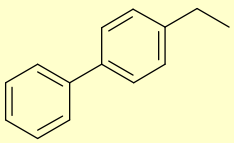
Previously, various pharmacological agents of diverse structures have been reported for their inhibition of 15-PGDH. Among those inhibitors, **CT-8** and its derivatives thiazolidinediones appear to be the most potent inhibitors for 15-PGDH. This indicates that the benzylidene thiazolidine-2, 4-dione analog showed significantly higher inhibitory potency than the benzyl thiazolidine-2, 4-dione analog. It was also interesting to discover that the amine group of thiazolidine-2, 4-dione plays an important role in the inhibitory potency. These were confirmed by the synthesis of various thiazolidinedione derivatives in this study. We synthesized several TD derivatives and checked their activity against 15-PGDH. SAR of TD derivatives indicate that many compounds have strong 15-PGDH inhibitory activities at the nanomolar range.The synthesized compounds were evaluated for their inhibitory activity for 15-PGDH (IC_{50} value).

Table 2.2.1. Inhibitory potency of the compounds **1b - 36b**



Compound	*R*	*IC_{50} (μM)*
1b	Cyclohexyl	0.584
2b	Cyclohexylmethyl	0.218
3b	Cyclohexylethyl	0.051
4b	Cyclohexylpropyl	0.129
5b	Cyclohexylbutyl	0.689
6b	2-Thiomorpholine-1,1-dioxideethyl	0.274
7b	3-Thiomorpholine-1,1-dioxidepropyl	1.960
8b	Thiophen-2-ylmethyl	0.287
9b	2-(Thiophen-2yl)ethyl	0.030
10b	Furan-2-ylmethyl	0.892

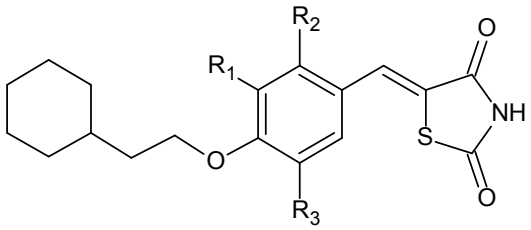
11b	Thiophen-3-ylmethyl		0.428
12b	2-(Thiophen-3-yl)ethyl		0.060
13b	2-Morpholinoethyl		0.713
14b	2-Isopropoxyethyl		1.248
15b	2-(Cyclohexyloxy)ethyl		0.218
16b	2-(Cyclohexylamino)ethyl		3.718
17b	Pyridine-2-ylmethyl		2.585
18b	2-(Pyridine-2-yl)ethyl		0.659
19b	2-(Tetrahydro-2H-pyran-2-yl)ethyl		0.750
20b	2-(Piperidin-1-yl)ethyl		1.441
21b	2-(4-Methylthiazol-5-yl)ethyl		0.635
22b	Cyclopentylmethyl		0.116
23b	2-Cyclopentylethyl		0.044
24b	4-Methoxybenzyl		0.529

25b	4-Methylbenzyl		0.231
26b	Benzo[d][1,3]dioxol-5-ylmethyl		0.124
27b	4-(Chloromethyl)benzyl		0.252
28b	4-(Methylcyclohexyl)methyl		0.050
29b	Phenyl		>20
30b	Benzyl		0.263
31b	Phenylethyl		0.117
32b	Phenylpropyl		0.225
33b	Phenylbutyl		0.186
34b	(2,3-Dihydrobenzo[b] [1,4]dioxin-2yl)methyl		0.814
35b	2-(4-Methylcyclohex-3-en-1-yl)propoxyl		0.028
36b	Biphenyl-4-ylmethyl		0.172

The enzyme was assayed fluorometrically. The IC_{50} value was determined using NAD^+ (250 μM) as coenzyme and PGE_2 (21 μM) as substrate.15-PGDH was expressed as a GST fusion enzyme using pGEX-2T vector. ND: No detectable activity.

We introduced -CH_2 group between cyclohexyl ring and ether linkage of phenyl in CT-8. The number of -CH_2 was increased and the optimal for inhibitory activity observed at two -CH_2 linkage **(1b - 5b)**. Replacement of the cyclohexyl ring with a benzene ring (**29b - 33b**) decreased the inhibitory potency significantly. Replacement of cyclohexane by the 5-member ring resulted in a significant increase in its 15-PGDH inhibitory potency, as indicated for compounds **9b, 12b** and **23b**. However, replacement of the cyclohexylethyl group with the hetero 6-member ring decreased the inhibitory potency significantly **(7b, 13b, 18b** and **20b)**. Interestingly, 4-(methylcyclohexyl) methyl group and the 2-(4-methylcyclohex-3en-1-yl) propoxyl group also increased the 15-PGDH inhibitory potency significantly **(28b** and **35b).** The most potent inhibitor of this series of TDs was **35b** 5-{4-[2-(4-methylcyclohex-3-en-1-yl)propoxy]benzylidene}-1,3-thiazolidine-2,4-dione with an IC_{50} of 0.0284 μM.

Table 2.2.2. Inhibitory potency of the compounds **37b - 50b**



Compound	*R_1*	*R_2*	*R_3*	*IC_{50} (μM)*

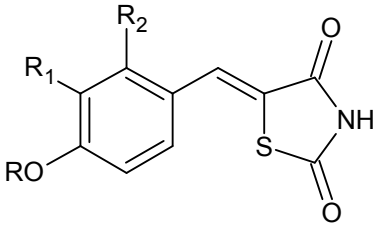
37b	NO_2	H	H	0.059
38b	OCH_3	H	H	0.025
39b	OCH_2CH_3	H	H	0.258
40b	CH_3	H	H	0.044
41b	CF_3	H	H	0.072
42b	F	H	H	0.069
43b	Cl	H	H	0.007
44b	Br	H	H	0.018
45b	H	Cl	H	0.013
46b	H	OCH_3	H	3.562
47b	H	CF_3	H	0.136
48b	OCH_3	H	OCH_3	0.062
49b	Cl	H	OCH_3	0.050
50b	Cl	H	F	0.177

The enzyme was assayed fluorometrically. The IC_{50} value was determined using NAD^+ (250 μM) as coenzyme and PGE_2 (21 μM) as substrate.15-PGDH was expressed as a GST fusion enzyme using pGEX-2T vector. ND: No detectable activity.

Substitutions on the central aromatic ring with either electron with drawing or donating group (i.e. NO_2, CH_3, F, Cl, Br, OCH_3, OCH_2CH_3, CF_3) resulted in increasing of the 15-PGDH inhibitory activity. Substitutions at the R_1-position in phenyl ring play a critical role in 15-PGDH inhibitory activity. Presented in **Scheme 2.1.2**, -Cl group at R_1 position **43b** shows the best IC_{50} value. The R_1-positions -Cl analog **43b** was about two times more potent in vitro than the R_2-position -Cl analog **45b** and -CF_3 analog **41b** was also about two times more potent than -CF_3 analog **47b**. We introduced methoxy group at different position (R_1, R_2 and R_3) are compared the IC_{50} value. The compound contains -OCH_3 group at R1-positions **38b** was about a hundred times stronger than -OCH_3 group at R_2-positions **46b. 38b** was also 2 times stronger than -OCH_3 group at R_3-position **49b.** Thus, we introduce two substituents in the pheny ring, Compounds **48b** with -OCH_3 group at

R_1-position, $-OCH_3$ group at R_3-position; **49b** with -Cl group at R_1-position, $-OCH_3$ group at R_3-position; **50b** with -Cl group at R_1-position, -F group at R_3-position. These compounds are weaker inhibitors than one substitution. The most potent inhibitor of this series of TDs was compound **43b** 5-(3-chloro-4-(2-cyclohexylethoxy)benzylidene)thiazolidine-2,4-dione with an IC_{50} of 7.7 nM.

Table 2.2.3. Inhibitory potency of the compounds **51b - 77b**



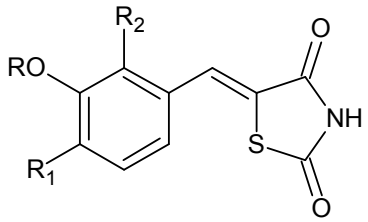
Compound	*R*	*R_1*	*R_2*	*IC_{50} (μM)*
51b	Cyclohexyl	Cl	H	0.047
52b	Cyclohexylmethyl	Cl	H	0.027
53b	Cyclohexylpropyl	Cl	H	0.010
54b	Cyclohexylbutyl	Cl	H	0.024
55b	Cyclohexyl	H	Cl	0.233
56b	Cyclohexylmethyl	H	Cl	2.449
57b	Cyclohexylpropyl	H	Cl	0.284
58b	Cyclohexylbutyl	H	Cl	1.645
59b	Benzyl	Cl	H	0.047
60b	Phenylethyl	Cl	H	0.019
61b	Phenylpropyl	Cl	H	0.038
62b	Phenylbutyl	Cl	H	0.047
63b	Benzyl	H	Cl	0.487
64b	Phenylethyl	H	Cl	0.178
65b	Phenylpropyl	H	Cl	0.052

66b	Phenylbutyl	H	Cl	0.081
67b	Cyclohexylpropyl	NO_2	H	0.324
68b	Phenylbutyl	NO_2	H	1.082
69	Cyclohexylmethyl	CH_3	H	0.049
70	Cyclohexylpropyl	CH_3	H	0.104
71	Cyclohexylbutyl	CH_3	H	0.399
72	4-Nitrobenzyl	H	Cl	ND
73	2-Thiomorpholine-1,1-dioxideethyl	Cl	H	0.223
74	2-Thiomorpholine-1,1-dioxideethyl	NO_2	H	2.449
75	2-(Thiophen-2yl)ethyl	CF_3	H	0.031
76	2-(Thiophen-2yl)ethyl	OCH_3	H	0.084
77	4-(Methylcyclohexyl)methyl	Cl	H	0.681

The enzyme was assayed fluorometrically. The IC_{50} value was determined using NAD^+ (250 μM) as coenzyme and PGE_2 (21 μM) as substrate.15-PGDH was expressed as a GST fusion enzyme using pGEX-2T vector. ND: No detectable activity.

TDs **51b - 54b** exhibited significant 15-PGDH inhibitory activity at lower concentrations at nanomolar range. TDs **59b - 62b** also showed potent activity than TDs **63b - 66b.** SAR study revealed that most compounds contain -Cl at R_1-position showed significant inhibitory activity than other positions. The most potent inhibitor of this series of TDs was **53b** 5-(3-chloro-4-(2-cyclohexylpropoxy) benzylidene)thiazolidine-2,4-dione with an IC_{50} of 0.010 μM.

Table 2.2.4. Inhibitory potency of the compounds **78b - 92b**

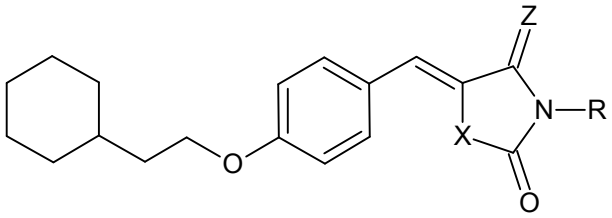


Compound	R	R_1	R_2	IC_{50} (μM)
78b	Cyclohexyl	Cl	H	0.212
79b	Cyclohexylmethyl	Cl	H	0.058
80b	Cyclohexylethyl	Cl	H	0.029
81b	Cyclohexylpropyl	Cl	H	0.059
82b	Cyclohexylbutyl	Cl	H	0.095
83b	Benzyl	Cl	H	0.257
84b	Phenylethyl	Cl	H	0.122
85b	Phenylpropyl	Cl	H	0.044
86b	Cyclohexylbutyl	Cl	H	0.054
87b	Cyclohexylethyl	H	OCH_3	1.157
88b	Cyclohexylethyl	H	NO_2	2.820
89b	Cyclohexylethyl	Cl	OCH_3	0.109
90b	4-(Methylcyclohexyl)methyl	Cl	H	0.135
91b	4-Nitrobenzyl	H	H	1.671
92b	2-(Thiophen-2yl)ethyl	Cl	OCH_3	11.700

The enzyme was assayed fluorometrically. The IC_{50} value was determined using NAD^+ (250 μM) as coenzyme and PGE_2 (21 μM) as substrate.15-PGDH was expressed as a GST fusion enzyme using pGEX-2T vector. ND: No detectable activity.

In this series of compounds, we evaluated ether linkage at 3-position in phenyl ring. SAR shows that this linkage was also good 15-PGDH inhibitory properties. As we increased $–CH_2$ chain between cyclohexyl and ether linkage, we found that TDs contains two $–CH_2$ chains between cyclohexyl and ether linkage are optimal for 15-PGDH inhibitory activity. TDs contains –Cl group at R_1-position **80b** 5-(2-chloro-3-(2-cyclohexylethoxy)benzylidene)thiazolidine-2,4-dione is the best 15-PGDH inhibitor with an IC_{50} of 0.010 μM in this series.

Table 2.2.5. Inhibitory potency of the compounds **93 - 98**

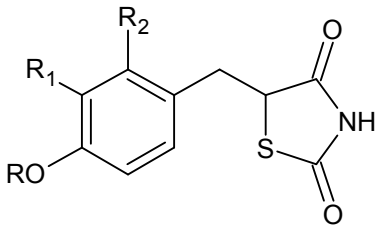


Compound	*Z*	*X*	*R*	*IC_{50} (μM)*
93	S	S	H	0.689
94	S	O	CH_2CH_3	ND
95	O	NH	H	0.865
96	O	CH_2	H	3.788
97	O	S	CH_3	ND
98	O	S	CH_2CH_2OH	0.526

The enzyme was assayed fluorometrically. The IC_{50} value was determined using NAD^+ (250 μM) as coenzyme and PGE_2 (21 μM) as substrate.15-PGDH was expressed as a GST fusion enzyme using pGEX-2T vector. ND: No detectable activity.

It was interesting to discover that the amine group of thiazolidine-2, 4-dione plays an important role in the inhibitory potency. This was confirmed by the synthesis of another *N*-methylated derivative **(97)**, in which protection of the amine group in the molecule by methylation rendered the compound totally inactive. In order to demonstrate the role of the amine group in the molecule, an ethyl hydroxyl group was introduced instead of hydrogen and the inhibitory potency of the compounds **(98)** was compared. The introduction of an ethyl hydroxyl group at the amine group in **CT-8** still produced a good inhibitory effect. This suggests that the hydrogen bond donating groups of thiazolidine-2, 4-dione are essential to orient the molecule more favorably toward the binding site in the enzyme. Further structure-activity analysis indicated that the replacement of S in thiazolidine-2, 4-dione with NH or CH_2 decreased the inhibitory potency of **CT-8** significantly, as shown in **Table 2.2.5**. Replacement of 2, 4-thiazolidindione ring with other analogue such as rhodanine **(93)**, 3-ethyl-2-thioxolidinone **(94)** decrease 15-PGDH inhibitory activity. These information suggested that the thiazolidinedione is important for binging with enzyme 15-PGDH.

Table 2.2.6. Inhibitory potency of the compounds **99 - 106**

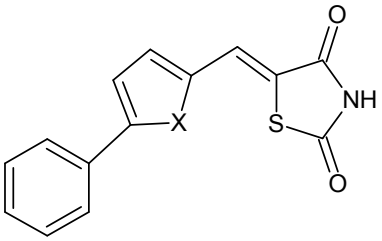


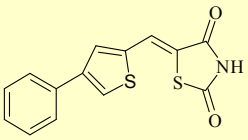
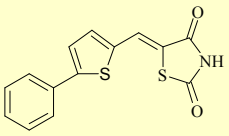
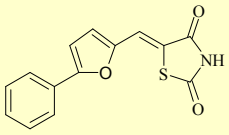
Compound.	*R*	*R_1*	*R_2*	*IC_{50} (μM)*
99	Cyclohexylethyl	H	H	0.977
100	Cyclohexylmethyl	H	H	4.190
101	Cyclohexylethyl	Cl	H	0.147
102	Cyclopentylmethyl	H	H	0.854
103	Benzyl	H	H	5.061
104	2-Cyclopentylethyl	H	Cl	0.251
105	Biphenyl-4-ylmethyl	H	H	20.726
106	Cyclohexylethyl	H	H	2.232

The enzyme was assayed fluorometrically. The IC_{50} value was determined using NAD^+ (250 μM) as coenzyme and PGE_2 (21 μM) as substrate.15-PGDH was expressed as a GST fusion enzyme using pGEX-2T vector. ND: No detectable activity.

Interestingly, the benzylidene analog showed increase in 15-PGDH inhibitory potency. The olefinic bond between central aromatic ring and 2,4-thiazolidinedione ring appears to orient the molecule more favorably toward the binging site in the enzyme. This is conformed by the synthesis of other benzyl derivatives **(99 - 106)** in which the introduction of olefinic bond in the molecule increased dramatically the inhibitory potency of substituted benzyl 2, 4-thiazolidinediones.

Table 2.2.7. Inhibitory potency of the compounds **107 - 109**



Compound		*IC50 (uM)*
107	 	0.182
108		3.843
109		2.975

The enzyme was assayed fluorometrically. The IC_{50} value was determined using NAD^+ (250 μM) as coenzyme and PGE_2 (21 μM) as substrate.15-PGDH was expressed as a GST fusion enzyme using pGEX-2T vector. ND: No detectable activity.

This series of TDs decreased 15-PGDH inhibitory potency. It proved that ether linkage at 3-or4-position in phenyl ring is important.

3. Experimental

3.1. Materials and chemical agents

PGE_2, NAD^+, NADH, Glutathione-Sepharose 4B, Dithiothretitol (DTT), Sodium dodecylsulfate (SDS), EDTA and reduced glutathione were obtained from Sigma. The cDNA of human 15-PGDH was cloned from a human placenta cDNA libraryAll chemical reagents were commercially available. The UV spectra were obtained using a UV-VIS spectrophotometer (SHIMADZU). TLC plates were prepared by using Kieselgel 60 PF254. Column chromatography was performed using silica gel (230-400 mesh, Whatman Inc). The NMR spectra were recorded on a JEOL JNM-LA 300 spectrometer (JOEL, Tokyo, Japan). Chemical shifts were reported in parts per million (δ) and signala were quoted as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet).

3.2. Expression and purification of 15-PGDH

The sequence of 15-PGDH cDNA plasmid cantaining BamHI and EcoRI sites of the pGEX-2T expression vector was used to transform Escherichia coli BL-21 LysS. Cells were grown in 500 mL LB medium containing 50 μg/mL ampicillin at 37℃ with 220rpm until OD_{600} reached 0.6. Isopropyl ß-D-thiogalactoside (1 mM) was added and cells were allowed to grow for 12 h at 25℃. Cells were then harvested by centrifugation at 4000 x g for 30min at 4℃. The cell pellets was resuspended in 20 mL of cold cell lysis buffer [1 × PBS buffer (pH 7.4) containing 1 mM EDTA and 0.1 mM DTT] and sonicated (14 ×10 s at 4℃). Disrupted cells were centrifuged at 4000g for 20min at 4℃. The supernatant was slowly applied to the Glutathione-Sepharose 4B column (about 3ml) which was equilibrated at 4℃ with lysis buffer [1×PBS buffer (pH 7.4) containing 1 mM EDTA and 0.1 mM DTT]. After washing with lysis buffer until the OD_{280} reached less than 0.005. The 15-PGDH was eluted from the Glutathione-Sepharose 4B column by incubation at room temperature for 5min with the elution buffer [50 mM Tris-HCL (pH 8.0) containing 10 mM reduced glutathione 1 mM EDTA and 0.1 mM DTT]. The concentration of the purified enzyme was determined and the purity of the 15-PGDH was assessed by SDS-PAGE.

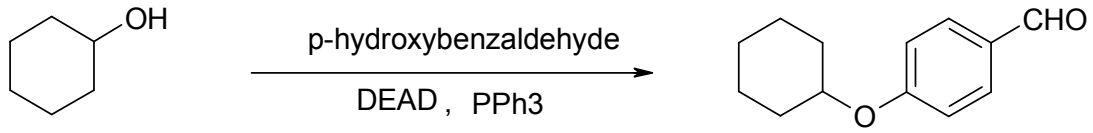
3.3. 15-PGDH inhibitors activity assay

Assays for activity of 15-PGDH inhibitors was performed using a fluorescence spectrophotometer by measuring the formation of NADH at 468nm following excitation at 340nm. 50 mM Tris-HCl (pH 7.5), 0.1 mM DTT, 0.25 mM NAD^+, 10 μg of purified enzyme, 21 μM PGE_2, and various concentrations of inhibitors (total 2 mL) were added in cell. Each concentration was assayed in triplicate. The absorbance of the reaction mixture was read at 340nm and the activity of 15-PGDH inhibitors was determined from a standard curve prepared various concentrations of NADH absorbance at 340nm.

3.4. General procedure for the synthesis of compounds

Synthesis of compounds 1 - 36

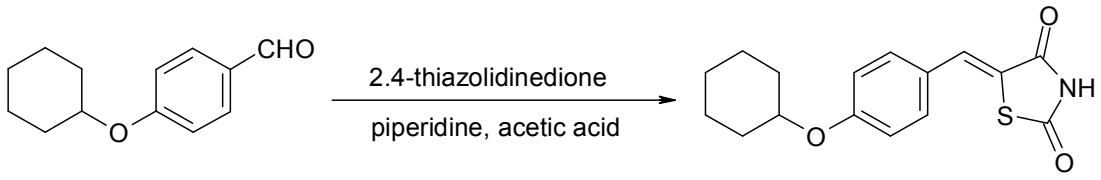
1a: 4-(cyclohexyloxy)benzaldehyde



1a

Diethyl azodicarboxylate (40% in toluene, 4.79 g, 11 mmol) was added slowly to a stirring solution of cyclohexanemethanol (1 g, 10 mmol), *p*-hydroxybenzaldehyde (1.22 g, 10 mmol) and triphenylphosphine (2.89 g, 11 mmol) in THF (20 mL) for 10 min. at 0℃. The mixture was then stirred at room temperature until the starting materials (TLC analysis) began to disappear. The resulting solution was concentrated under reduced pressure and purified by column chromatography over silica gel (elution with hexane/ethyl acetate, 20 : 1) to afford 1.5 g of **1a** (87%), as a yellow oil.^{1}H NMR (300 MHz, $CDCl_3$) δ10.235 (s, 1H), 7.398 (d, *J* = 8.7 Hz, 2H), 6.946 (d, *J* = 8.7 Hz, 2H), 4.387 (q, 1H), 1.724-1.976 (m, 2H), 1.498-1.697 (m, 2H), 1.323-1.498 (m, 3H), 1.123-1.297 (m, 3H), 1.056-1.186 (m, 1H).

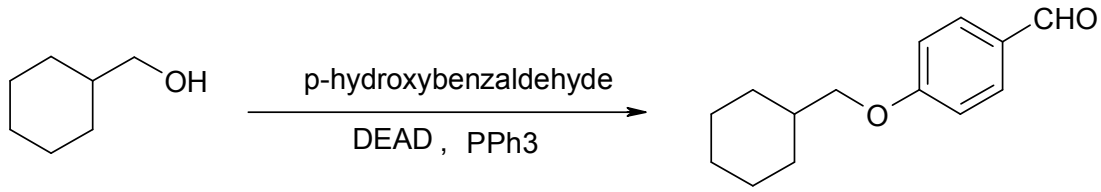
1b: 5-(4-(cyclohexyloxy)benzylidene)thiazolidine-2,4-dione



1a **1b**

A mixture of **1a** (1.0 g, 4.9 mmol), 2,4-thiazolidinedione (573 mg, 4.9 mmol), piperidine (0.24 ml, 2.45 mmol) and acetic acid (0.14 ml, 2.45 mmol) in toluene (20 mL) was then added to a round bottom flask fitted with a Dean-Stark water trap and stirred under reflux for overnight. After cooling to room temperature, the precipitate was washed with hexane and dried to afford compound **1b** as a yellow solid (1.3 g, 88%); ^{1}H NMR (300 MHz, $CDCl_3$) δ12.496 (s, 1H), 7.724 (s, 1H) 7.532 (d, *J* = 8.7 Hz, 2H), 7.091 (d, *J* = 8.7 Hz, 2H), 4.455 (q, 1H), 1.865-2.073 (m, 2H), 1.675-1.865 (m, 2H), 1.446-1.547 (m, 3H), 1.257-1.415 (m, 3H), 1.160-1.257 (m, 1H).

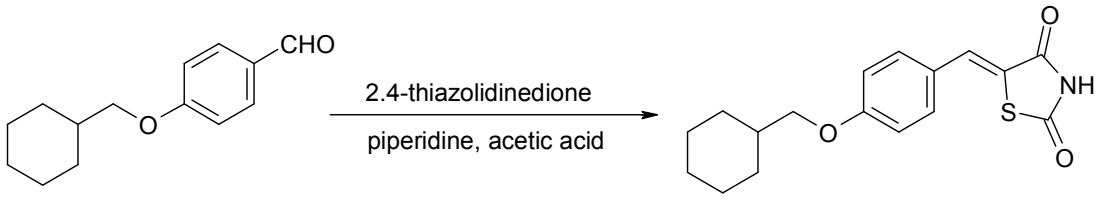
2a: 4-(cyclohexylmethoxy)benzaldehyde



2a

2a: yield 72%; ^{1}H NMR (300 MHz, $CDCl_3$) δ10.354 (s, 1H), 7.245 (d, *J* = 11.7 Hz, 2H), 6.786 (d, *J* = 11.7 Hz, 2H), 3.534 (d, *J* = 6.0 Hz, 2H), 1.587-1.768 (m, 6H), 1.098-1.265 (m, 3H), 0.897-1.045 (m, 2H).

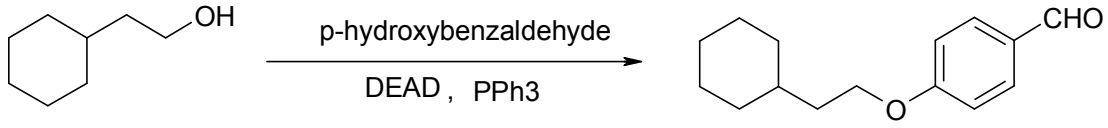
2b: 5-(4-(cyclohexylmethoxy)benzylidene)thiazolidine-2,4-dione



2a **2b**

2b: yield 83%; ^{1}H NMR (300 MHz, $CDCl_3$) δ8.345 (s, 1H), 7.748 (s, 1H), 7.390 (d, *J* = 11.7 Hz, 2H), 6.895 (d, *J* = 11.7 Hz, 2H), 3.752 (d, *J* = 6.0 Hz, 2H), 1.629-1.819 (m, 6H), 1.152-1.301 (m, 3H), 0.926-1.072 (m, 2H).

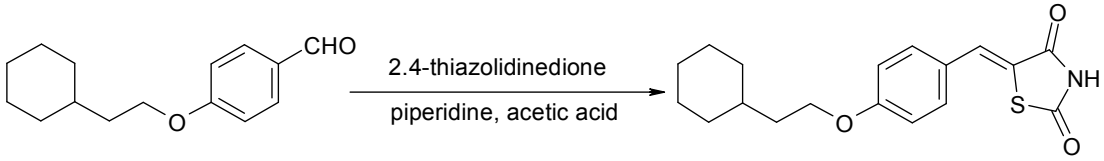
3a: 4-(2-cyclohexylethoxy)benzaldehyde



3a

3a: yield 79%; ^{1}H NMR (300 MHz, $CDCl_3$) δ9.857 (s, 1H), 7.849 (d, *J* = 13.5 Hz, 2H), 7.087 (d, *J* = 13.5 Hz, 2H), 4.178 (t, *J* = 13.5 Hz, 2H), 1.697-1.798 (m, 6H), 1.217-1.290 (m, 5H), 0.969-1.007 (m, 2H).

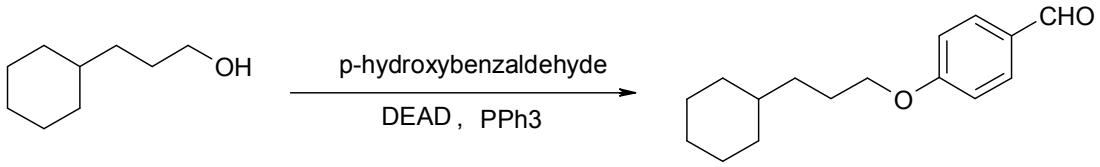
3b: 5-(4-(2-cyclohexylethoxy)benzylidene)thiazolidine-2,4-dione



3a **3b**

3b: yield 84%; ^{1}H NMR (300 MHz, $CDCl_3$) δ8.195 (s, 1H), 7.675 (s, 1H), 7.473 (d, *J* = 14.7 Hz, 2H), 6.895 (d, *J* = 14.7 Hz, 2H), 4.036(t, *J* = 11.7 Hz, 2H), 1.565-1.727 (m, 5H), 1.437-1.469 (m, 1H), 1.041-1.223 (m, 3H), 0.807-1.034 (m, 2H).

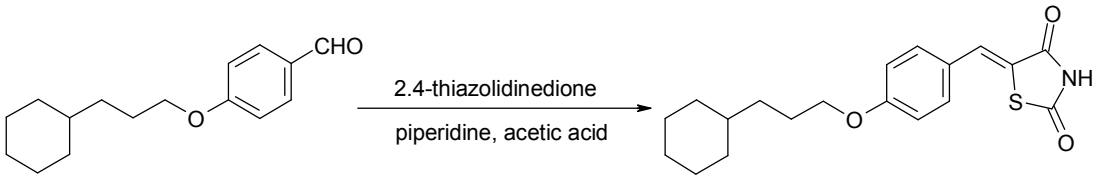
4a: 4-(3-cyclohexylpropoxy)benzaldehyde



4a

4a: yield 81%; ^{1}H NMR (300 MHz, $CDCl_3$) δ10.324 (s, 1H) 7.398 (d, *J* = 9.0 Hz, 2H), 7.120 (d, *J* = 9.0 Hz, 2H), 3.947(t, *J* = 12.9 Hz, 2H), 1.423-1.612 (m, 7H), 1.011-1.278 (m, 6H), 0.786-0.899 (m, 2H).

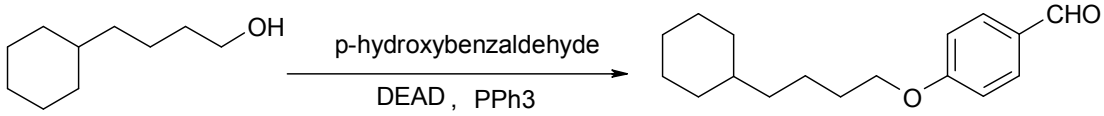
4b: 5-(4-(3-cyclohexylpropoxy)benzylidene)thiazolidine-2,4-dione



4a **4b**

4b: yield 86%; ^{1}H NMR (300 MHz, $CDCl_3$) δ12.505 (s, 1H) 7.730 (s, 1H), 7.547 (d, *J* = 9.0 Hz, 2H), 7.084 (d, *J* = 9.0 Hz, 2H), 4.028(t, *J* = 12.9 Hz, 2H), 1.628-1.711 (m, 7H), 1.143-1.300 (m, 6H), 0.839-0.911 (m, 2H).

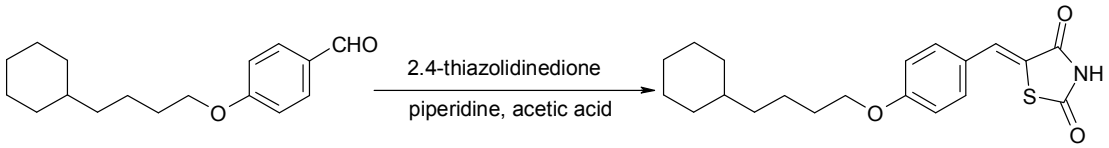
5a: 4-(4-cyclohexylbutoxy)benzaldehyde



5a

5a: yield 76%; ^{1}H NMR (300 MHz, $CDCl_3$) δ10.189 (s, 1H), 7.243 (d, *J* = 8.7 Hz, 2H), 6.878 (d, *J* = 8.7 Hz, 2H), 3.895 (t, *J* = 12.3 Hz, 2H), 1.497-1.601 (m, 6H), 1.219-1.290 (m, 3H), 1.012-1.197 (m, 4H), 0.809-0.977 (m, 4H).

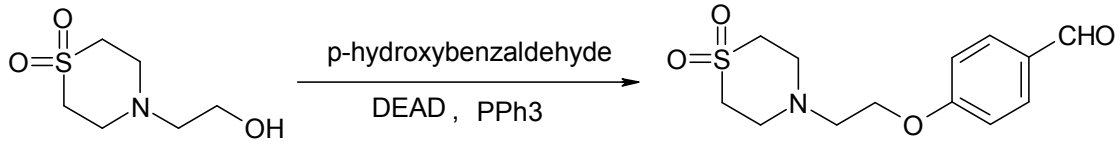
5b: 5-(4-(4-cyclohexylbutoxy)benzylidene)thiazolidine-2,4-dione



5a **5b**

5b: yield 84%; ^{1}H NMR (300 MHz, DMSO-d_6) δ12.453 (s, 1H), 7.407 (s, 1H), 7.357 (d, J = 8.7 Hz, 2H), 6.933 (d, J = 8.7 Hz, 2H), 4.003 (t, J = 12.3 Hz, 2H), 1.625-1.692 (m, 6H), 1.37-1.398 (m, 3H), 1.133-1.215 (m, 4H), 0.815-0.956 (m, 4H).

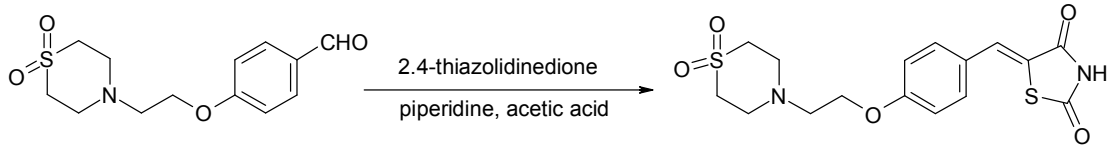
6a: 4-(2-Thiomorpholine 1,1-Dioxideethoxy)benzaldehyde



6a

6a: yield 87%; ^{1}H NMR (300 MHz, $CDCl_3$) δ9.90 (s, 1H), 7.87 (d, J = 8.7 Hz, 2H), 7.03 (d, J = 8.7 Hz, 2H), 4.20 (t, J = 10.5 Hz, 2H), 3.20 (t, J = 10.2 Hz, 4H), 3.105 (t, J = 10.2 Hz, 4H), 3.04 (t, J = 10.5 Hz, 2H).

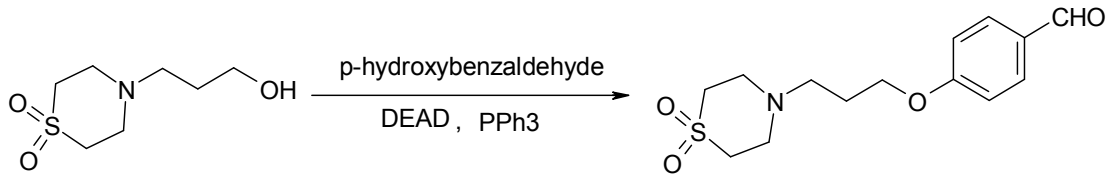
6b: 5-(4-(2-Thiomorpholine 1,1-Dioxideethoxy)benzylidene)-2,4-thiazolidinedione



6a **6b**

6b: yield 88%; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.19 (s, 1H), 7.73 (s, 1H), 7.56 (d, J = 8.7 Hz, 2H), 7.11 (d, J = 8.7 Hz, 2H), 4.169 (t, J = 10.8 Hz, 2H), 3.086 (t, J = 10.2 Hz, 4H), 3.033 (t, J = 10.2 Hz, 4H), 2.945 (t, J = 10.8 Hz, 2H).

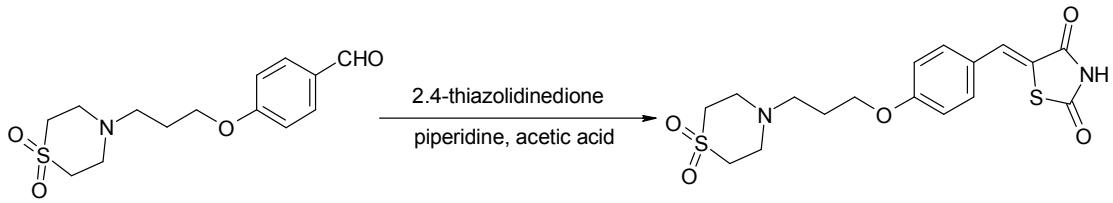
7a: 4-(3-Thiomorpholine 1,1-Dioxidepropoxy)benzaldehyde



7a

7a: yield 87%;^{1}H NMR (300 MHz, $CDCl_3$) δ9.891 (s, 1H), 7.865 (d, *J* = 11.4 Hz, 2H), 7.014 (d, *J* = 11.4 Hz, 2H), 4.158 (t, *J* = 12 Hz, 2H), 3.077 (m, 8H), 2.749 (t, *J* = 14.4 Hz, 2H), 1.953-2.047 (m, 2H).

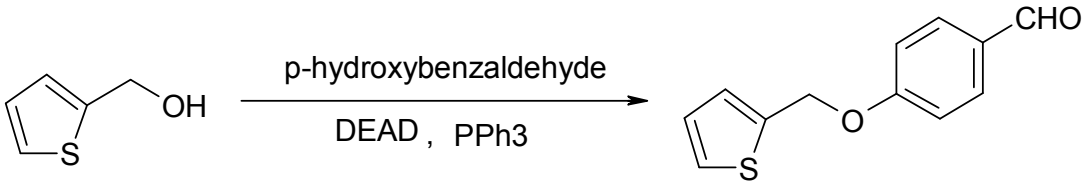
7b: 5-[4-(3-Thiomorpholine-1,1-dioxidepropoxy)benzylidene]-thiazolidine-2,4-dione



7a **7b**

7b: yield 81.1%; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.19 (s, 1H), 7.705 (s, 1H), 7.540 (d, *J* = 8.1 Hz, 2H), 7.088 (d, *J* = 8.1 Hz, 2H), 4.09 (t, *J* = 12 Hz, 2H), 3.06-3.89 (m, 8H), 2.616 (t, *J* = 14.1 Hz, 2H), 1.819-1.911 (m, 2H).

8a: 4-(Thiophen-2-ylmethoxy)benzaldehyde

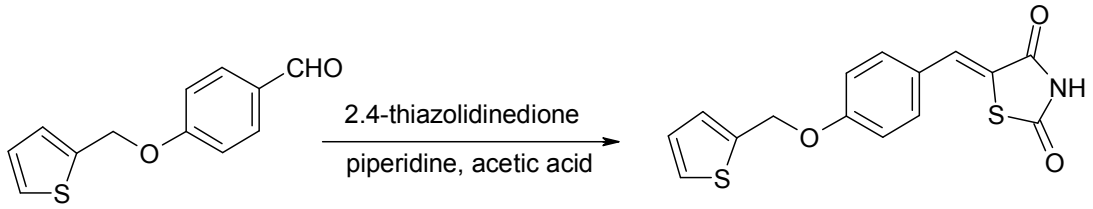


8a

8a: yield 86%;^{1}H NMR (300 MHz, $CDCl_3$) δ9.893 (s, 1H), 7.862 (d, *J* = 8.4 Hz, 2H), 7.368 (d, *J*

= 5.1 Hz, 1H), 7.153 (d, *J* = 3.3 Hz, 1H), 7.103 (d, *J* = 8.4 Hz, 2H), 7.042 (m, 1H), 5.309 (s, 2H).

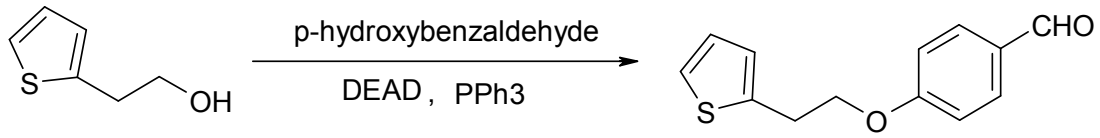
8b: 5-(4-(Thiophen-2-ylmethoxy)benzylidene)thiazolidine-2,4-dione



8a **8b**

8b: yield 80.7% yield; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.513 (s, 1H), 7.745 (s, 1H), 7.569 (d, *J* = 8.4 Hz, 2H), 7.559 (t, *J* = 2.4 Hz, 1H), 7.248 (t, *J* = 3.3 Hz, 1H), 7.194 (d, *J* = 8.4 Hz, 2H), 7.052 (m, 1H), 5.37 (s, 2H).

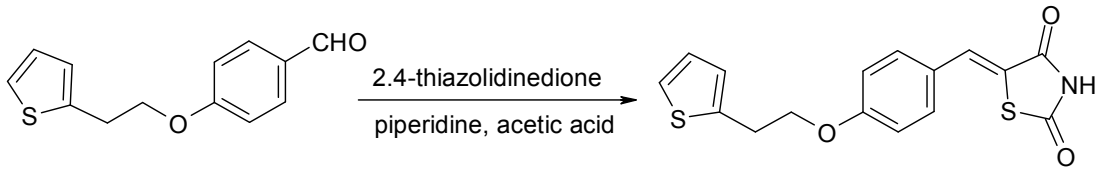
9a: 4-(2-(Thiophen-2-yl)ethoxy)benzaldehyde



9a

9a: yield 79%; ^{1}H NMR (300 MHz, $CDCl_3$) δ9.89 (s, 1H), 7.85 (d, *J* = 10.2 Hz, 2H), 7.20 (d, *J* = 6.3 Hz, 1H), 7.03 (d, *J* = 10.2 Hz, 2H), 6.92-6.98 (m, 2H), 4.30 (t, *J* = 13.2 Hz, 2H), 3.37 (t, *J* = 13.2 Hz, 2H).

9b: 5-(4-(2-(Thiophen-2-yl)ethoxy)benzylidene)thiazolidine-2,4-dione

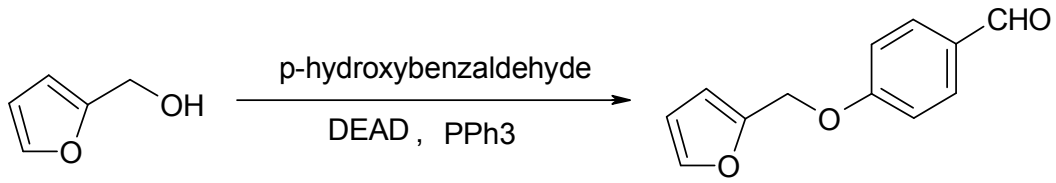


9a **9b**

9b: yield 87.8% yield; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.12 (s, 1H), 7.73 (s, 1H), 7.558 (d, *J* =

8.7 Hz, 2H), 7.354 (d, *J* = 6.0 Hz, 1H), 7.12 (d, *J* = 8.7 Hz, 2H), 6.942- 6.973 (m, 2H), 4.28 (t, *J* = 12.6 Hz, 2H), 3.285 (t, *J* = 12.6 Hz, 2H).

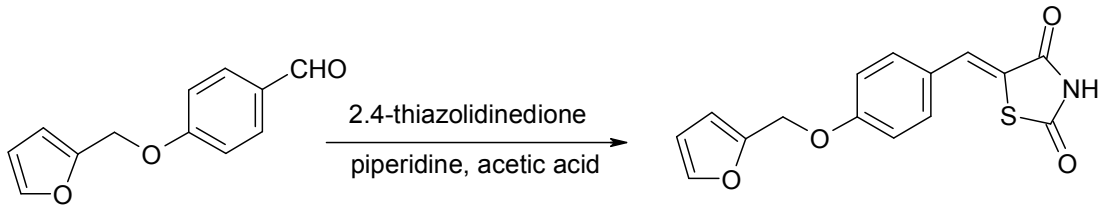
10a: 4-(furan-2-ylmethoxy)benzaldehyde



10a

10a: yield 83%; ^{1}H NMR (300 MHz, $CDCl_3$) δ9.895 (s, 1H) 7.872 (d, *J* = 11.4 Hz, 2H), 7.473 (q, 1H), 7.118 (d, *J* = 11.4 Hz, 2H), 6.483 (d, *J* = 3.3 Hz, 1H), 6.413(d, *J* = 5.4 Hz, 1H), 5.093 (s, 2H).

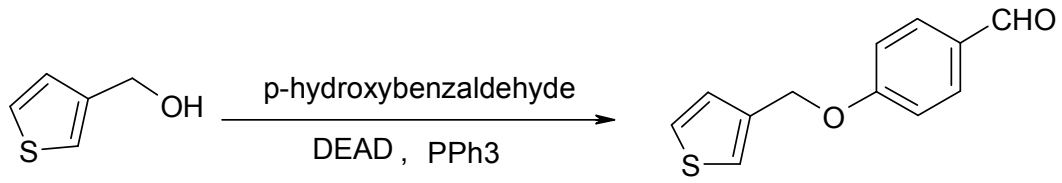
10b: 5-[4-(furan-2-ylmethoxy) benzylidene] thiazolidine-2,4-dione



10a **10b**

10b: yield 87%; ^{1}H NMR (300 MHz, DMSO-d_6) δ12.518 (s, 1H), 7.747 (s, 1H), 7.705 (t, *J* = 1.8 Hz, 1H), 7.572 (d, *J* = 8.4 Hz, 1H), 7.200 (d, *J* = 8.4 Hz, 2H), 6.630 (d, *J* = 3.0 Hz, 1H), 6.481 (d, *J* = 1.8 Hz, 1H), 5.142 (s, 2H).

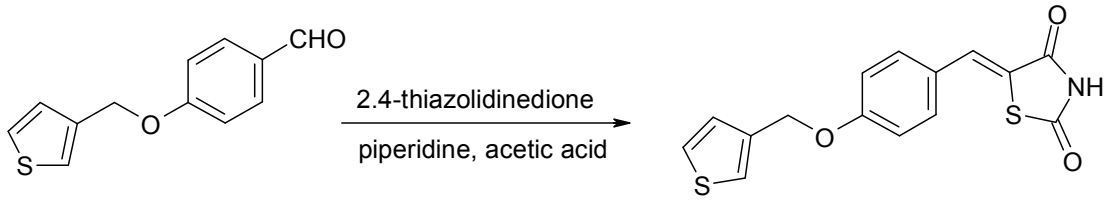
11a: 4-(Thiophen-3-ylmethoxy)benzaldehyde



11a

11a: yield 83%; ^{1}H NMR (300 MHz, $CDCl_3$) δ9.926 (s, 1H), 7.865 (d, *J* = 13.8 Hz, 2H), 7.382 (d, *J* = 10.2 Hz, 1H), 7.367 (s, 1H), 7.164 (d, *J* = 10.2 Hz, 1H), 7.092 (d, *J* = 13.8 Hz, 2H), 5.160 (s, 2H).

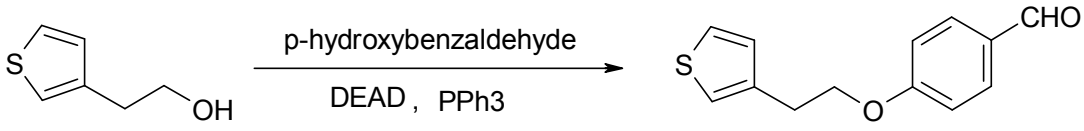
11b: 5-[4-(Thiophen-3-ylmethoxy)benzylidene]thiazolidine-2,4-dione



11a **11b**

11b: yield 86%; ^{1}H NMR (300 MHz, $CDCl_3$) δ12.504 (s, 1H), 8.590 (s, 1H), 7.864 (d, *J* = 7.8 Hz, 1H), 7.733 (s, 1H), 7.573 (d, *J* = 8.7 Hz, 2H), 7.521 (d, *J* = 7.8 Hz, 1H), 7.197 (d, *J* = 8.7 Hz, 2H), 5.252 (s, 2H).

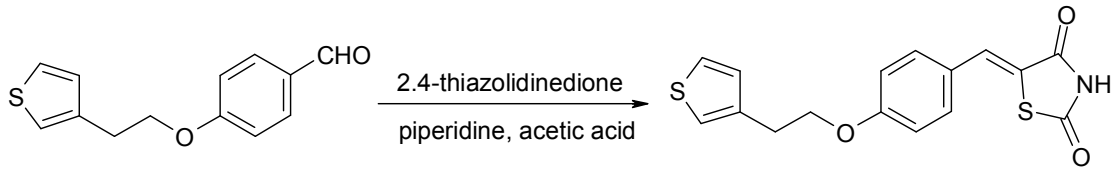
12a: 4-(2-(Thiophen-3-yl)ethoxy)benzaldehyde



12a

12a: yield 83%;^{1}H NMR (300 MHz, $CDCl_3$) δ9.89 (s, 1H), 7.876 (d, *J* = 13.8 Hz, 2H), 7.03 (d, *J* = 13.8 Hz, 2H), 7.383 (d, *J* = 6.0 Hz, 1H), 7.357 (s, 1H), 7.164 (d, *J* = 6.0 Hz, 1H), 4.28 (t, *J* = 13.5 Hz, 2H), 3.18 (t, *J* = 13.5 Hz, 2H).

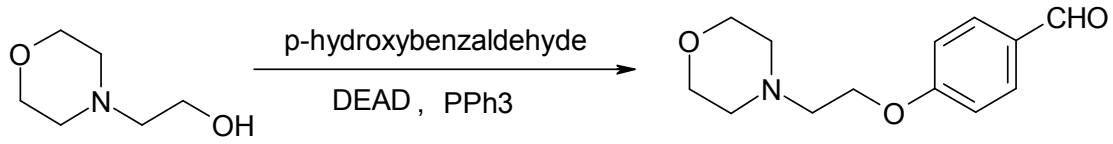
12b: 5-(4-(2-(Thiophen-3-yl)ethoxy)benzylidene)thiazolidine-2,4-dione



12a **12b**

12b: yield 86%; ^{1}H NMR (300 MHz, DMSO-d_6) N 8.12 (s, 1H), 7.69 (s, 1H), 7.556 (d, J = 11.7 Hz, 2H), 7.45 (d, J = 7.8 Hz, 1H), 7.305 (d, J = 7.8Hz, 1H), 7.11 (d, J = 11.7 Hz, 2H), 7.088 (s, 1H), 4.28 (t, J = 13.8 Hz, 2H), 3.07 (t, J = 13.8 Hz, 2H).

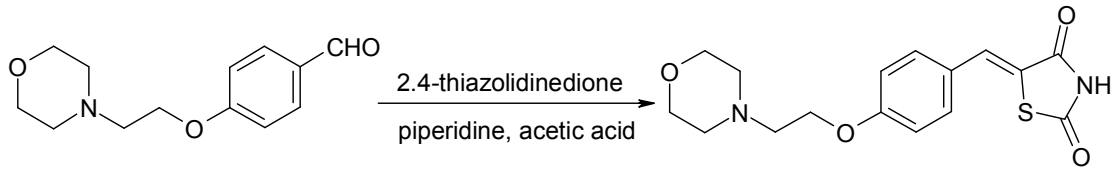
13a: 4-(2-(morpholinoethoxy))benzaldehyde



13a

13a: yield 79%; ^{1}H NMR (300 MHz, $CDCl_3$) δ10.17 (s, 1H), 7.85 (d, J = 8.7 Hz, 2H), 7.00 (d, J = 8.7 Hz, 2H), 4.19 (t, J = 11.4 Hz, 2H), 3.74 (t, J = 9.0 Hz, 4H), 2.83(t, J = 11.4 Hz, 2H), 2.59 (t, J = 9.0 Hz, 4H).

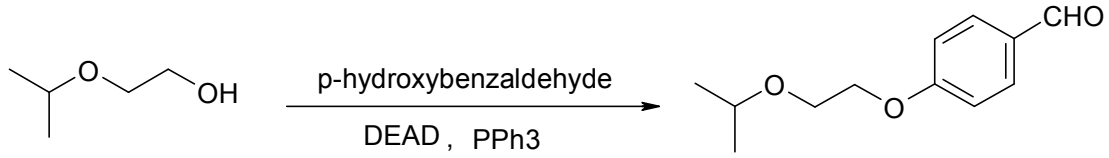
13b: 5-(4-(2-Morpholinoethoxy)benzylidene)thiazolidine-2,4-dione



13a **13b**

13b: yield 81.7%; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.14 (s, 1H), 7.705 (s, 1H), 7.544 (d, J = 8.7 Hz, 2H), 7.104 (d, J = 8.7 Hz, 2H), 4.219 (t, J = 11.4 Hz, 2H), 3.808 (t, J = 9.6 Hz, 4H), 3.134 (t, J = 11.4 Hz, 2H), 2.764 (t, J = 9.6 Hz, 4H).

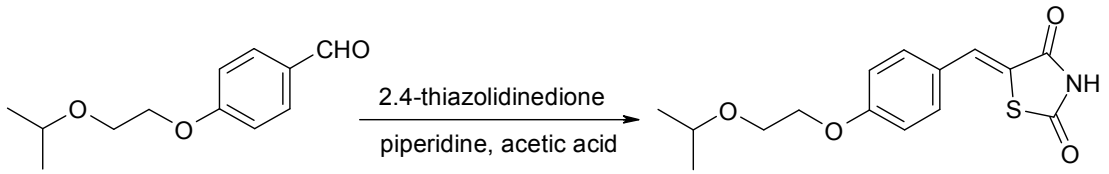
14a: 4-(2-isopropoxyethoxy)benzaldehyde



14a

14a: yield 82%; ^{1}H NMR (300 MHz, $CDCl_3$) δ9.88 (s, 1H), 7.82 (d, *J* = 10.8 Hz, 2H), 6.97 (d, *J* = 10.8 Hz, 2H), 4.19 (t, *J* = 10.2 Hz, 2H), 3.81 (t, *J* = 10.2 Hz, 2H), 3.63-3.75 (m, 1H), 1.20 (d, *J* = 6.0 Hz, 6H).

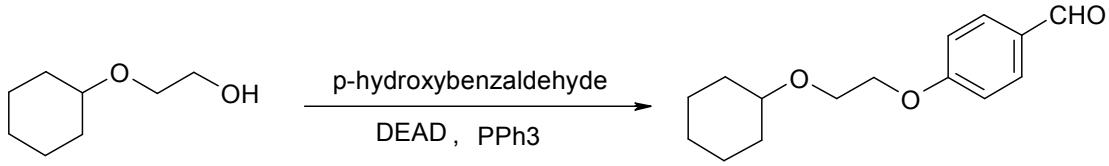
14b: 5-(4-(2-Isopropoxyethoxy)benzylidene)thiazolidine-2,4-dione



14a **14b**

14b: yield 85.7%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.805 (s, 1H), 7.432 (d, *J* = 9.0 Hz, 2H), 7.022 (d, *J* = 9.0 Hz, 2H), 4.19 (t, *J* = 9.6 Hz, 2H), 3.84 (t, *J* = 9.6 Hz, 2H), 3.65-3.76 (m, 1H), 1.24 (d, *J* = 6.0 Hz, 6H).

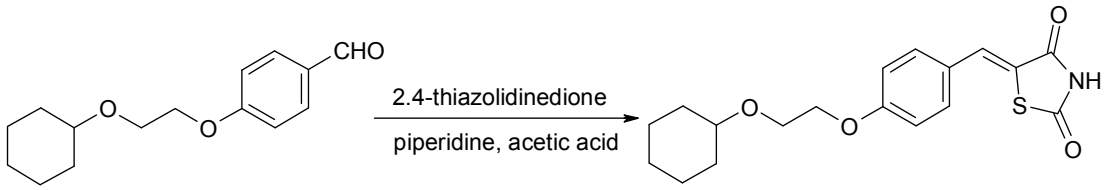
15a: 4-(2-(Cyclohexyloxy)ethoxy)benzaldehyde



15a

15a: yield 85%;^{1}H NMR (300 MHz, $CDCl_3$) δ 9.923 (s, 1H), 7.852 (d, *J* = 14.1 Hz, 2H), 7.052 (d, *J* = 14.1 Hz, 2H), 4.212 (t, *J* = 9.9 Hz, 2H), 3.862 (t, *J* = 9.9 Hz, 2H), 3.300-3.373 (m, 1H), 1.964-2.175 (m, 2H), 1.731-1.822 (m, 2H), 1.523-1.567 (m, 1H), 1.167-1.426 (m, 5H).

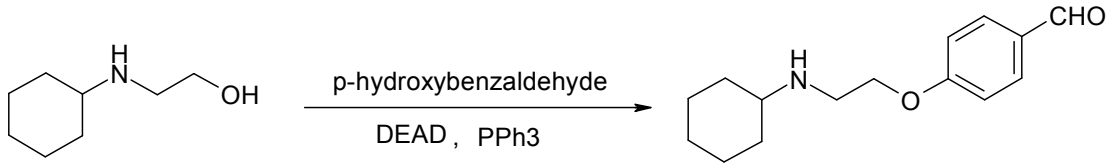
15b: 5-(4-(2-(Cyclohexyloxy)ethoxy)benzylidene)thiazolidine-2,4-dione



15a **15b**

15b: yield 82.0%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.645 (s, 1H), 7.733 (s, 1H), 7.437 (d, J = 14.7 Hz, 2H), 7.020 (d, J = 14.7 Hz, 2H), 4.197 (t, J = 9.9 Hz, 2H), 3.302 (t, J = 9.9 Hz, 2H), 3.321-3.397 (m, 1H), 1.956-2.179 (m, 2H), 1.754-1.770 (m, 2H), 1.549-1.592 (m, 1H), 1.218-1.389 (m, 5H).

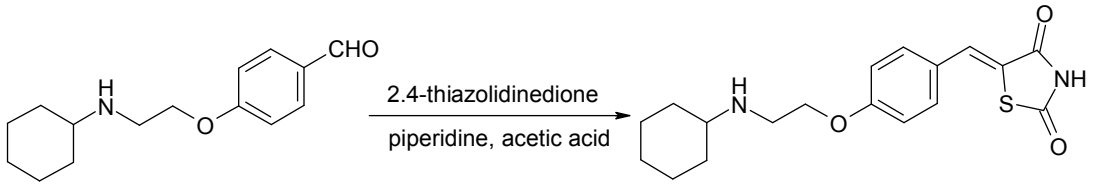
16a: 4-(2-cyclohexylamino)ethoxybenzaldehyde



16a

16a: yield 75%; ^{1}H NMR (300 MHz, $CDCl_3$) δ9.885 (s, 1H), 7.855 (d, J = 14.1 Hz, 2H), 7.034 (d, J = 14.1 Hz, 2H), 4.173 (t, J = 10.5 Hz, 2H), 3.082 (t, J = 10.5 Hz, 2H), 2.452-2.546 (s, 1H), 1.834-1.943 (m, 2H), 1.734-1.788 (m, 2H), 1.642-1.649 (m, 3H), 1.264-1.449(m, 2H), 1.041-1.179(m, 2H).

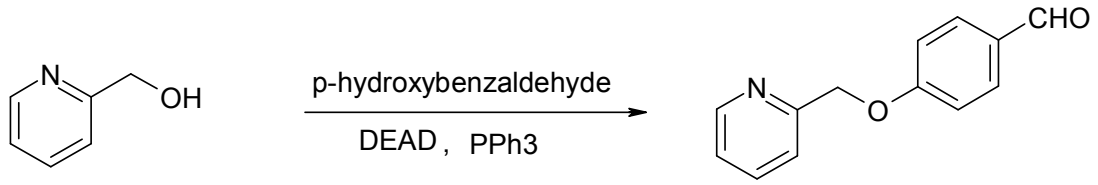
16b: 5-(4-(2-(Cyclohexylamino)ethoxy)benzylidene)thiazolidine-2,4-dione



16a **16b**

16b: 75.5% yield; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.504 (d, J = 8.7 Hz, 2H), 7.310 (s, 1H), 7.069 (d, J = 8.7 Hz, 2H), 4.244 (t, J = 9.9 Hz, 2H), 3.302 (t, J = 9.9 Hz, 2H), 2.876-2.942 (m, 1H), 2.284 (s, 1H), 1.894-2.071 (m, 2H), 1.733-1.894 (m, 2H), 1.571-1.610 (m, 1H), 1.094-1.304 (m, 4H).

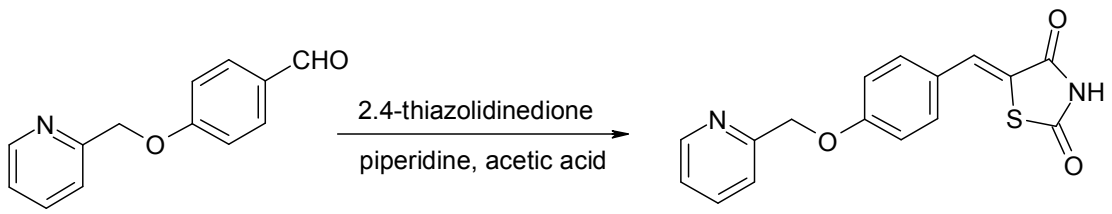
4-(piridin-2-ylmethoxy)benzaldehyde (17a)



17a

17a: yield 83%; ^{1}H NMR (300 MHz, $CDCl_3$) δ9.932 (s, 1H), 8.630 (d, J = 4.8 Hz, 1H), 7.870 (d, J = 14.4 Hz, 2H), 7.767 (t, J = 17.1 Hz, 1H), 7.513 (d, J = 7.8 Hz, 1H), 7.284 (t, J = 12.6 Hz, 1H), 7.129 (d, J = 14.4 Hz, 2H), 5.295 (s, 2H).

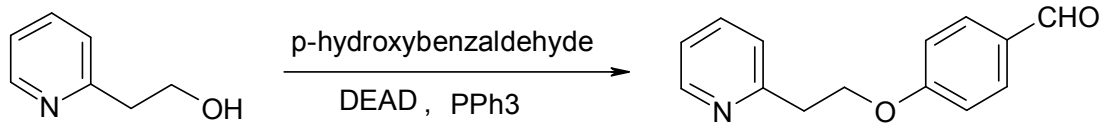
17b: 5-(4-(piridin-2-ylmethoxy)benzylidene)thiazolidine-2,4-dione



17a **17b**

17b: yield 87%; ^{1}H NMR (300 MHz, DMSO-d_6) δ12.525 (s, 1H), 8.585 (d, J = 4.2 Hz, 1H), 7.865 (t, J = 16.8 Hz, 1H), 7.735 (s, 1H), 7.575 (d, J = 9.0 Hz, 2H), 7.527 (d, J = 7.8 Hz, 1H), 7.372 (m, 1H), 7.197 (d, J = 9.0 Hz, 2H), 5.251 (s, 2H).

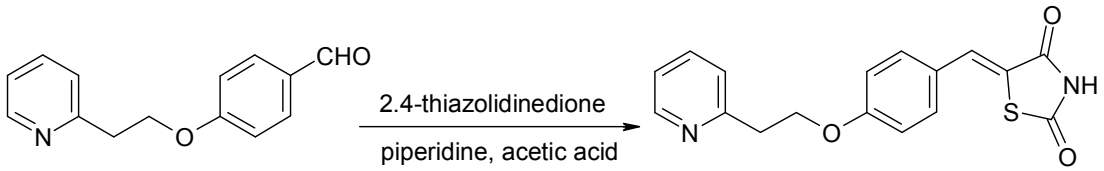
18a: 4-(2-(piridin-2-yl)ethoxy)benzaldehyde



18a

18a: yield 84%; ^{1}H NMR (300 MHz, DMSO-d_6) δ9.86 (s, 1H), 8.572 (d, J = 4.5 Hz, 1H), 7.834 (d, J = 8.4 Hz, 2H), 7.64 (d, J = 1.8 Hz, 1H), 7.199-7.288 (m, 1H), 7.183-7.196 (m, 1H), 7.015 (d, J = 8.4 Hz, 2H), 4.489 (t, J = 13.5 Hz, 2H), 3.32 (t, J = 13.5 Hz, 2H).

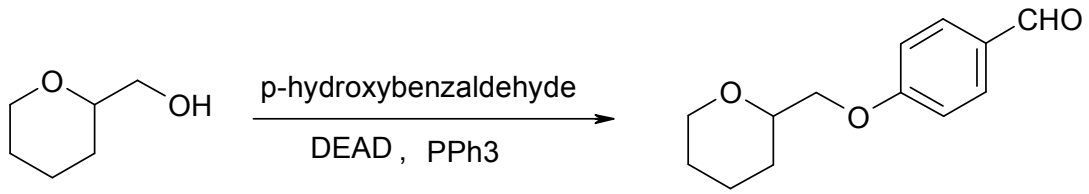
18b: 5-(4-(2-(Pyridin-2-yl)ethoxy)benzylidene)thiazolidine-2,4-dione



18a **18b**

18b: yield 84.6%; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.36 (s, 1H), 8.452 (d, J = 4.8 Hz, 1H), 7.783 (s, 1H), 7.719-7.277 (m, 1H), 7.488 (d, J = 8.4 Hz, 2H), 7.277 (d, J = 7.8 Hz, 1H), 7.190-7.232 (m, 1H), 6.924 (d, J = 8.4 Hz, 2H), 4.169 (t, J = 14.7 Hz, 2H), 3.048 (t, J = 14.7 Hz, 2H).

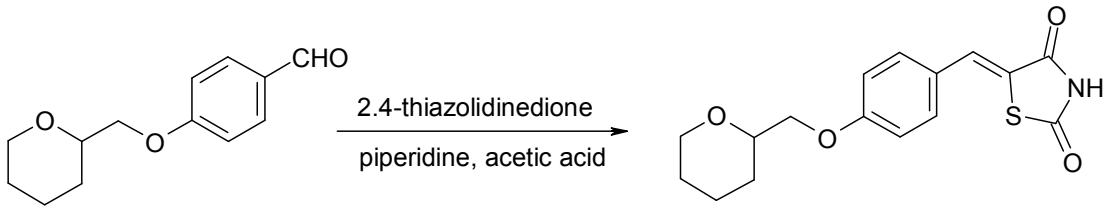
19a: 4-(tetrahydropyran-2-methoxy)benzaldehyde



19a

19a: yield 86;^{1}H NMR (300 MHz, $CDCl_3$) δ 9.881 (s, 1H), 7.839 (d, J =14.1 Hz, 2H), 7.044 (d, J = 14.1 Hz, 2H), 4.034-4.087 (m, 2H), 3.943-3.990 (m, 1H), 3.703-3.780 (m, 1H), 3.481-3.566 (m, 1H), 1.908-1.948 (m, 1H), 1.451-1.692 (m, 5H).

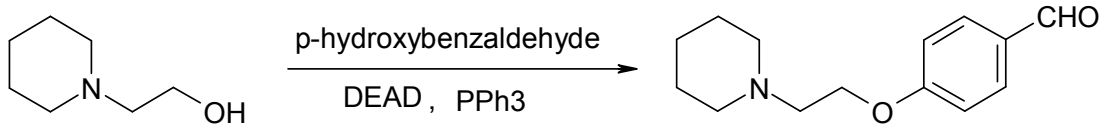
19b: 5-(4-(tetrahydropyran-2-methoxy)thiazolidine)-2,4-dione



19a **19b**

19b: yield 88%; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.290 (s, 1H), 7.726 (s, 1H), 7.545 (d, J = 9.0 Hz, 2H), 7.10(d, J = 9.0 Hz, 2H), 3.978 (d, J = 5.1 Hz, 2H), 3.850-3.892 (m, 2H), 3.595-3.638 (m, 1H), 1.974-2.119 (m, 4H), 1.601-1.858 (m, 2H), 1.279-1.470 (m, 2H).

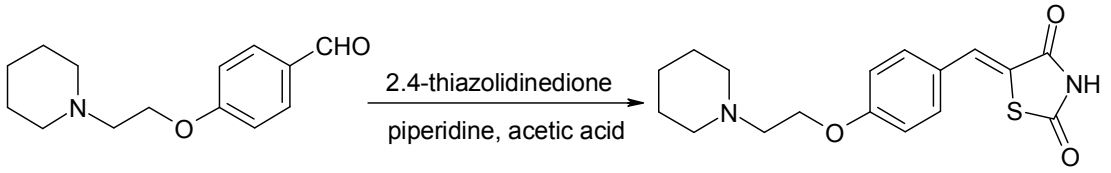
20a: 4-(2-(piperidin-1-yl)ethoxy)benzaldehyde



20a

20a: yield 85%; ^{1}H NMR (300 MHz, $CDCl_3$) δ9.88 (s, 1H), 7.839 (d, J = 8.7 Hz, 2H), 7.013 (d, J = 8.7 Hz, 2H), 4.223 (t, J = 11.7 Hz, 2H), 2.828(t, J = 11.7 Hz, 2H), 2.544 (t, J = 10.5 Hz, 4H), 1.583-1.657 (m, 4H), 1.418-1.494 (m, 2H).

20b: 5-[4-(2-(piperidin-1-yl)ethoxy)benzylidene]thiazolidine-2,4-dione

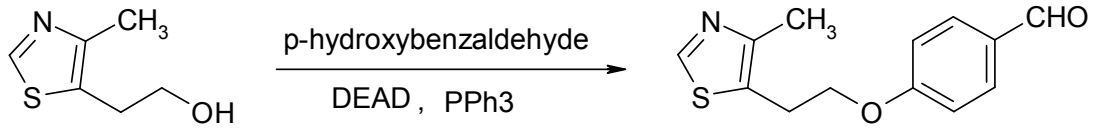


20a **20b**

20b: yield 87%; ^{1}H NMR (300 MHz, DMSO-d_6) δ7.522 (s, 1H), 7.411 (d, J = 10.2 Hz, 2H), 6.967 (d, J = 10.2 Hz, 2H), 4.096 (t, J = 11.1 Hz, 2H), 2.814 (t, J = 11.1 Hz, 2H), 2.379 (m, 4H),

1.410-1.513 (m, 4H), 1.291-1.307 (m, 2H).

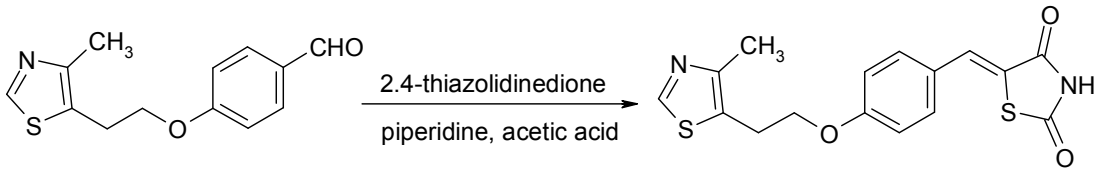
21a: 4-(2-(4-methylthiazol-5-yl)ethoxy)benzaldehyde



21a

21a: yield 85%;[1]H NMR (300 MHz, $CDCl_3$) δ9.89 (s, 1H), 8.612 (s, 1H), 7.854 (d, *J* = 10.2 Hz, 2H), 7.014 (d, *J* = 10.2 Hz, 2H), 4.247 (t, *J* = 11.7 Hz, 2H), 3.309 (t, *J* = 11.7 Hz, 2H), 2.463 (s, 3H).

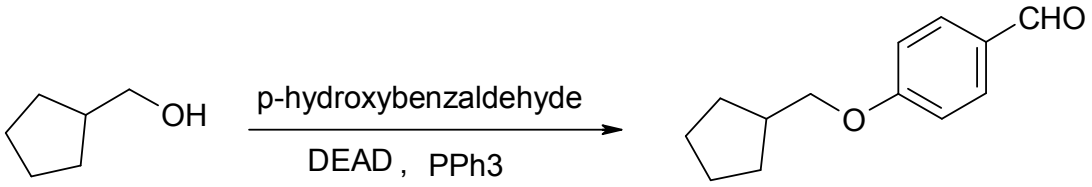
21b: 5-(4-(2-(4-methylthiazol-5-yl)ethoxy)benzylidene)thiazolidine-2,4-dione



21a **21b**

21b: yield 88%; [1]H NMR (300 MHz, DMSO-d_6) δ12.487 (s, 1H), 8.824 (s, 1H), 7.721 (s, 1H), 7.556 (d, *J* = 8.7 Hz, 2H), 7.102 (d, *J* = 8.7 Hz, 1H), 4.238 (t, *J* = 12.3 Hz, 2H), 3.250 (t, *J* = 12.3 Hz, 2H), 2.284 (s, 3H).

22a: 4-(cyclopentylmethoxy)benzaldehyde

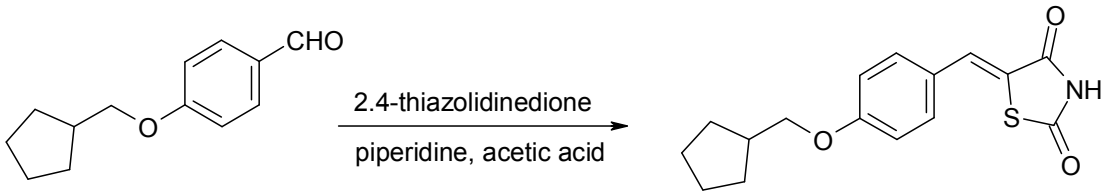


22a

22a: yield 86%;[1]H NMR (300 MHz, $CDCl_3$) δ9.878 (s, 1H), 7.848 (d, *J* = 11.4 Hz, 2H), 7.018

(d, *J* = 11.4 Hz, 2H), 3.928 (d, *J* = 7.2 Hz, 2H), 2.340-2.439 (m, 1H), 1.822-1.911 (m, 2H), 1.581-1.808 (m, 4H), 1.312-1.424 (m, 2H).

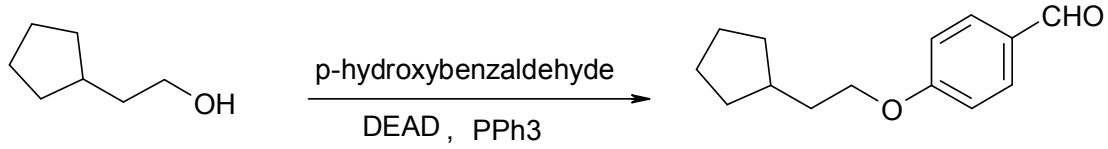
22b: 5-(4-(cyclopentylmethoxy)benzylidene)thiazolidine-2,4-dione



22a **22b**

22b: yield 86%; ^{1}H NMR (300 MHz, DMSO-d_6) δ12.503 (s, 1H), 7.732 (s, 1H), 7.547 (d, *J* = 9.0 Hz, 2H), 7.094 (d, *J* = 9.0 Hz, 2H), 3.922 (d, *J* = 7.2 Hz, 2H), 2.253-2.351 (m, 1H), 1.750-1.770 (m, 2H), 1.525-1.603 (m, 4H), 1.283-1.344 (m, 2H).

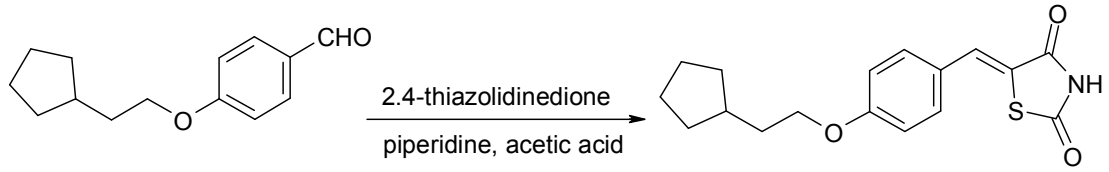
23a: 4-(2-cyclopentylethoxy)benzaldehyde



23a

23a: yield 89%; ^{1}H NMR (300 MHz, $CDCl_3$) δ9.878 (s, 1H), 7.850 (d, *J* = 11.4 Hz, 2H), 7.014 (d, *J* = 11.4 Hz, 2H), 4.085 (t, *J* = 13.5 Hz, 2H), 1.878-2.031 (m, 1H), 1.698-1.870 (m, 4H), 1.494-1.675 (m, 4H), 1.109-1.228 (m, 2H).

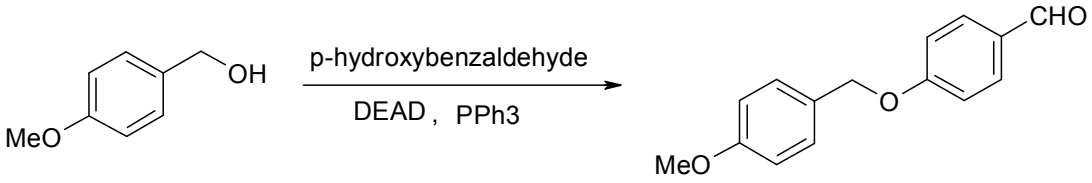
23b: 5-(4-(2-cyclopentylethoxy)benzylidene)thiazolidine-2,4-dione



23a **23b**

23b: yield 81%; ^{1}H NMR (300 MHz, DMSO-d_6) δ12.502 (s, 1H), 7.737 (s, 1H), 7.550 (d, J = 8.7 Hz, 2H), 7.093 (d, J = 8.7 Hz, 2H), 4.136 (t, J = 13.2 Hz, 2H), 1.807-1.976 (m, 1H), 1.700-1.769 (m, 4H), 1.455-1.611 (m, 4H), 1.102-1.185 (m, 2H).

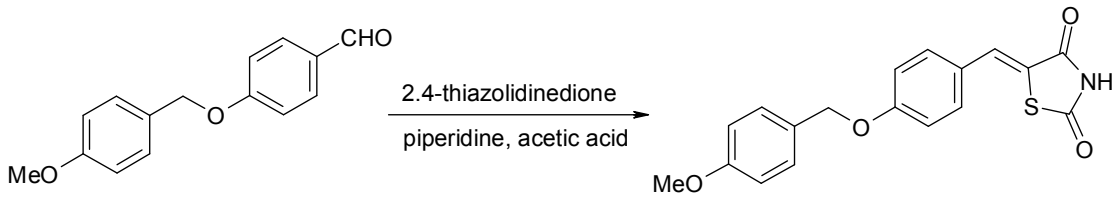
24a: 4-(4-methoxybenzyloxy)benzaldehyde



24a

24a: yield 86%;^{1}H NMR (300 MHz, $CDCl_3$) δ9.889 (s, 1H), 7.854 (d, J = 8.7 Hz, 2H), 7.378 (d, J = 8.4 Hz, 2H), 7.087 (d, J = 8.7 Hz, 2H), 7.095 (d, J = 8.4 Hz, 2H), 5.077 (s, 2H), 3.826 (s, 3H).

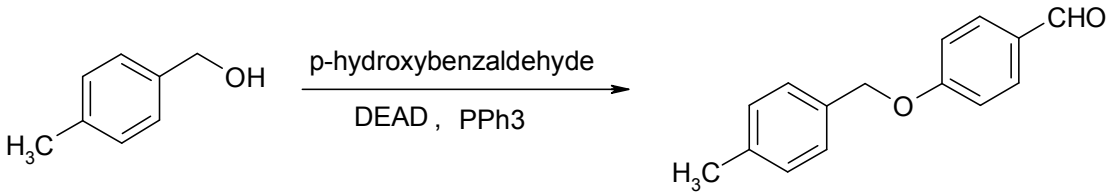
24b: 5-[4-(4-methoxybenzyloxy)benzylidene]thiazolidine-2,4-dione



24a **24b**

24b: yield 86%; ^{1}H NMR (300 MHz, DMSO-d_6) δ12.523 (s, 1H), 7.897 (s, 1H) 7.470 (d, J = 8.7 Hz, 2H), 7.249 (d, J = 8.7 Hz, 2H), 7.307 (d, J = 8.4 Hz, 2H), 7.165 (d, J = 8.4 Hz, 2H), 5.055 (s, 2H), 3,785 (s, 3H).

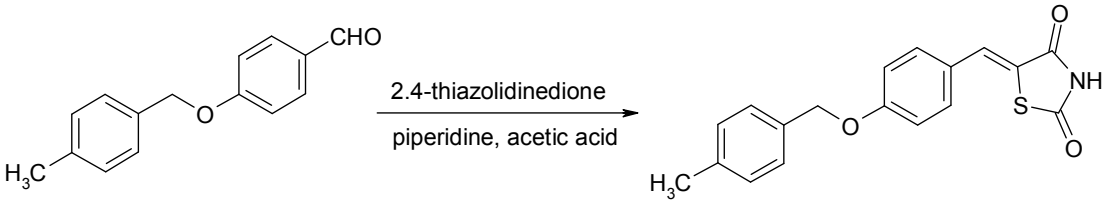
25a: 4-(4-methylbenzyloxy)benzaldehyde



25a

25a: yield 86%;[1]H NMR (300 MHz, $CDCl_3$) δ9.885 (s, 1H) 7.891 (d, *J* = 11.7 Hz, 2H), 7.335 (d, *J* = 7.5 Hz, 2H), 7.261 (d, *J* = 7.5 Hz, 2H) 7.095 (d, *J* = 11.7 Hz, 2H), 5.11 (s, 2H), 2.371 (s, 3H).

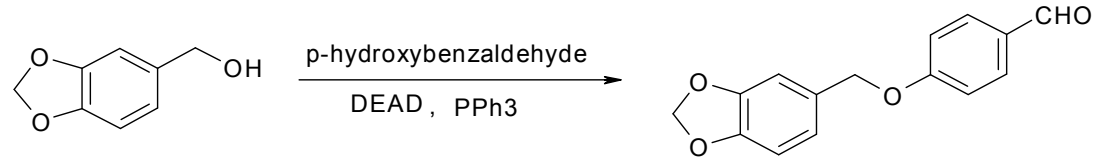
25b: 5-(4-(4-metylbenzyloxy)benzylidene)thiazolidine-2,4-dione



25a **25b**

25b: yield 80%; [1]H NMR (300 MHz, DMSO-d_6) δ12.514 (s, 1H), 7.800 (s, 1H), 7.560 (d, *J* = 8.7 Hz, 2H), 7.346 (d, *J* = 7.8 Hz, 2H), 7.206 (d, *J* = 7.8 Hz, 2H), 7.165 (d, *J* = 8.7 Hz, 2H), 5.125 (s, 2H), 2.295 (s, 3H).

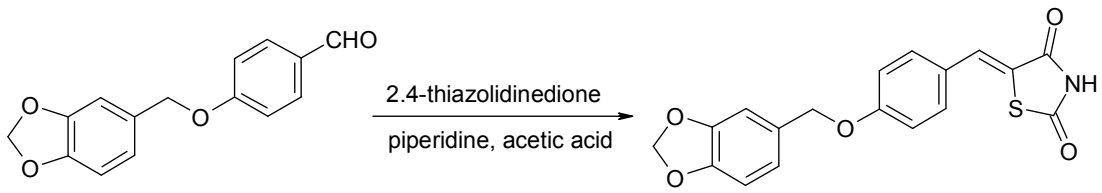
26a: 5-(4-benzo[d][1,3]dioxol-5-ylmethoxy)benzaldehyde



26a

26a: yield 86%;[1]H NMR (300 MHz, $CDCl_3$) δ9.887 (s, 1H), 7.861 (d, *J* = 13.2 Hz, 2H), 7.084 (d, *J* = 13.2 Hz, 2H), 6.923 (d, *J* = 1.8 Hz, 2H), 6.884 (d, *J* = 1.8 Hz, 1H), 6.771 (s, 1H), 5.98 (s, 2H), 5.042 (s, 2H).

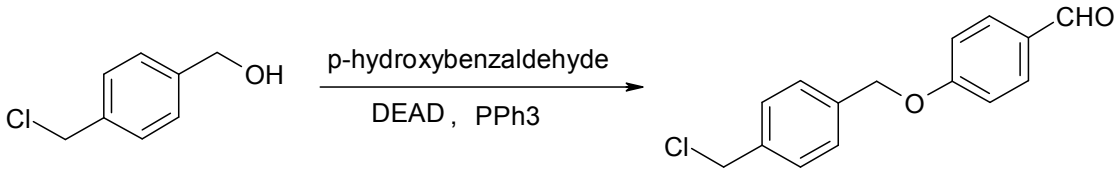
26b: 5-[4-(benzo[d][1,3]dioxol-5-ylmethoxy)benzylidene]thiazolidine-2,4-dione



26a **26b**

26b: yield 84%; ^{1}H NMR (300 MHz, DMSO-d_6) δ12.498 (s, 1H), 7.722 (s, 1H), 7.558 (d, J = 9.0 Hz, 2H), 7.157 (d, J = 9.0 Hz, 2H), 7.014 (s, 1H), 6.962 (d, J = 8.1 Hz, 2H), 6.919 (d, J = 8.1 Hz, 1H), 6.011 (s, 2H), 5.059 (s, 2H).

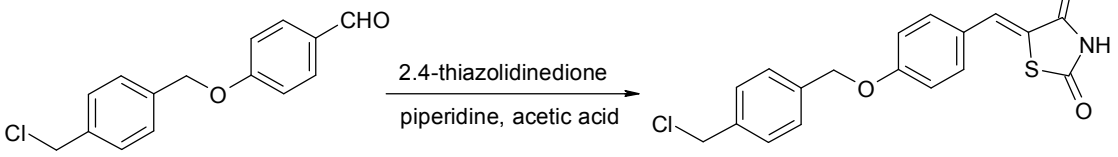
27a: 4-(4-(chloromethylbenzyloxy)benzaldehyde



27a

27a: yield 87%;^{1}H NMR (300 MHz, $CDCl_3$) δ9.932 (s, 1H), 7.87 (d, J = 14.4 Hz, 2H), 7.433 (d, J = 5.1 Hz, 4H), 7.096 (d, J = 14.4 Hz, 2H), 5.157 (s, 2H), 4.605 (s, 2H).

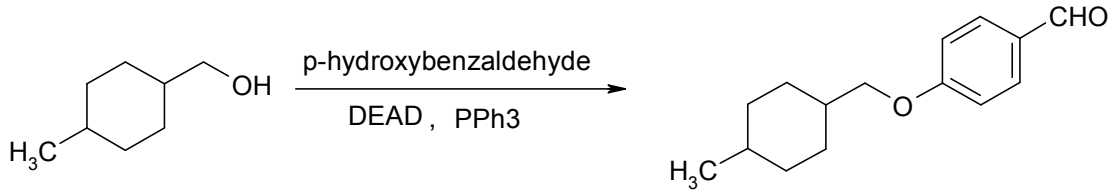
27b: 5-[4-(4-(chlorometyl)benzyloxy)benzylidene]thiazolidine-2,4-dione



27a **27b**

27b: yield 87%; ^{1}H NMR (300 MHz, DMSO-d_6) δ12.549 (s, 1H), 7.748 (s, 1H), 7.58 (d, J = 12.3 Hz, 2H), 7.454 (m, 4H), 7.190 (d, J = 12.3 Hz, 2H), 5.219 (s, 2H), 4.760 (s, 2H).

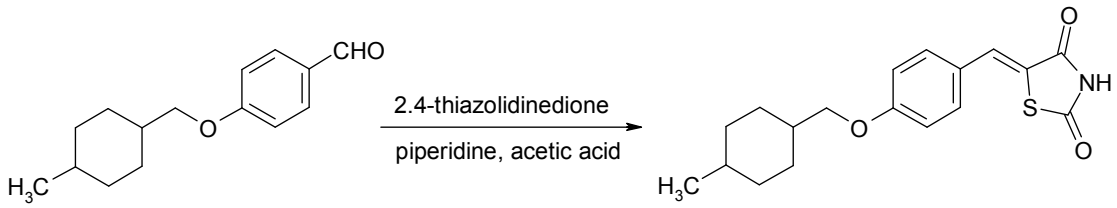
28a: 4-(4-methylcyclohexylmethoxy)benzaldehyde



28a

28a: yield 89%; ^{1}H NMR (300 MHz, $CDCl_3$) δ9.371 (s, 1H), 7.378 (d, *J* = 8.7 Hz, 2H), 6.66 (d, *J* = 8.7 Hz, 2H), 3.531 (d, *J* = 7.2 Hz, 1H), 3.419 (d, *J* = 6.6 Hz, 1H), 1.19-1.499 (m, 3H), 0.943-1.047 (m, 4H), 0.64-0.821 (m, 2H), 0.375-0.596 (m, 4H).

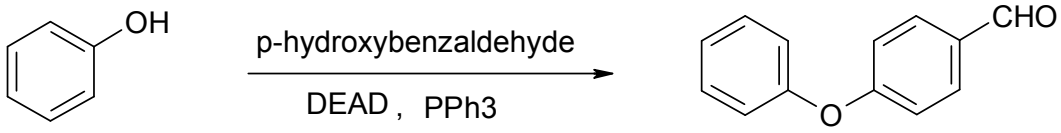
28b: 5-[4-((4-metylcyclohexyl)methoxy)benzylidene]thiazolidine-2,4-dione



28a **28b**

28b: yield 86%; ^{1}H NMR (300 MHz, DMSO-d_6) δ12.493 (s, 1H), 7.693 (s, 1H), 7.536 (d, *J* = 9.0 Hz, 2H), 7.101 (d, *J* = 9.0 Hz, 2H), 3.963 (d, *J* = 6.9 Hz, 1H), 3.851 (d, *J* = 6.6 Hz, 1H), 1.662-1.976 (m, 4H), 1.185-1.516 (m, 4H), 0.975-1.161 (m, 2H), 0.852-0.935 (m, 3H).

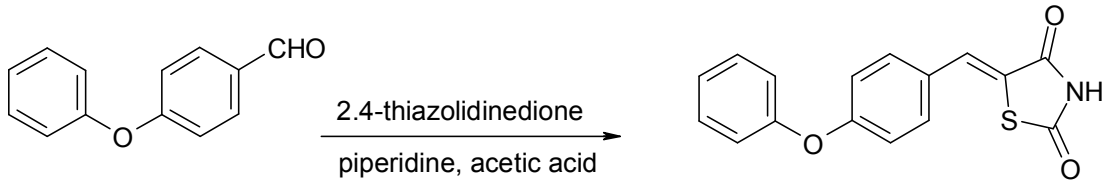
29a: 4-(phenoxy)benzaldehyde



29a

29a: yield 78%;^{1}H NMR (300 MHz, $CDCl_3$) δ10.065 (s, 1H), 7.432-7.569(m, 5H), 7.214 (d, *J* = 8.4 Hz, 2H), 6.763(d, *J* = 8.4 Hz, 2H).

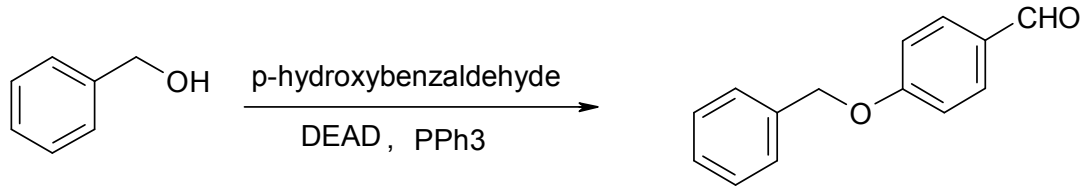
29b: 5-(4-phenoxybenzylidene)-1, 3-thiazolidine-2, 4-dione



29a **29b**

29b: yield 72.0%; ^{1}H NMR (300 MHz, DMSO-d_6) δ8.302 (s, 1H), 7.536-7.639(m, 5H), 7.349 (d, J = 8.4 Hz, 2H), 6.903(d, J = 8.4 Hz, 2H).

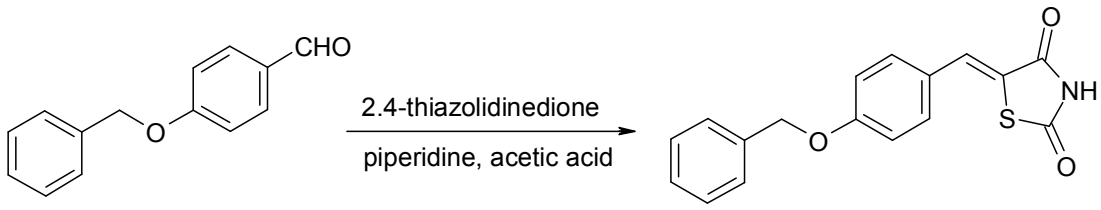
30a: 4-(benzyloxy)benzaldehyde



30a

30a: yield 79%; ^{1}H NMR (300 MHz, $CDCl_3$) δ10.088 (s, 1H), 7.395 (d, J = 8.7 Hz, 2H), 7.190-7.268 (m, 5H), 6.945 (d, J = 8.7 Hz, 2H), 5.008 (s, 2H).

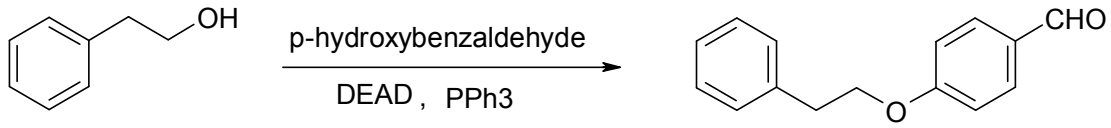
30b: 5-(4-(benzyloxy)benzylidene)thiazolidine-2,4-dione



30a **30b**

30b: yield 83%; ^{1}H NMR (300 MHz, DMSO-d_6) δ12.498 (s, 1H), 7.736 (s, 1H) 7.566 (d, J = 8.7 Hz, 2H), 7.306-7.468 (m, 5H), 7.18 (d, J = 8.7 Hz, 2H), 5.176 (s, 2H).

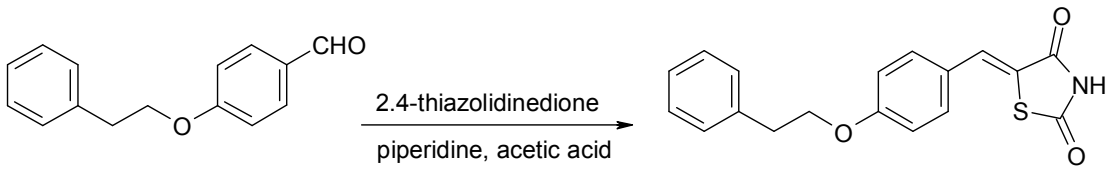
31a: 4-(2-phenylethoxy)benzaldehyde



31a

31a: yield 78%; ^{1}H NMR (300 MHz, $CDCl_3$) δ10.006 (s, 1H), 7.325 (d, *J* = 8.7 Hz, 2H), 7.123-7.241 (m, 5H), 6.954 (d, *J* = 8.7Hz, 2H), 4.045 (t, *J* = 14.1 Hz, 2H), 3.009 (t, *J* = 14.1 Hz, 2H).

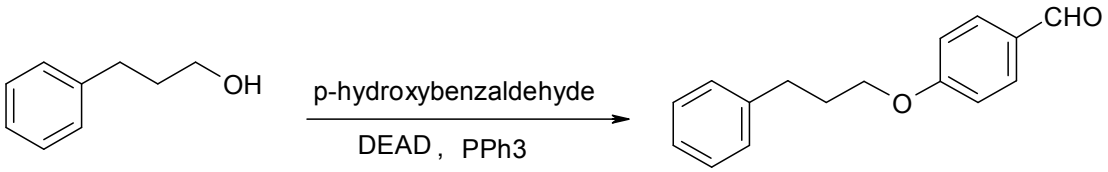
31b: 5-[4-(2-phenylethoxy)benzylidene]-1,3-thiazolidine-2,4-dione



31a **31b**

31b: yield 62.7%; ^{1}H NMR (300 MHz, $CDCl_3$) δ7.806 (s, 1H), 7.466 (d, *J* = 8.7 Hz, 2H), 7.262-7.369 (m, 5H), 7.196 (d, *J* = 8.7Hz, 2H), 4.261 (t, *J* = 14.1 Hz, 2H), 3.153 (t, *J* = 14.1 Hz, 2H).

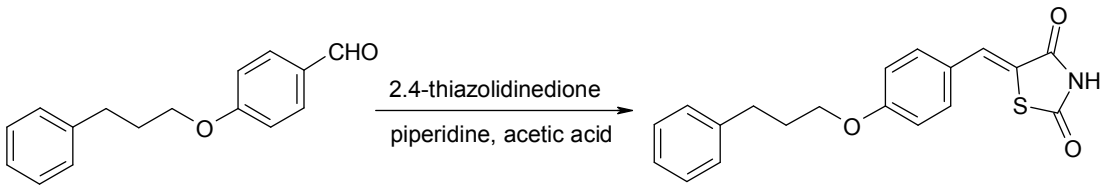
32a: 4-(2-phenylpropoxy)benzaldehyde



32a

32a: yield 82%; ^{1}H NMR (300 MHz, $CDCl_3$) δ10.02 (s, 1H), 7.327 (d, *J* = 8.7 Hz, 2H), 7.008-7.215 (m, 5H), 6.894 (d, *J* = 8.7 Hz, 2H), 3.998 (t, *J* = 12.3 Hz, 2H), 2.687 (t, *J* = 15.0 Hz, 2H), 1.995-2.067 (m, 2H).

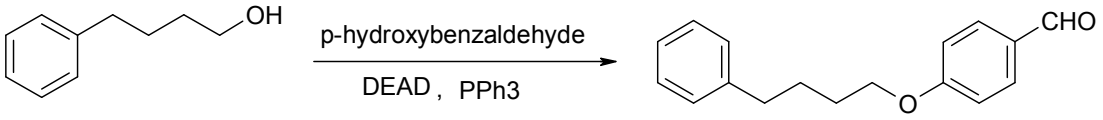
32b: 5-[4-(2-phenylpropoxy)benzylidene]-1,3-thiazolidine-2,4-dione



32a **32b**

32b: yield 80.1%; ^{1}H NMR (300 MHz, $CDCl_3$) δ7.820 (s, 1H), 7.465 (d, *J* = 8.7 Hz, 2H), 7.201-7.329 (m, 5H), 6.993 (d, *J* = 8.7 Hz, 2H), 4.020 (t, *J* = 12.3 Hz, 2H), 2.851 (t, *J* = 15.0 Hz, 2H), 2.094-2.187 (m, 2H).

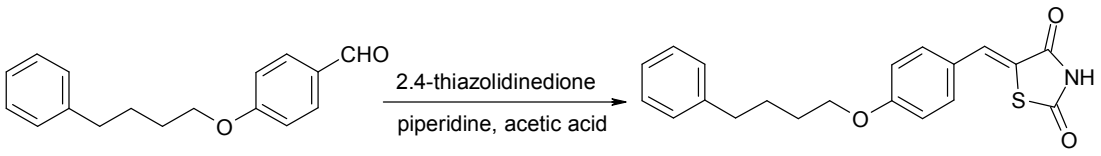
33a: 4-(2-phenylbutoxy)benzaldehyde



33a

33a: yield 84%; ^{1}H NMR (300 MHz, DMSO-d_6) δ10.012 (s, 1H), 7.239 (d, *J* = 8.7 Hz, 2H), 7.062-7.187 (m, 5H), 6.887 (d, *J* = 8.7 Hz, 2H), 3.910 (t, *J* = 11.7 Hz, 2H), 2.647 (t, *J* = 13.8 Hz, 2H), 1.589-1.721 (m, 4H).

33b: 5-[4-(2-phenylbutoxy)benzylidene]-1,3-thiazolidine-2,4-dione

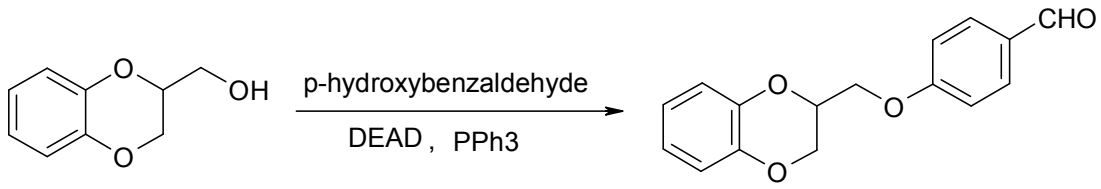


33a **33b**

33b: yield 85.0%; ^{1}H NMR (300 MHz, $CDCl_3$) δ7.816 (s, 1H), 7.468 (d, *J* = 8.7 Hz, 2H), 7.174-7.323(m, 5H), 6.903 (d, *J* = 8.7 Hz, 2H), 4.048 (t, *J* = 11.7 Hz, 2H), 2.724 (t, *J* = 13.8 Hz, 2H),

1.786-1.876 (m, 4H).

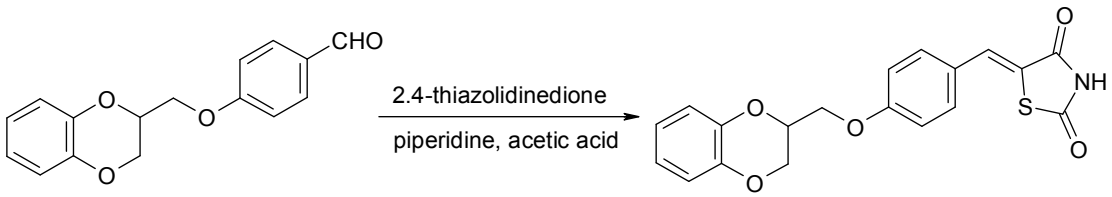
34a: 4-((2,3-Dihydrobenzo[b][1,4]dioxin-2-yl)methoxy)benzaldehyde



34a

34a: yield 83%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.904 (s, 1H), 7.880 (d, J = 8.4 Hz, 2H), 7.15 (d, J = 8.4 Hz, 2H), 6.843-6.941 (m, 4H), 4.556-4.643 (m, 1H), 4.386-4.433 (m, 1H), 4.311-4.361 (m, 1H), 4.061-4.279 (m, 2H).

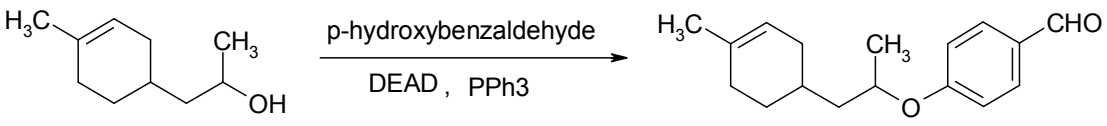
34b: 5-(4-((2,3-Dihydrobenzo[b][1,4]dioxin-2-yl)methoxy)benzylidene)thiazolidine-2,4-dione



34a **34b**

34b: yield 82.4%;^{1}H NMR (300 MHz, DMSO-d_6) δ 12.513 (s, 1H), 7.733 (s, 1H), 7.576 (d, J = 8.7 Hz, 2H), 7.167 (d, J = 8.7 Hz, 2H), 6.817-6.922 (m, 4H), 4.458-4.578 (m, 1H), 4.409-4.455 (m, 1H), 4.263-4.409 (m, 2H), 4.111-4.173 (m, 1H).

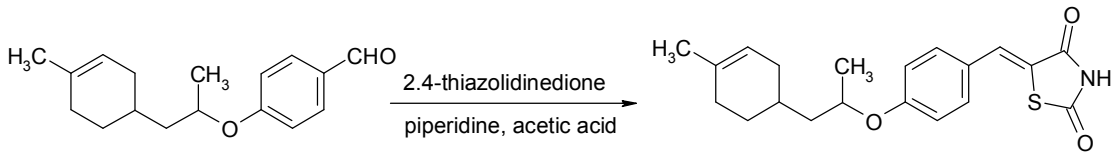
35a: 4-[2-(4-methylcyclohex-3-en-1-yl)propoxy]benzaldehyde



35a

35a: yield 81.4%; ^{1}H NMR (300 MHz, DMSO-d_6) δ12.496 (s, 1H), 7.726 (s, 1H), 7.547 (d, J = 9.0 Hz, 2H), 7.106 (d, J = 9.0 Hz, 2H), 5.344 (s, 1H), 3.991-4.042 (m, 1H), 3.844-3.898 (m, 1H), 1.085-2.069 (m, 7H), 1.711 (s, 3H), 1.347-1.637 (m, 2H), 1.257 (t, J = 13.8 Hz, 3H), 0.860-0.882 (m, 1H).

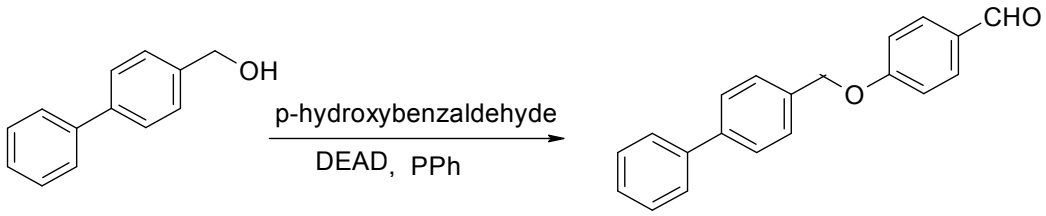
35b: 5-{4-[2-(4-methylcyclohex-3-en-1-yl)propoxy]benzylidene}-1,3-thiazolidine-2,4-dione



35a **35b**

35b: yield 89.8%; ^{1}H NMR (300 MHz, DMSO-d_6) δ12.496 (s, 1H), 7.726 (s, 1H), 7.547 (d, J = 9.0 Hz, 2H), 7.106 (d, J = 9.0 Hz, 2H), 5.344 (s, 1H), 3.991-4.042 (m, 1H), 3.844-3.898 (m, 1H), 1.085-2.069 (m, 7H), 1.711 (s, 3H), 1.347-1.637 (m, 2H), 1.257 (t, J = 13.8 Hz, 3H), 0.860-0.882 (m, 1H).

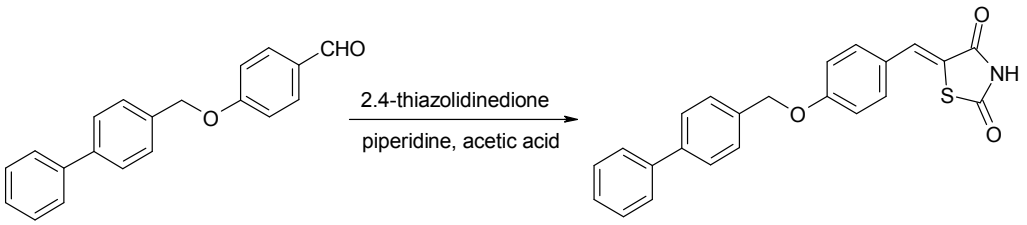
36a: 4-(biphenyl-4-ylmethoxy)benzaldehyde



36a

36a: yield 83%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.897 (s, 1H), 7.881 (d, J = 13.8 Hz, 2H), 7.584-7.788 (m, 4H), 7.428-7.555 (m, 4H), 7.334-7.391 (m, 1H), 7.130 (d, J = 13.8 Hz, 2H), 5.194 (s, 2H).

36b: 5-(4-(Biphenyl-4-ylmethoxy)benzylidene)thiazolidine-2,4-dione

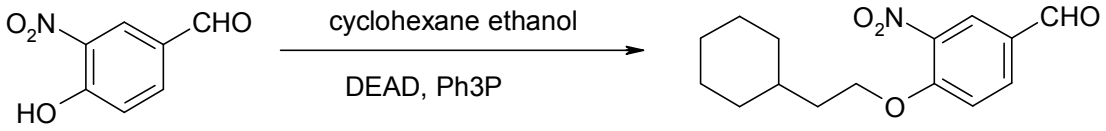


36a **36b**

36b: yield 83.6%; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.513 (s, 1H), 7.735 (s, 1H), 7.703 (t, J = 15.9 Hz, 4H), 7.580 (t, J = 15.9 Hz, 4H), 7.486 (t, J = 14.7 Hz, 2H), 7.384 (m, 1H), 7.206 (d, J = 8.7 Hz, 2H), 5.235 (s, 2H).

Synthesis of compounds 37 - 50

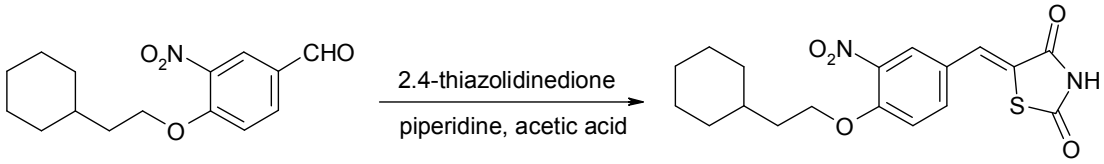
37a: 4-(2-cyclohexylethoxy)-3-nitrobenzaldehyde



37a

37a: yield 84%;^{1}H NMR (300 MHz, $CDCl_3$) δ9.931 (s, 1H), 8.345 (s, 1H), 8.081 (d, J = 10.2 Hz, 1H), 7.267 (d, J = 10.2 Hz, 1H), 4.190 (t, J = 12.9 Hz, 2H), 1.839-1.934 (m, 2H), 1.644-1.754 (m, 4H), 1.335-1.408 (m, 2H), 1.086-1.262 (m, 3H), 0.864-0.970 (m, 2H).

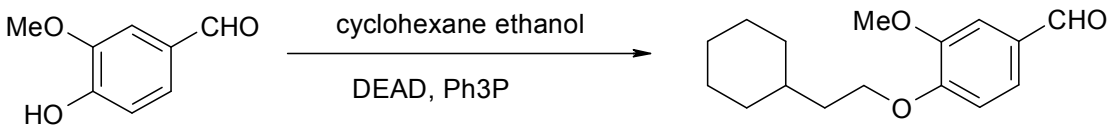
37b: 5-(4-(2-cyclohexylethoxy)-3-nitrobenzylidene)thiazolidine-2,4-dione



37a **37b**

37b: yield 89%; ^{1}H NMR (300 MHz, DMSO-d_6) δ12.649 (s, 1H), 8.165 (s, 1H), 7.931 (s, 1H), 7.800 (d, J = 9.0 Hz, 1H), 7.539 (d, J = 9.0 Hz, 1H), 4.276 (t, J = 13.2 Hz, 2H), 1.662-1.976 (m, 4H), 1.594-1.725 (m, 6H), 1.444-1.457 (m, 1H), 1.090-1.212 (m, 4H), 0.874-0.981 (s, 2H).

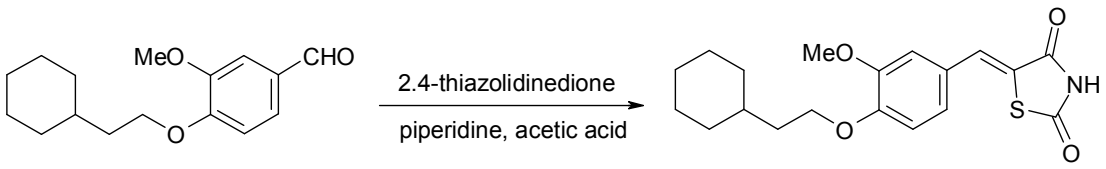
38a: 4-(2-cyclohexylethoxy-3-methoxy)benzaldehyde



38a

38a: yield 82%; ^{1}H NMR (300 MHz, $CDCl_3$) δ9.774 (s, 1H), 7.383 (s, 1H), 7.365 (d, *J* = 11.7 Hz, 1H), 6.912 (d, *J* = 11.7 Hz, 1H), 4.096(t, *J* = 9.9 Hz, 2H), 3.892 (s, 3H), 1.617-1.755 (m, 6H), 1.388-1.46 (m, 1H), 1.146-1.258 (m, 4H), 0.87-0.978 (m, 2H) .

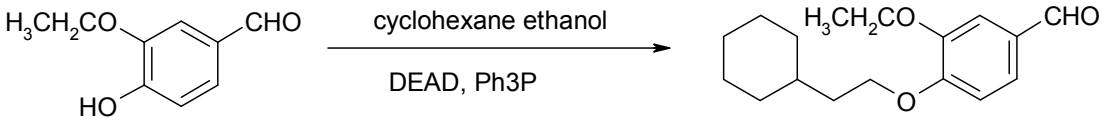
38b: 5-(4-(2-cyclohexylethoxy)-3-methoxybenzylidene)thiazolidine-2,4-dione



38a **38b**

38b: yield 89%; ^{1}H NMR (300 MHz, DMSO-d_6) δ8.221 (s, 1H), 7.728 (s, 1H), 7.028 (d, *J* = 10.2 Hz, 2H), 6.924(d, *J* = 10.2 Hz, 2H), 6.895 (s, 1H), 4.074 (t, *J* = 14.4 Hz, 2H), 3.846 (s, 3H), 1.716 (t, *J* = 14.4 Hz, 2H), 1.434-1.515 (m, 4H), 1.078-1.214 (m, 4H), 0.782-0.976 (m, 3H).

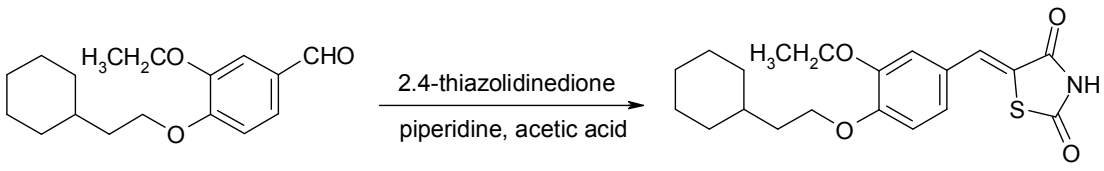
39a: 4-(2-cyclohexylethoxy-3-ethoxy)benzaldehyde



39a

39a: yield 78%; ^{1}H NMR (300 MHz, $CDCl_3$) δ9.832 (s, 1H), 7.434-7.440 (m, 1H), 7.413 (d, *J* = 8.4 Hz, 1H), 7.976 (d, *J* = 8.4 Hz, 1H), 4.109-4.178 (m, 4H), 1.634-1.811 (m, 7H), 1.400-1.583 (m, 4H), 1.148-1.327 (m, 3H), 0.904-1.140 (m, 2H).

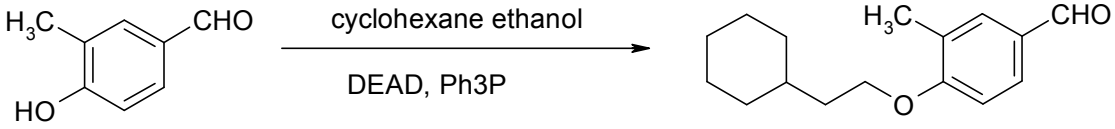
39b: 5-(4-(2-cyclohexylethoxy)-3-ethoxybenzylidene)thiazolidine-2,4-dione



39a **39b**

39b: yield 83.0%; ^{1}H NMR (300 MHz, $CDCl_3$) δ12.582 (s, 1H), 7.786 (s, 1H), 7.116 (d, *J* = 10.8 Hz, 1H), 6.959 (d, *J* = 10.8 Hz, 1H), 7.000 (s, 1H), 4.089 (m, 4H), 1.653-1.795 (m, 7H), 1.459-1.577 (m, 4H), 1.146-1.282 (m, 3H), 0.941-1.05 (m, 2H).

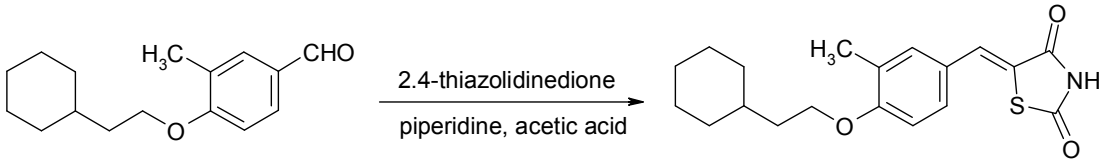
40a: 4-(2-cyclohexyleyhoxy)-3-methylbenzaldehyde



40a

40a: yield 76.0%; ^{1}H NMR (300 MHz, $CDCl_3$) δ9.845 (s, 1H), 7.707 (d, *J* = 8.7 Hz, 2H), 7.678 (s, 1H), 6.89 (d, *J* = 8.7 Hz, 2H), 4.111 (t, *J* = 13.2 Hz, 2H), 2.259 (s, 3H), 1.749 (t, *J* = 13.2 Hz, 2H), 1.493-1.585 (m, 5H), 1.217-1.325 (m, 5H), 1.009-1.048 (m, 1H).

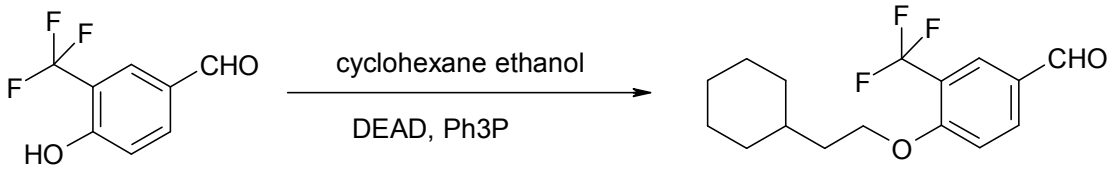
40b: 5-(4-(2-cyclohexylethoxy)-3-methylbenzylidene)thiazolidine-2,4-dione



40a **40b**

40b: yield 75.7%; ^{1}H NMR (300 MHz, $CDCl_3$) δ8.20 (s, 1H), 7.783 (s, 1H), 7.087 (d, *J* = 8.7 Hz, 2H), 7.058 (s, 1H), 6.788 (d, *J* = 8.7 Hz, 2H), 4.023 (t, *J* = 14.7 Hz, 2H), 2.196 (s, 3H), 1.739 (t, *J* = 14.7 Hz, 2H), 1.577 (m, 1H), 1.213-1.284 (m, 2H), 0.965-1.044 (m, 4H), 0.826-0.880 (m, 4H).

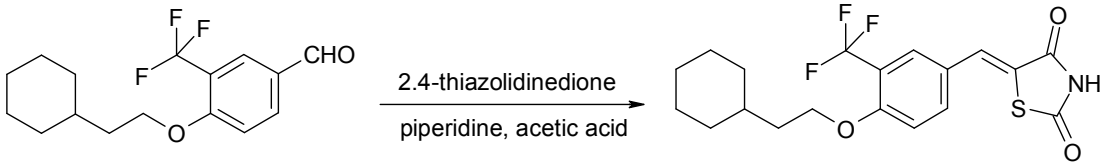
41a: 4-(2-cyclohexylethoxy)-3-(trifluoromethyl)benzaldehyde



41a

41a: yield 64.0%; ^{1}H NMR (300 MHz, $CDCl_3$) δ9.915 (s, 1H), 8.102 (s, 1H), 8.044 (d, *J* = 10.5 Hz, 1H), 7.125 (d, *J* = 8.7 Hz, 1H), 4.208 (t, *J* = 12.6 Hz, 2H), 1.639-1.788 (m, 6H), 1.466-1.567 (m, 1H), 1.177-1.338 (m, 4H), 0.882-1.041 (m, 2H).

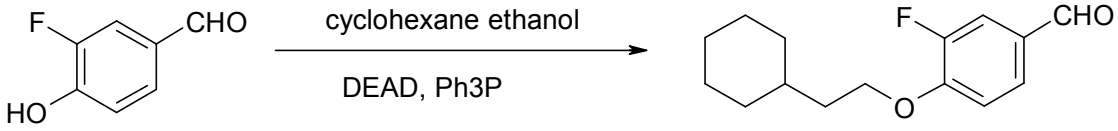
41b: 5-(4-(2-cyclohexylethoxy)-3-(trifluromethyl)benzylidene)thiazolidine-2,4-dione



41a **41b**

41b: yield 79.7%; ^{1}H NMR (300 MHz, DMSO-d_6) δ8.270 (s, 1H), 7.812(s, 1H), 7.461 (d, *J* = 8.7 Hz, 2H), 7.262 (s, 1H), 6.934 (d, *J* = 8.7 Hz, 2H), 4.080 (t, *J* = 13.5 Hz, 2H), 1.576-1.738 (m, 7H), 1.284-1.506 (m, 1H), 1.035-1.245 (m, 3H), 0.926-0.995 (m, 2H).

42a: 4-(2-cyclohexylethoxy)-3-fluorobenzaldehyde

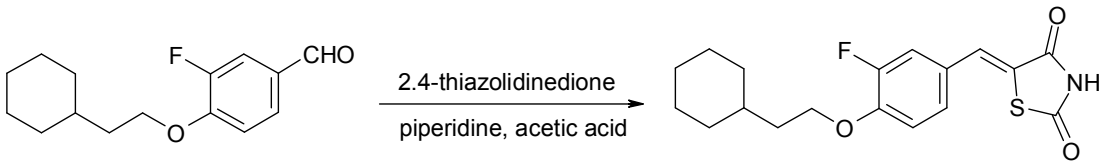


42a

42a: yield 84.0%; ^{1}H NMR (300 MHz, $CDCl_3$) δ9.857 (s, 1H), 7.633 (d, *J* = 16.5 Hz, 2H), 7.087 (d, *J* = 16.5 Hz, 1H), 4.178 (t, *J* = 13.5 Hz, 2H), 1.697-1.798 (m, 6H), 1.217-1.290 (m, 5H), 0.969-

1.007 (m, 2H).

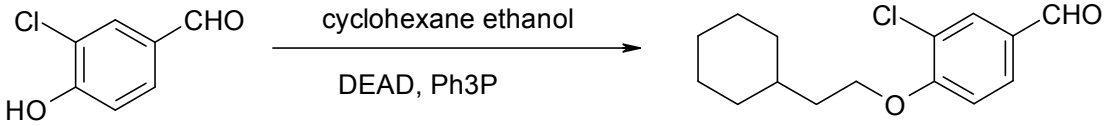
42b: 5-(3-chloro-4-(2-cyclohexylethoxy)benzylidene)thiazolidine-2,4-dione



42a **42b**

42b: yield 82%; ^{1}H NMR (300 MHz, DMSO-d6) δ8.19 (s, 1H), 7.738 (s, 1H), 7.522 (s, 1H), 7.386 (d, *J* = 10.5 Hz, 1H), 7.012 (d, *J* = 10.5 Hz, 1H)), 4.155 (t, *J* = 13.2 Hz, 2H), 1.800 (t, *J* = 13.2 Hz, 2H), 1.657-1.800 (m, 4H), 1.500-1.606 (m, 1H), 1.151-1.335 (m, 4H), 0.854-1.052 (m, 2H).

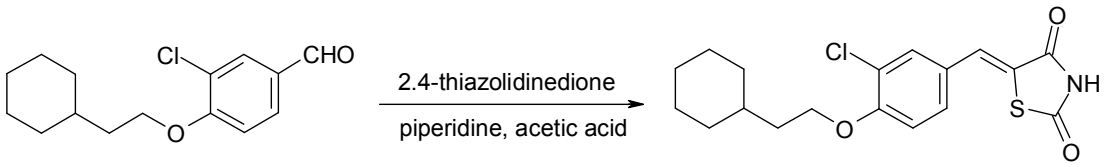
43a: 3-chloro-4-(2-cyclohexylethoxy)benzaldehyde



43a

43a: yield 81.2%; ^{1}H NMR (300 MHz, $CDCl_3$) δ9.859 (s, 1H), 7.906 (s, 1H), 7.759 (d, *J* = 8.4 Hz, 2H), 7.034 (d, *J* = 8.4 Hz, 2H), 4.158(t, *J* = 13.5 Hz, 2H), 1.815(t, *J* = 13.5 Hz, 2H), 1.698-1.892 (m, 2H), 1.483-1.659 (m, 1H), 1.184-1.350 (m, 4H), 0.896-1.152 (m, 4H).

43b: 5-(3-chloro-4-(2-cyclohexylethoxy)benzylidene)thiazolidine-2,4-dione

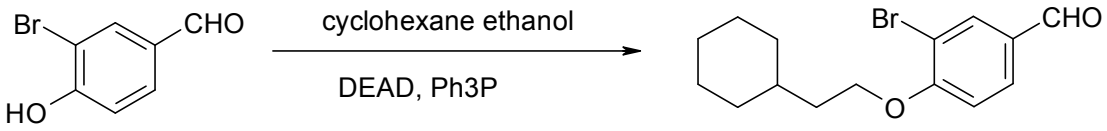


43a **43b**

43b: yield 88.3%; ^{1}H NMR (300 MHz, $CDCl_3$) δ8.19 (s, 1H), 7.738 (s, 1H), 7.522 (s, 1H), 7.386

(d, *J* = 10.5 Hz, 1H), 7.012 (d, *J* = 10.5 Hz, 1H)), 4.155 (t, *J* = 13.2 Hz, 2H), 1.800 (t, *J* = 13.2 Hz, 2H), 1.657-1.800 (m, 4H), 1.500-1.606 (m, 1H), 1.151-1.335 (m, 4H), 0.854-1.052 (m, 2H).

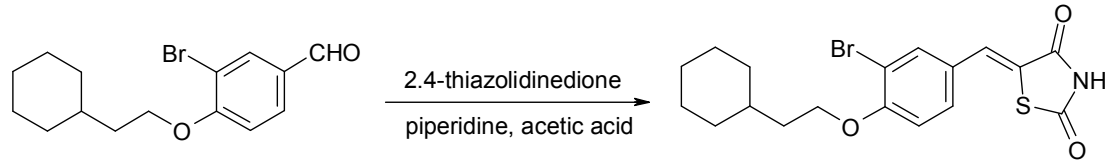
44a: 3-bromo-4-(2-cyclohexylethoxy)benzaldehyde



44a

44a: yield 87.6%; ^{1}H NMR (300 MHz, $CDCl_3$) δ9.831 (s, 1H), 8.077 (s, 1H), 7.808 (d, *J* = 8.4 Hz, 1H), 6.995 (d, *J* = 8.4 Hz, 1H), 4.223 (t, *J* = 14.4 Hz, 2H), 1.650-1.811 (m, 7H), 1.468-1.627 (m, 1H), 1.142-1.296 (m, 3H), 0.947-1.111 (m, 2H).

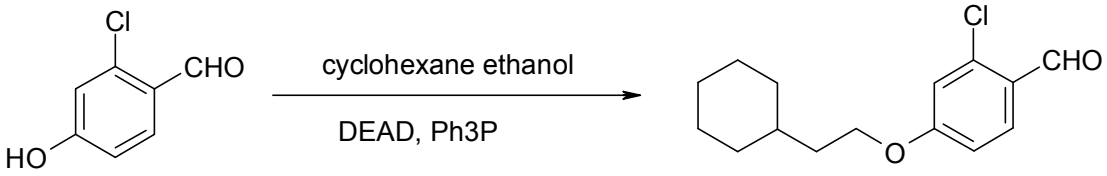
44b: 5-(3-bromo-4-(2-cyclohexylethoxy)benzylidene)thiazolidine-2,4-dione



44a **44b**

44b: yield 82.4%; ^{1}H NMR (300 MHz, DMSO-d_6) δ12.576 (s, 1H), 7.841 (s, 1H), 7.833 (s, 1H), 7.570 (d, *J* = 10.8 Hz, 1H), 7.284 (d, *J* = 10.8 Hz, 1H)), 4.174 (t, *J* = 12.6 Hz, 2H), 1.617-1.750 (m, 7H), 1.460-1.529 (m, 1H), 1.062-1.265 (m, 3H), 0.896-0.966 (m, 2H).

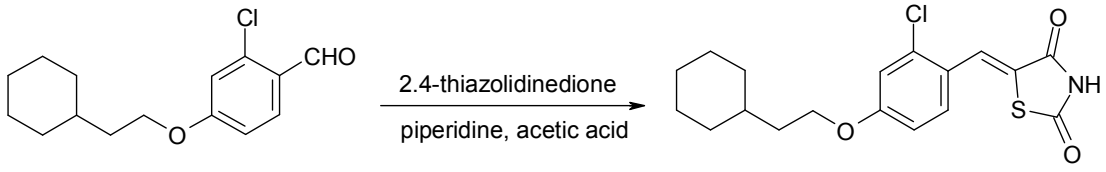
45a: 2-chloro-4-(2-cyclohexylethoxy)benzaldehyde



45a

45a: yield 78.8%; ^{1}H NMR (300 MHz, $CDCl_3$) δ9.447 (s, 1H), 7.867 (d, *J* = 8.4 Hz, 1H), 7.369 (s, 1H), 7.043 (d, *J* = 8.4 Hz, 1H), 4.195 (t, *J* = 13.2 Hz, 2H), 1.221-1.475 (m, 6H), 1.183-1.434 (m, 1H), 1.095-1.161 (m, 4H), 0.847-0.945 (m, 2H).

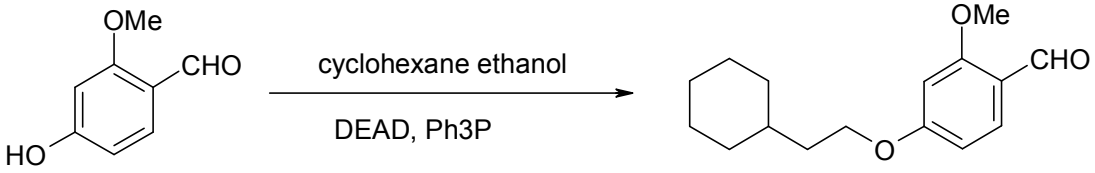
45b: 5-(2-chloro-4-(2-cyclohexylethoxy)benzylidene)thiazolidine-2,4-dione



45a **45b**

45b: yield 80.3%; ^{1}H NMR (300 MHz, DMSO-d_6) δ12.654 (s, 1H), 7.877 (s, 1H), 7.517 (d, *J* = 9.0 Hz, 1H), 7.110 (s, 1H), 7.012 (d, *J* = 9.0 Hz, 1H)), 4.111 (t, *J* = 13.2 Hz, 2H), 1.434-1.642 (m, 6H), 1.263-1.434 (m, 1H), 1.094-1.221 (m, 4H), 0.847-0.989 (m, 2H).

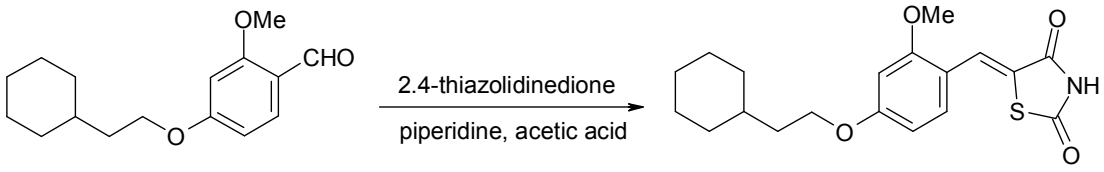
46a: 4-(2-cyclohexylethoxy-2-methoxy)benzaldehyde



46a

46a: yield 81.9%; ^{1}H NMR (300 MHz, $CDCl_3$) δ10.280 (s, 1H), 7.809 (d, *J* = 9.0 Hz, 1H), 6.552 (d, *J* = 9.0 Hz, 1H), 6.434 (s, 1H), 4.085 (t, *J* = 13.5 Hz, 2H), 3.901 (s, 3H), 1.552-1.783 (m, 7H), 1.341-1.538 (m, 1H), 1.107-1.297 (m, 3H), 0.912-1.042 (m, 2H).

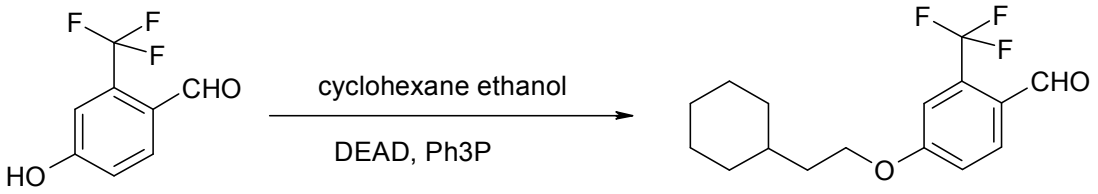
46b: 5-(4-(2-cyclohexylethoxy)-2-methoxybenzylidene)thiazolidine-2,4-dione



46a **46b**

46b: yield 83.9%; ^{1}H NMR (300 MHz, DMSO-d_6) δ12.446 (s, 1H), 7.915 (s, 1H), 7.907 (d, J = 8.4 Hz, 1H), 6.709 (d, J = 8.4 Hz, 1H), 6.667 (s, 1H), 4.102 (t, J = 5.1 Hz, 2H), 3.878 (s, 3H), 1.587-1.750 (m, 7H), 1.451-1.586 (m, 1H), 1.104-1.271 (m, 3H), 0.884-0.994 (m, 2H).

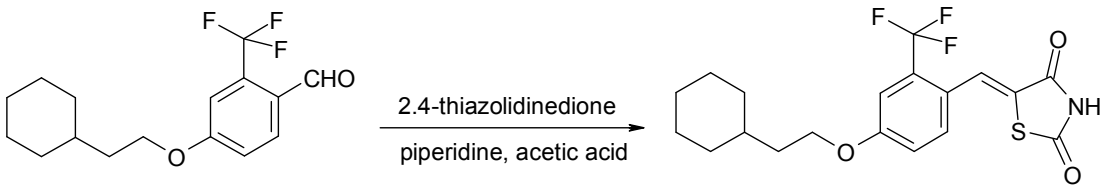
47a: 4-(2-cyclohexylethoxy)-2-(trifluoromethyl)benzaldehyde



47a

47a: yield 75.2%; ^{1}H NMR (300 MHz, $CDCl_3$) δ9.477 (s, 1H), 7.164 (d, J = 10.5 Hz, 1H), 7.111 (s, 1H), 7.083 (d, J = 10.5 Hz, 1H), 4.1868 (t, J = 12.6 Hz, 2H), 1.639-1.788 (m, 7H), 1.466-1.567 (m, 1H), 1.177-1.338 (m, 3H), 0.882-1.041 (m, 2H).

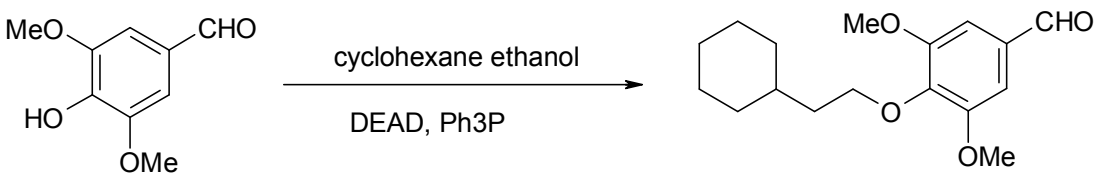
47b: 5-(4-(2-cyclohexylethoxy)-2-(trifluromethyl)benzylidene)thiazolidine-2,4-dione



47a **47b**

47b: yield 79.7%; ^{1}H NMR (300 MHz, DMSO-d_6) δ12.731 (s, 1H), 7.778 (s, 1H), 7.689 (d, J = 9.0 Hz, 1H), 7.407 (d, J = 9.0 Hz, 1H), 7.371 (s, 1H), 4.168 (t, J = 12.9 Hz, 2H), 1.598-1.750 (m, 7H), 1.455-1.598 (m, 1H), 1.099-1.265 (m, 3H), 0.884-0.994 (m, 2H).

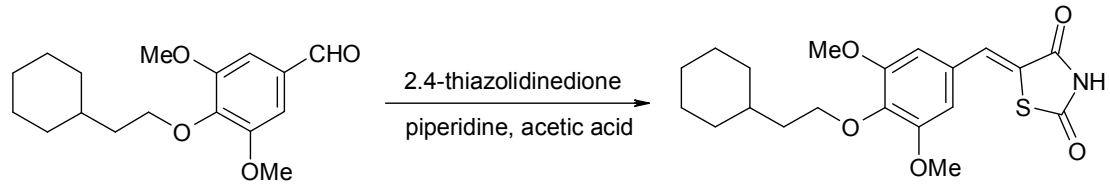
48a: 4-(2-cyclohexylethoxy)-3,5-dimethoxybenzaldehyde



48a

48a: yield 82.0%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.904 (s, 1H), 7.273 (s, 2H), 4.129 (t, *J* = 13.2 Hz, 2H), 3.914 (s, 6H), 1.646 (t, *J* = 13.2 Hz, 2H), 1.424-1.781 (m, 5H), 1.095-1.169 (m, 4H), 0.882-0.989 (m, 2H).

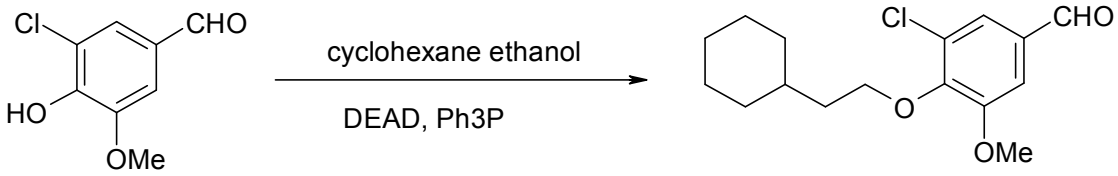
48b: 5-(4-(2-cyclohexylethoxy)-3,5-dimethoxybenzylidene)thiazolidine-2,4-dione



48a **48b**

48b: yield 84.2% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ8.623 (s, 1H), 7.781 (s, 1H), 6.768 (s, 2H), 4.10 (t, *J* = 13.5 Hz, 2H), 3.887 (s, 6H), 1.620 (t, *J* = 13.5 Hz, 2H), 1.505-1.738 (m, 6H), 1.096-1.325 (m, 3H), 0.884-0.951 (m, 2H).

49a: 3-chloro-4-(2-cyclohexylethoxy)-5-methoxybenzaldehyde

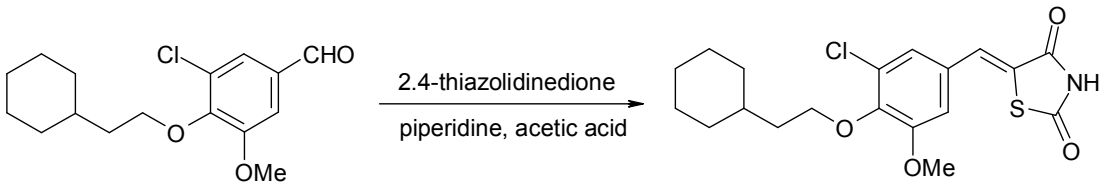


49a

49a: yield 88.7%;^{1}H NMR (300 MHz, $CDCl_3$) δ10.346 (s, 1H), 7.734 (d, *J* = 8.7 Hz, 2H), 6.926 (d, *J* = 8.7 Hz, 2H), 4.067(t, *J* = 13.2 Hz, 2H), 3.94 (s, 3H), 1.554-1.823(m, 5H), 1.751(t, *J* = 13.2

Hz, 2H), 1.098-1.352 (m, 4H), 0.901-1.028 (m, 2H).

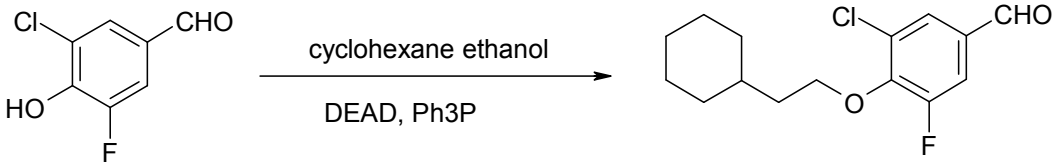
49b: 5-(3-chloro-4-(2-cyclohexylethoxy)-5-methoxybenzylidene)thiazolidine-2,4-dione



49a **49b**

49b: yield 84.2%; ^{1}H NMR (300 MHz, DMSO-d_6) δ12.656 (s, 1H), 7.738 (s, 1H), 7.262 (s, 1H), 7.239 (s, 1H), 4.043 (t, J = 12.6 Hz, 2H), 3.872 (s, 3H), 1.557-1.754 (m, 8H), 1.144-1.239 (m, 3H), 0.891-0.964 (m, 2H).

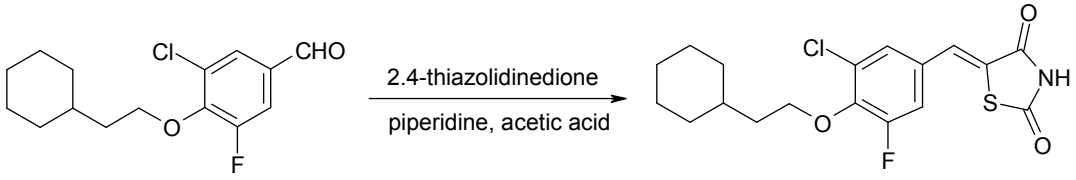
50a: 3-chloro-5-fluoro-4-(2-cyclohexylethoxy)benzaldehyde



50a

50a: yield 85.1%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.843 (s, 1H), 7.710 (s, 1H), 7.531 (s, 1H), 4.332 (t, J = 15.6 Hz, 2H), 1.595-2.047 (m, 7H), 1.446-1.502 (m, 1H), 1.109-1.329 (m, 3H), 0.895-1.024 (m, 2H).

50b: 5-(3-chloro-5-fluoro-4-(2-cyclohexylethoxy)benzylidene)thiazolidine-2,4-dione

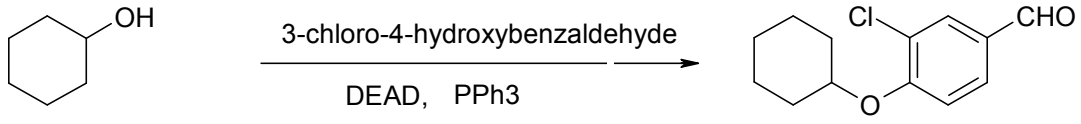


50a **50b**

50b: yield 75.4%; ^{1}H NMR (300 MHz, DMSO-d_6) δ12.061 (s, 1H), 7.950 (s, 1H), 7.532 (s, 1H), 7.488 (s, 2H), 4.178 (t, J = 15.5 Hz, 2H), 1.588-1.749 (m, 7H), 1.505-1.580 (m, 1H), 1.107-1.237 (m, 3H), 0.903-0.980 (m, 2H).

Synthesis of compounds 51 - 77

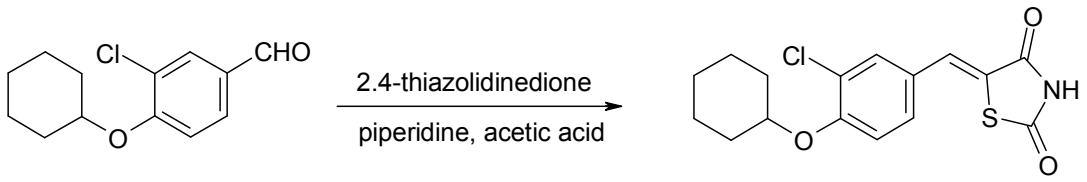
51a: 3-chloro-4-(cyclohexyloxy)benzaldehyde



51a

51a: yield 86%; ^{1}H NMR (300 MHz, $CDCl_3$) δ9.834 (s, 1H), 7.906 (s, 1H), 7.745 (d, J = 8.4 Hz, 1H), 7.046 (d, J = 8.4 Hz, 1H), 4.443-4.521(m, 1H), 1.943-1.972 (m, 2H), 1.825-1.889 (m, 2H), 1.684-1.803 (m, 2H), 1.511-1.673 (m, 1H), 1.351-1.489 (m, 3H).

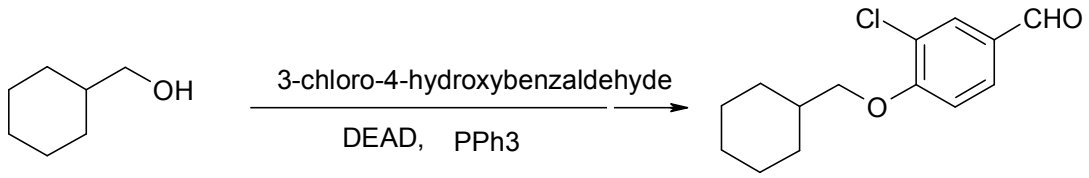
51b: 5-(3-chloro-4-(cyclohexyloxy)benzylidene)thiazolidine-2,4-dione



51a **51b**

51b: yield 88%; ^{1}H NMR (300 MHz, DMSO-d_6) δ12.587 (s, 1H), 7.724 (s, 1H), 7.699 (s, 1H), 7.516 (d, J = 13.2 Hz, 1H), 7.371 (d, J = 13.2 Hz, 1H), 4.564-4.615 (m, 1H), 2.029-2.496 (m, 2H), 1.693-1.861 (m, 2H), 1.509-1.537 (m, 2H), 1.350-1.450 (m, 4H).

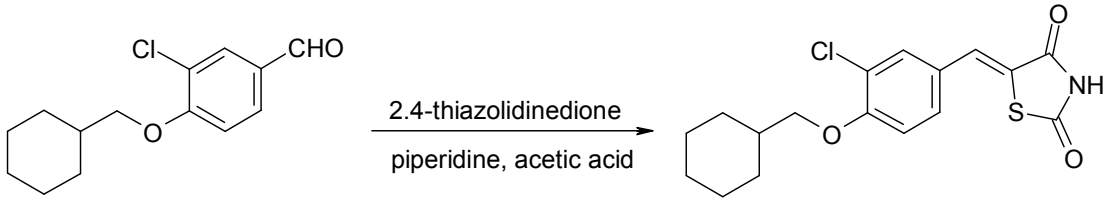
52a: 3-chloro-4-(cyclohexylmethoxy)benzaldehyde



52a

52a: yield 85%; ^{1}H NMR (300 MHz, $CDCl_3$) δ9.840 (s, 1H), 7.900 (s, 1H), 7.759 (d, *J* = 8.4 Hz, 1H), 7.018 (d, *J* = 8.4 Hz, 1H), 3.914 (d, *J* = 5.7 Hz, 2H), 1.889-2.046 (m, 3H), 1.748-1.862 (m, 3H), 1.240-1.424 (m, 3H), 1.042-1.231 (m, 2H).

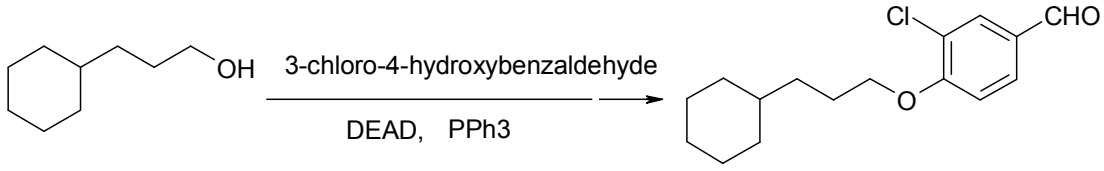
52b: 5-(3-chloro-4-(cyclohexylmethoxy)benzylidene)thiazolidine-2,4-dione



52a **52b**

52b: yield 88%; ^{1}H NMR (300 MHz, DMSO-d_6) δ12.586 (s, 1H), 7.721 (s, 1H), 7.697 (s, 1H), 7.527 (d, *J* = 8.7 Hz, 1H), 7.305 (d, *J* = 8.7 Hz, 1H), 3.949 (d, *J* = 6.0 Hz, 2H), 1.626-1.826 (m, 6H), 1.034-1.269 (m, 5H).

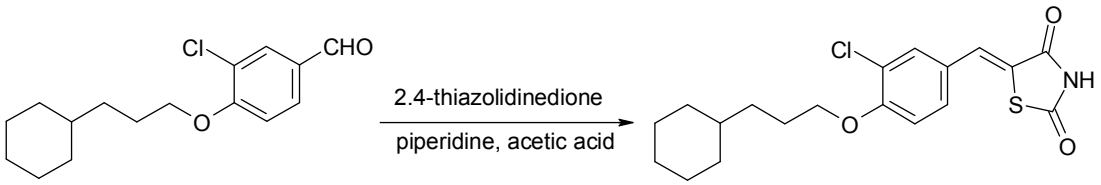
53a: 3-chloro-4-(3-cyclohexylpropoxy)benzaldehyde



53a

53a: yield 89%;^{1}H NMR (300 MHz, $CDCl_3$) δ9.843(s, 1H), 7.908 (s, 1H), 7.766 (d, *J* = 10.5 Hz, 1H), 7.026 (d, *J*= 10.5 Hz, 1H), 4.123 (t, *J* = 13.2 Hz, 2H), 1.864-1.938 (m, 2H), 1.69-1.842 (m, 5H), 1.344-1.679 (m, 2H), 1.078-1.306 (m, 4H), 0.854-0.974 (m, 2H).

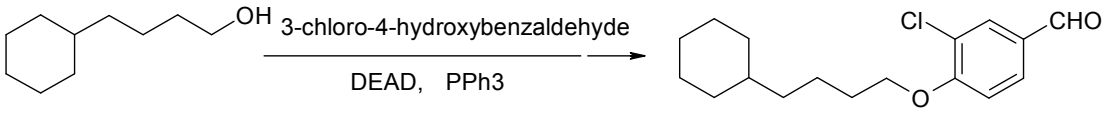
53b: 5-(3-chloro-4-(cyclohexylpropoxy)benzylidene)thiazolidine-2,4-dione



53a **53b**

53b: yield 88%; ^{1}H NMR (300 MHz, DMSO-d_6) δ12.587 (s, 1H), 7.717 (s, 1H), 7.695 (s, 1H), 7.531 (d, J = 8.4Hz, 1H), 7.302 (d, J = 8.4Hz, 1H), 4.125 (t, J = 12.6 Hz, 2H), 1.625-1.772 (m, 7H), 1.079-1.348 (m, 6H), 0.837-0.911 (m, 2H).

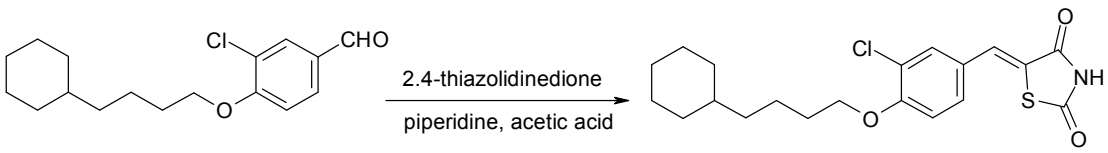
54a: 3-chloro-4-(4-cyclohexylbutoxy)benzaldehyde



54a

54a: yield 86%; ^{1}H NMR (300 MHz, $CDCl_3$) δ9.842 (s, 1H), 7.905 (s, 1H), 7.764 (d, J = 11.7 Hz, 1H), 7.029 (d, J = 11.7 Hz, 1H), 4.136(t, J = 12.6 Hz, 2H), 1.830-1.903 (m, 2H), 1.679-1.809 (m, 6H), 1.461-1.675 (m, 2H), 1.112-1.294 (m, 7H), 0.859-0.93 (m, 2H).

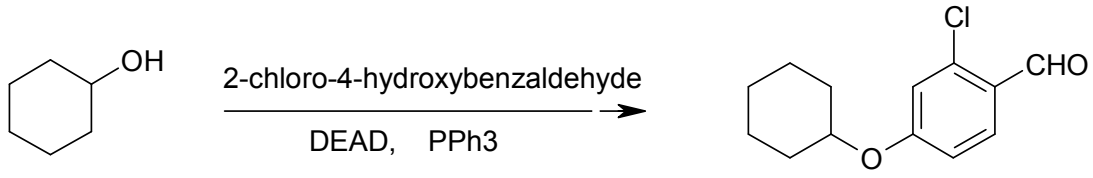
54b: 5-(3-chloro-4-(cyclohexylbutoxy)benzylidene)thiazolidine-2,4-dione



54a **54b**

54b: yield 87%;^{1}H NMR (300 MHz, DMSO-d_6) δ12.582 (s, 1H), 7.730 (s, 1H), 7.695 (s, 1H), 7.532 (d, J = 9.0 Hz, 1H), 7.309 (d, J = 9.0 Hz, 1H), 4.141 (t, J = 12.3 Hz, 2H), 1.652-1.761 (m, 7H), 1.227-1.615 (m, 2H), 1.067-1.205 (m, 6H), 0.818-0.889 (m, 2H).

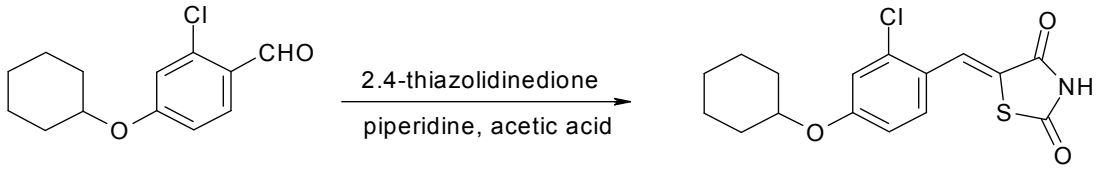
55a: 2-chloro-4-(cyclohexyloxy)benzaldehyd



55a

55a: yield 86%; ^{1}H NMR (300 MHz, $CDCl_3$) δ10.406 (s, 1H), 8.00 (d, *J* = 10.8 Hz, 1H), 7.222 (d, *J* = 10.8 Hz, 1H), 7.03 10.406 (s, 1H), 1.578- 2.047 (m, 6H). 1.177- 1.284 (m, 4H), 0.910- 0.948 (m, 1H)

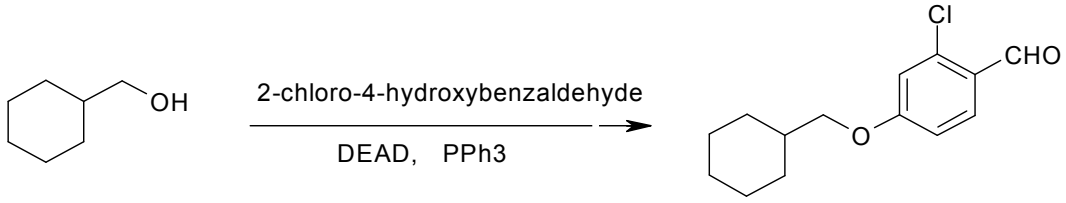
55b: 5-(2-chloro-4-(cyclohexyloxy)benzylidene)thiazolidine-2,4-dione



55a **55b**

55b: yield 71.1%; ^{1}H NMR (300 MHz, DMSO-d_6) δ10.581 (s, 1H), 7.658 (s, 1H), 7.529 (s, 1H), 7.398 (d, *J* = 8.4 Hz, 1H), 7.273 (d, *J* = 8.4 Hz, 1H), 1.451- 1.465 (m, 11H).

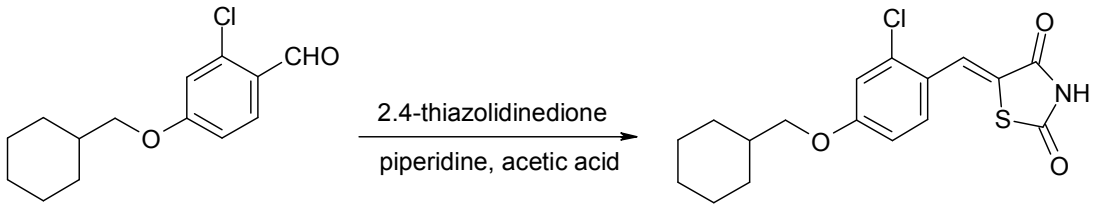
56a: 2-chloro-4-(3-cyclohexylmethoxy)benzaldehyde



56a

56a: yield 85%;^{1}H NMR (300 MHz, $CDCl_3$) δ10.463 (s, 1H), 7.465 (d, *J* = 8.7 Hz, 1H), 7.147 (s, 1H), 7.098 (d, *J* = 8.7 Hz, 1H), 3.685 (d, *J* = 6.0 Hz, 2H), 1.521-1.644 (m, 6H), 1.003-1.144 (m, 3H), 0.988-1.021 (m, 2H).

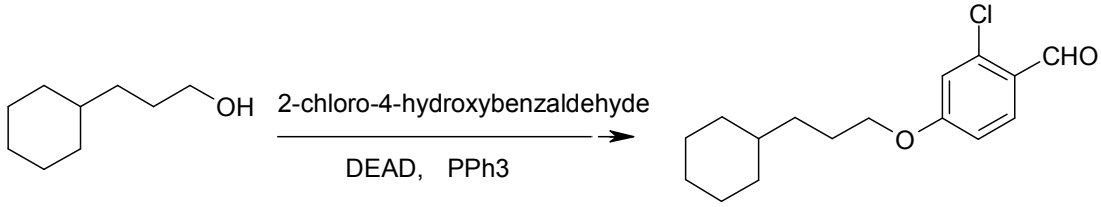
56b: 5-(2-chloro-4-(3-cyclohexylmethoxy)benzylidene)thiazolidine-2,4-dione



56a **56b**

56b: yield 75.5%; ^{1}H NMR (300 MHz, DMSO-d_6) δ12.637 (s, 1H), 7.838 (s, 1H), 7.656 (d, J = 8.7 Hz, 1H), 7.223 (s, 1H), 7.110 (d, J = 8.7 Hz, 1H), 3.881 (d, J = 6.0 Hz, 2H), 1.641-1.797 (m, 6H), 1.194-1.263 (m, 3H), 1.002-1.039 (m, 2H).

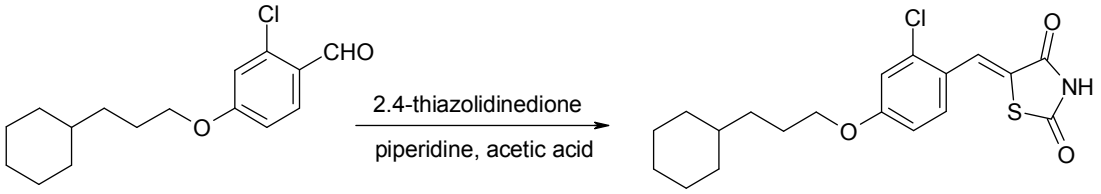
57a: 2-chloro-4-(3-cyclohexylpropoxy)benzaldehyde



57a

57a: yield 81.2%; ^{1}H NMR (300 MHz, $CDCl_3$) δ9.588 (s, 1H), 7.500 (s, 1H), 7.374 (d, J = 11.7 Hz, 1H), 7.133 (d, J = 11.7 Hz, 1H), 4.158 (t, J = 7.2 Hz, 2H), 1.598-2.047 (m, 4H), 1.09-1.62 (m, 7H), 0.802 – 0.928 (m, 4H).

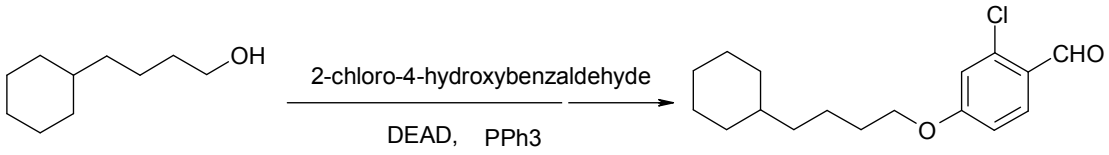
57b: 5-(2-chloro-4-(3-cyclohexylpropoxy)benzylidene)thiazolidine-2,4-dione



57a **57b**

57b: yield 72.6%; ^{1}H NMR (300 MHz, DMSO-d_6) δ7.785 (s, 1H), 7.439 (s, 1H), 7.654 (d, J = 11.7 Hz, 1H), 7.515 (d, J = 11.7 Hz, 1H), 3.014 (t, J = 7.2 Hz, 2H), 1.135-1.642 (m, 4H), 1.029-1.222 (m, 7H), 0.822 - 1.127 (m, 4H).

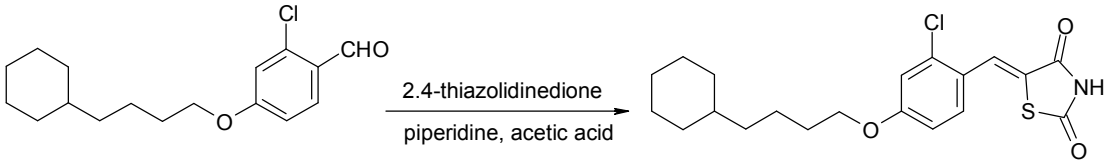
58a: 2-chloro-4-(3-cyclohexylbutoxy)benzaldehyde



58a

58a: yield 83%; ^{1}H NMR (300 MHz, $CDCl_3$) δ10.269 (s, 1H), 7.439 (s, 1H), 7.324 (d, J = 9.3 Hz, 1H), 7.115 (d, J = 9.3 Hz, 1H), 3.004 (t, J = 7.2 Hz, 2H), 1.602-1.693 (m, 4H), 1.289-1.421 (m, 4H), 1.052-1.154 (m, 7H), 0.810 – 0.844 (m, 2H).

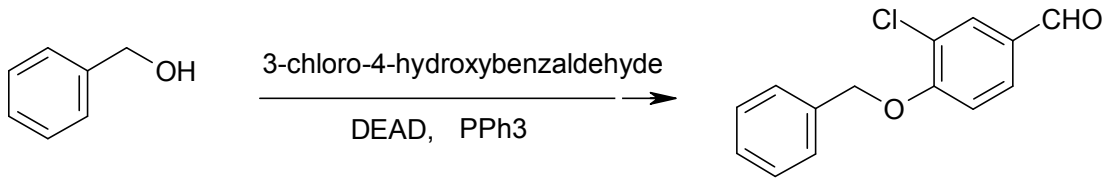
58b: 5-(2-chloro-4-(3-cyclohexylbutoxy)benzylidene)thiazolidine-2,4-dione



58a **58b**

58b: yield 76%; ^{1}H NMR (300 MHz, DMSO-d_6) δ12.649(s, 1H), 7.880 (s, 1H), 7.497 (s, 1H), 7.497 (d, J = 9.3 Hz, 1H), 7.515 (d, J = 9.3 Hz, 1H), 3.014 (t, J = 7.2 Hz, 2H), 1.653-1.724 (m, 4H), 1.315-1.642 (m, 4H), 1.069-1.215 (m, 7H), 0.820 – 0.852 (m, 2H).

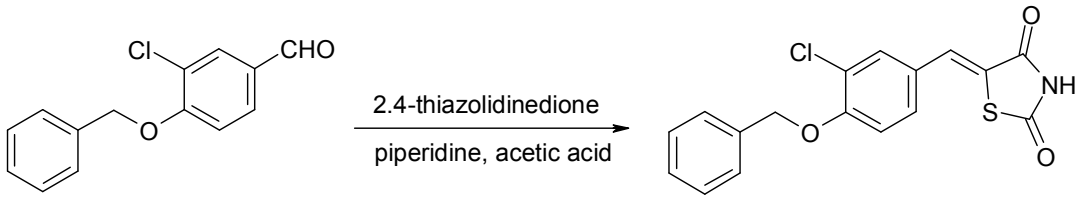
59a: 4-(benzyloxy)-3-chlorobenzaldehyde



59a

59a: yield 77.2%; ^{1}H NMR (300 MHz, $CDCl_3$) δ9.847 (s, 1H), 7.778 (s, 1H), 7.652 (d, *J* = 10.2 Hz, 1H), 7.116-7.338 (m, 5H), 6.987 (d, *J* = 10.2 Hz, 1H), 5.104 (s, 2H).

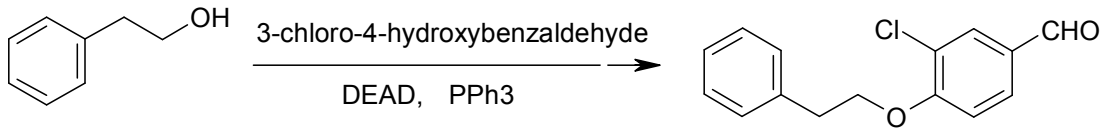
59b: 5-(4-(benzyloxy)-3-chlorobenzylidene)thiazolidine-2,4-dione



59a **59b**

59b: yield 86.4%; ^{1}H NMR (300 MHz, DMSO-d_6) δ8.024 (s, 1H), 7.936 (s, 1H), 7.747 (d, *J* = 10.2 Hz, 1H), 7.324-7.479 (m, 5H), 7.093 (d, *J* = 10.2 Hz, 1H), 5.259 (s, 2H).

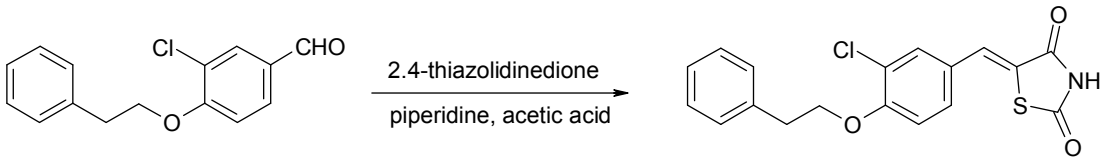
60a: 3-chloro-4-phenethoxybenzaldehyde



60a

60a: yield 79.3%;^{1}H NMR (300 MHz, $CDCl_3$) δ9.836 (s, 1H), 7.904 (s, 1H), 7.743 (d, *J* = 11.1 Hz, 1H), 7.230-7.344 (m, 5H), 7.003 (d, *J* = 11.1 Hz, 1H), 4.306 (t, *J* = 13.5 Hz, 2H), 3.195 (t, *J* = 13.5 Hz, 2H).

60b: 5-(3-chloro-4-phenethoxybenzylidene)thiazolidine-2,4-dione

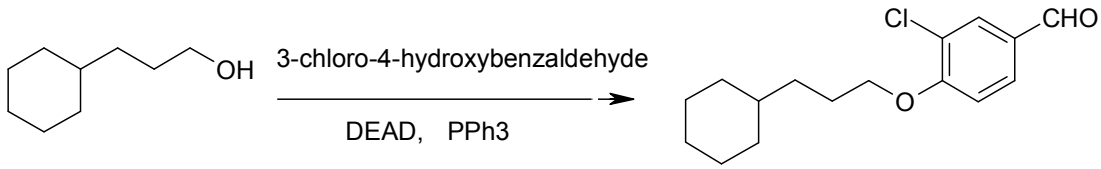


60a **60b**

60b: yield 86.2%; ^{1}H NMR (300 MHz, DMSO-d_6) δ12.547 (s, 1H), 7.894 (s, 1H), 7.694 (s, 1H),

7.533 (d, *J* = 11.1 Hz, 1H), 7.311-7.348 (m, 5H), 7.248 (d, *J* = 11.1 Hz, 1H), 4.367 (t, *J* = 13.5 Hz, 2H), 3.109 (t, *J* = 13.5 Hz, 2H).

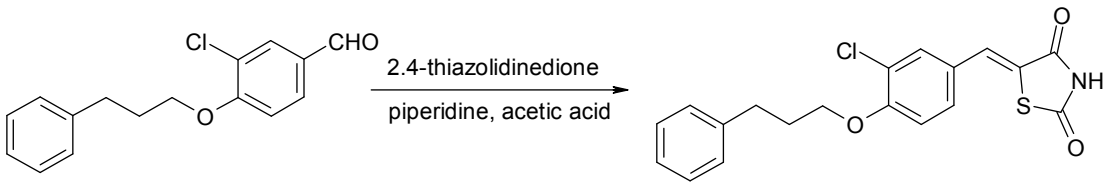
61a: 3-chloro-4-(3-phenylpropoxy)benzaldehyde



61a

61a: yield 73.6%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.588 (s, 1H), 7.467 (s, 1H), 7.533 (d, *J* = 10.8 Hz, 1H), 7.158 – 7.311 (m, 6H), 4.143 (t, *J* = 12.3 Hz, 2H), 2.802 (t, *J* = 12.8 Hz, 2H), 2.022-2.093 (m, 2H).

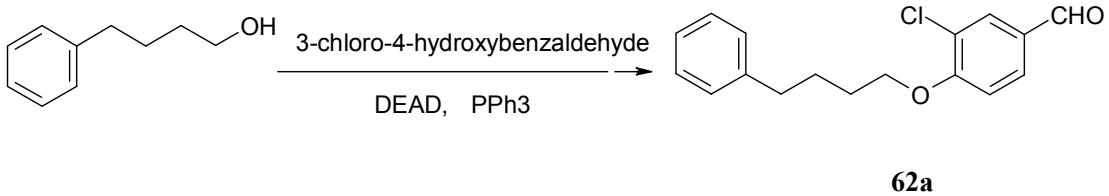
61b: 5-(3-chloro-4-(3-phenylpropoxy)benzylidene)thiazolidine-2,4-dione



61a **61b**

61b: yield 83.1%; ^{1}H NMR (300 MHz, DMSO-d_6) δ12.538 (s, 1H), 7.714 (s, 1H), 7.706 (s, 1H), 7.533 (d, *J* = 10.8 Hz, 1H), 7.158 – 7.311 (m, 6H), 4.143 (t, *J* = 12.3 Hz, 2H), 2.802 (t, *J* = 12.8 Hz, 2H), 2.022-2.093 (m, 2H).

62a: 3-chloro-4-(4-phenylbutoxy)benzaldehyde

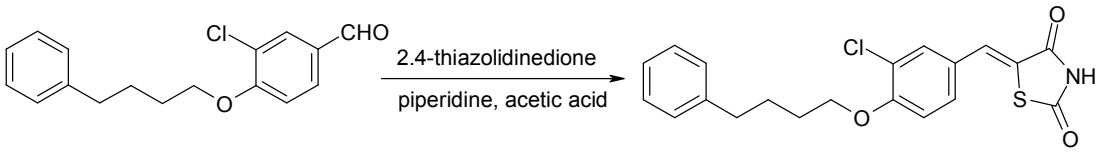


62a

62a: yield 74.5%; ^{1}H NMR (300 MHz, $CDCl_3$) δ9.838 (s, 1H), 7.900 (s, 1H), 7.893 (d, *J* = 10.5

Hz, 1H), 7.127-7.305 (m, 6H), 3.77 (t, *J* = 5.7 Hz, 2H), 2.648 (t, *J* = 7.2 Hz, 2H), 1.561-1.1.753 (m, 4H).

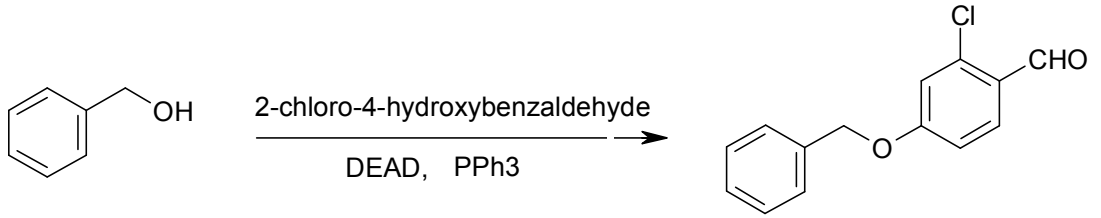
62b: 5-(3-chloro-4-(4-phenylbutoxy)benzylidene)thiazolidine-2,4-dione



62a **62b**

62b: yield 77.6%; ^{1}H NMR (300 MHz, DMSO-d_6) δ12.577 (s, 1H), 7.720 (s, 1H), 7.693 (s, 1H), 7.529 (d, *J* = 10.5 Hz, 1H), 7.135-7.304 (m, 6H), 4.155 (t, *J* = 5.7 Hz, 2H), 2.671 (t, *J* = 7.2 Hz, 2H), 1.741-1.761 (m, 4H).

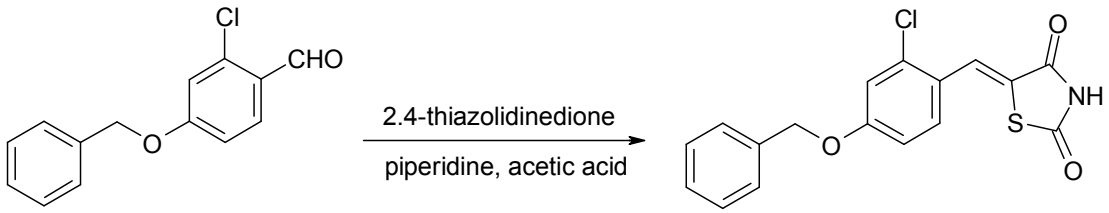
63a: 4-(benzyloxy)-2-chlorobenzaldehyde



63a

63a: yield 71.9%; ^{1}H NMR (300 MHz, $CDCl_3$) δ10.346 (s, 1H), 7.913(d, *J* = 9.9 Hz, 1H), 7.386-7.493 (m, 6H), 6.987 (s, 1H), 6.958 (d, *J* = 9.9 Hz, 1H), 5.133 (s, 2H).

63b: 5-(4-(benzyloxy)-2-chlorobenzylidene)thiazolidine-2,4-dione

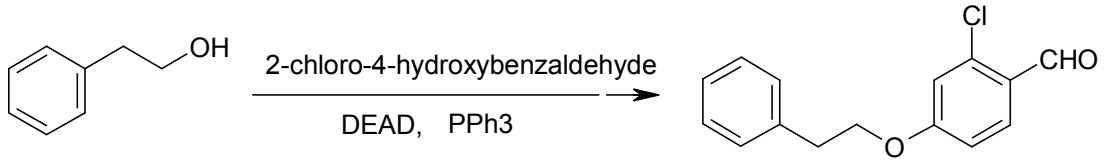


63a **63b**

63b: yield 70.1%; ^{1}H NMR (300 MHz, DMSO-d_6) δ7.850 (s, 1H), 7.561 (d, *J* = 9.9 Hz, 1H),

7.332-7.499 (m, 6H), 7.221 (d, *J* = 9.9 Hz, 1H), 5.224 (s, 2H).

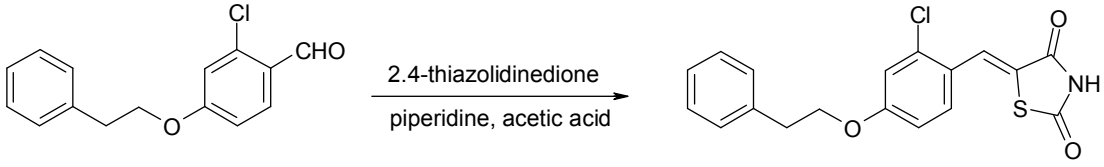
64a: 2-chloro-4-phenethoxybenzaldehyde



64a

64a: yield 77%; ^{1}H NMR (300 MHz, $CDCl_3$) δ10.317 (s, 1H), 7.913 (d, *J* = 7.8 Hz, 1H), 7.235-7.361 (m, 5H), 7.175(s, 1H), 6.986 (d, *J* = 7.8 Hz, 1H), 4.258 (t, *J* = 13.5 Hz, 2H), 3.144 (t, *J* = 13.8 Hz, 2H).

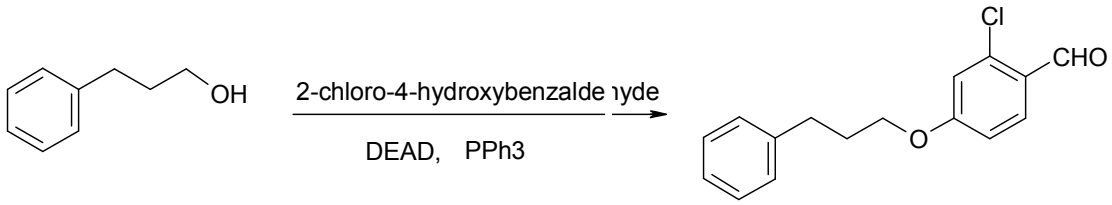
64b: 5-(2-chloro-4-phenethoxybenzylidene)thiazolidine-2,4-dione



64a **64b**

64b: yield 69.6%; ^{1}H NMR (300 MHz, DMSO-d_6) δ12.645 (s, 1H), 7.863 (s, 1H), 7.500 (d, *J* = 7.8 Hz, 1H), 7.188-7.274 (m, 6H), 7.127 (d, *J* = 7.8 Hz, 1H), 4.323 (t, *J* = 13.5 Hz, 2H), 3.064 (t, *J* = 13.8 Hz, 2H).

65a: 2-chloro-4-phenpropoxybenzaldehyde

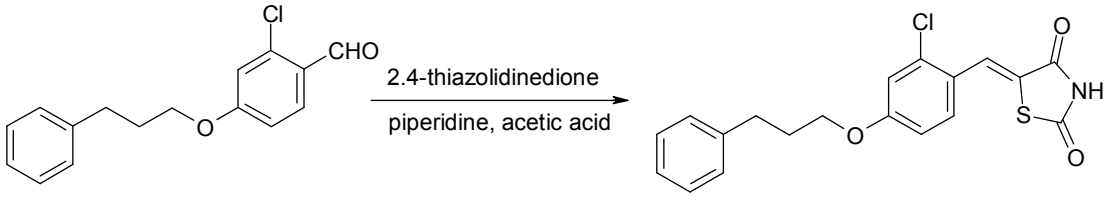


65a

65a: yield 69.7%; ^{1}H NMR (300 MHz, $CDCl_3$) δ10.324 (s, 1H), 7.933 (d, *J* = 7.8 Hz, 1H),

7.145-7.301(m, 6H), 7.028 (d, *J* = 7.8 Hz, 1H), 4.018 (t, *J* = 13.5 Hz, 2H), 2.812 (t, *J* = 13.8 Hz, 2H), 2.111-2.181 (m, 2H).

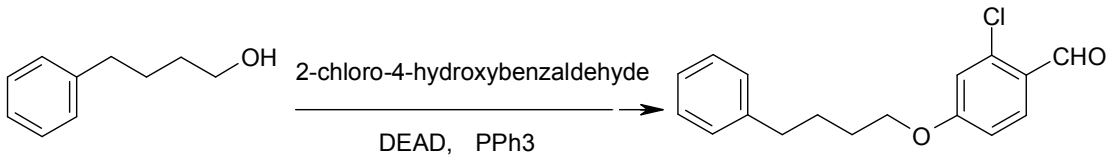
65b: 5-(2-chloro-4-phenpropoxybenzylidene)thiazolidine-2,4-dione



65a **65b**

65b: yield 72.7%; ^{1}H NMR (300 MHz, DMSO-d_6) δ12.548 (s, 1H), 7.924 (s, 1H), 7.482 (d, *J* = 7.8 Hz, 1H), 7.200-7.368(m, 6H), 7.212 (d, *J* = 7.8 Hz, 1H), 4.139 (t, *J* = 13.5 Hz, 2H), 3.156 (t, *J* = 13.8 Hz, 2H), 2.591-2.622 (m, 2H).

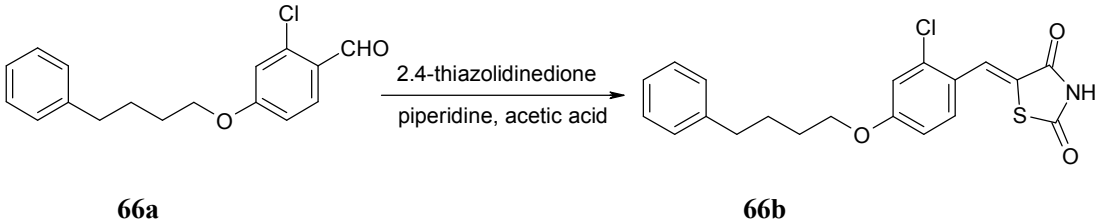
66a: 2-chloro-4-phenbutoxybenzaldehyde



66a

66a: yield 72.4%; ^{1}H NMR (300 MHz, $CDCl_3$) δ10.321 (s, 1H), 7.892 (d, *J* = 9.3 Hz, 1H), 7.138-7.319(m, 6H), 6.979 (d, *J* = 9.3 Hz, 1H), 4.048 (t, *J* = 12.9 Hz, 2H), 2.719 (t, *J* = 13.8 Hz, 2H), 1.801-1.841 (m, 4H).

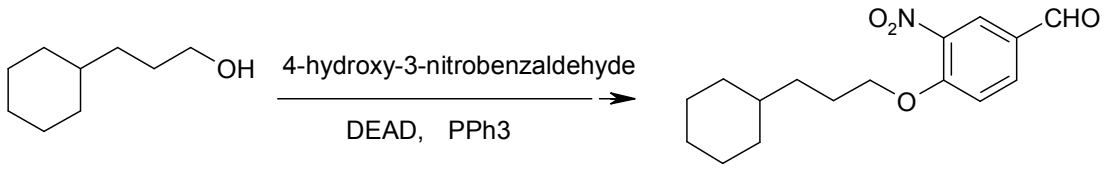
66b: 5-(2-chloro-4-phenbutoxybenzylidene)thiazolidine-2,4-dione



66a **66b**

66b: yield 73.1%; ^{1}H NMR (300 MHz, DMSO-d_6) δ12.64 (s, 1H), 7.81 (s, 1H), 7.511 (d, J = 9.3 Hz, 1H), 7.161-7.296(m, 6H), 7.105 (d, J = 9.3 Hz, 1H), 4.084 (t, J = 12.9 Hz, 2H), 2.654 (t, J = 13.8 Hz, 2H), 1.653-1.724 (m, 4H).

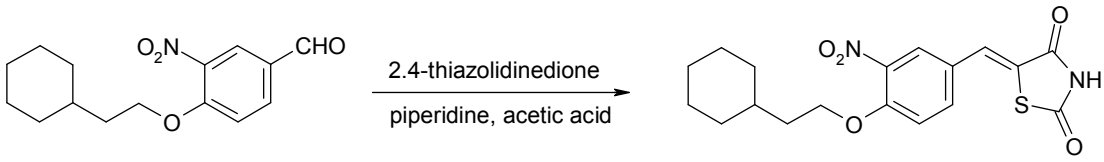
67a: 4-(3-cyclohexylpropoxy)-3-nitrobenzaldehyde



67a

67a: yield 87%; ^{1}H NMR (300 MHz, $CDCl_3$) δ9.858 (s, 1H), 8.271 (s, 1H), 7.679 (d, J = 8.7 Hz, 2H), 7.145 (d, J = 8.7 Hz, 2H), 4.118 (t, J = 13.2 Hz, 2H), 1.607-1.653 (m, 2H), 1.457-1.554 (m, 6H), 1.282-1.426 (m, 3H), 0.762-1.263 (m, 4H).

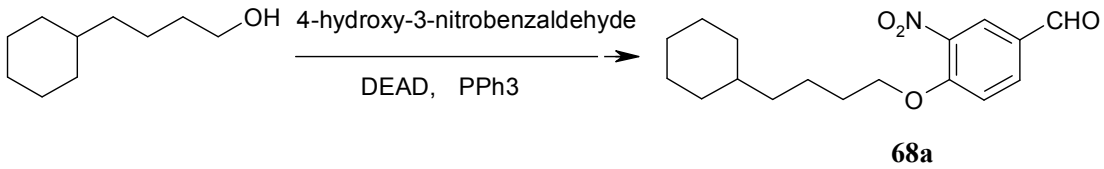
67b: 5-(4-(3-cyclohexylpropoxy)-3-nitrobenzylidene)thiazolidine-2,4-dione



67a **67b**

67b: yield 89%; ^{1}H NMR (300 MHz, $CDCl_3$) δ8.043 (s, 1H), 7.716 (s, 1H), 7.399 (d, J = 11.1 Hz, 1H), 7.262 (s, 1H), 7.041 (d, J = 8.7 Hz, 1H), 4.563 (d, J = 8.7 Hz, 1H), 4.048-4.087 (t, J = 14.1 Hz, 2H), 1.843-2.049 (m, 2H), 1.631-1.889 (m, 6H), 1.183-1.389 (m, 5H), 0.840-0.961 (m, 2H).

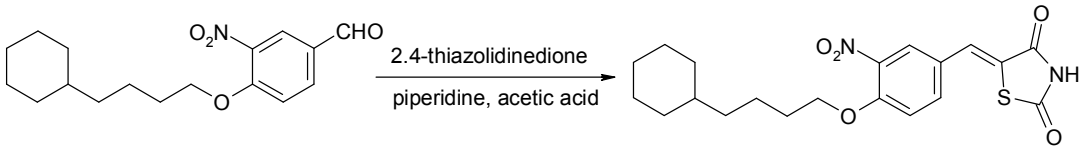
68a: 4-(2-cyclohexylbutoxy)-3-nitrobenzaldehyde (68a)



68a

68a: yield 81%; ^{1}H NMR (300 MHz, $CDCl_3$) δ9.858 (s, 1H), 8.264 (s, 1H), 7.698 (d, *J* = 9.0 Hz, 2H), 7.192 (d, *J* = 9.0 Hz, 2H), 4.040 (t, *J* = 12.3 Hz, 2H), 1.528-1.644 (m, 7H), 1.325-1.402 (m, 2H), 1.020-1.198 (m, 6H), 0.744-0.889 (m, 2H).

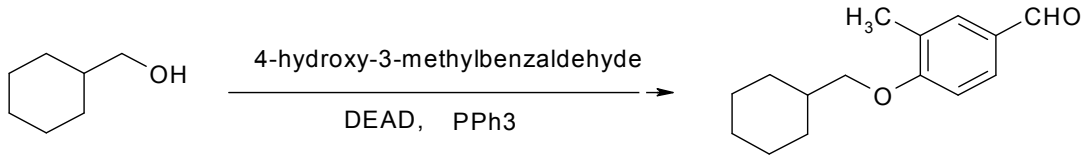
68b: 5-(4-(2-cyclohexylbutoxy)-3-nitrobenzylidene)thiazolidine-2,4-dione



68a **68b**

68b: yield 77.8%; ^{1}H NMR (300 MHz, DMSO-d_6) δ8.134 (s, 1H), 7.847 (d, *J* = 9.0 Hz, 2H), 7.787 (s, 1H), 7.527(d, *J* = 9.0 Hz, 2H), 4.225 (t, *J* = 12.3 Hz, 2H), 1.625-1.751 (m, 7H), 1.419-1.467 (m, 2H), 1.079-1.220 (m, 6H), 0.831-0.896 (m, 2H).

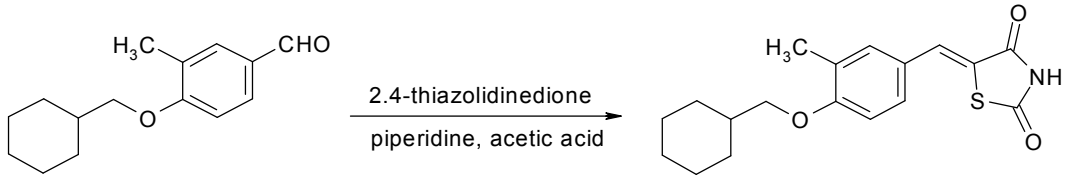
69a: 4-(2-cyclohexylmethoxy)-3-methylbenzaldehyde



69a

69a: yield 83%; ^{1}H NMR (300 MHz, $CDCl_3$) δ9.845(s, 1H), 7.707 (s, 1H), 7.678 (d, *J* = 9.0 Hz, 1H), 6.920 (d, *J* = 9.0 Hz, 1H), 4.111(d, *J* = 13.2 Hz, 2H), 2.259 (s, 3H), 1.705-1.771 (m, 6H), 1.660-1.727 (m, 1H), 0.832-1.111 (m, 4H).

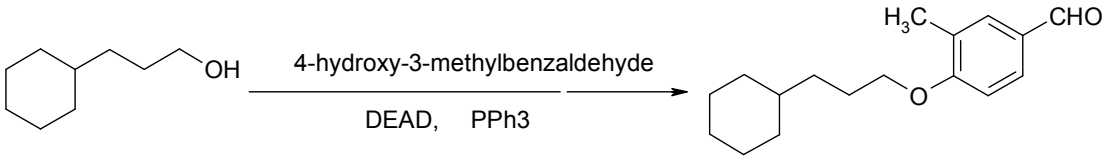
69b: 5-(4-(2-cyclohexylmethoxy)-3-methylbenzylidene)thiazolidine-2,4-dione



69a **69b**

69b: yield 77.5%; ^{1}H NMR (300 MHz, DMSO-d_6) δ7.784 (s, 1H), 7.345 (d, J = 8.4 Hz, 2H), 7.289 (s, 1H), 6.912(d, J = 8.4 Hz, 2H), 4.074 (d, J = 5.7 Hz, 2H), 2.302 (s, 3H), 1.706-1.894 (m, 6H), 1.257-1.380 (m, 3H), 1.070-1.225 (m, 2H).

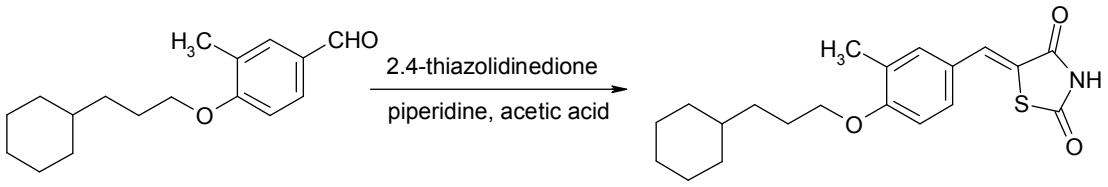
70a: 4-(2-cyclohexylpropoxy-3-methyl)benzaldehyde



70a

70a: yield 80%; ^{1}H NMR (300 MHz, $CDCl_3$) δ9.845(s, 1H), 7.707 (s, 1H), 7.678 (d, J = 9.0 Hz, 1H), 6.920 (d, J = 9.0 Hz, 1H), 4.111(d, J = 13.2 Hz, 2H), 2.259 (s, 3H), 1.705-1.771 (m, 6H), 1.660-1.727 (m, 1H), 0.832-1.111 (m, 4H).

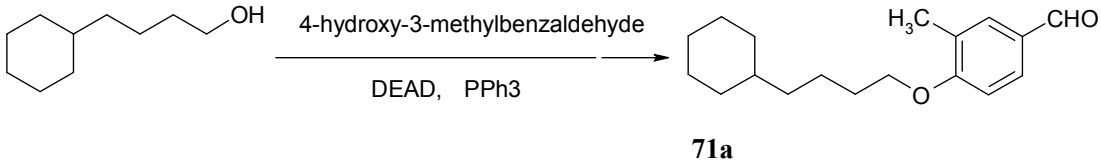
70b: 5-(4-(2-cyclohexylpropoxy)-3-methylbenzylidene)thiazolidine-2,4-dione



70a **70b**

70b: yield 89.1%; ^{1}H NMR (300 MHz, DMSO-d_6) δ7.793 (s, 1H), 7.349 (d, J = 8.4 Hz, 2H), 7.312 (s, 1H), 6.898(d, J = 8.4 Hz, 2H), 4.029 (t, J = 13.2 Hz, 2H), 1.650-2.041 (m, 8H), 1.089-1.397 (m, 4H), 0.860-0.968 (m, 3H).

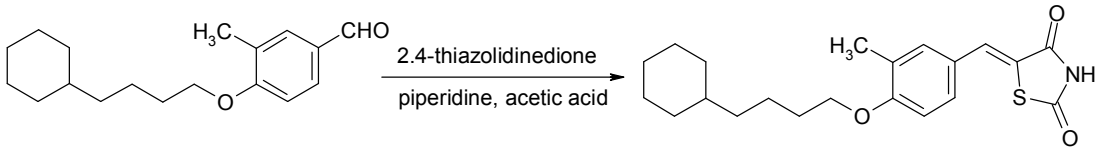
71a: 4-(2-cyclohexylbutoxy-3-methyl)benzaldehyde



71a

71a: yield 77.9%; ^{1}H NMR (300 MHz, $CDCl_3$) δ9.846(s, 1H), 7.707 (s, 1H), 7.700 (d, *J* = 8.7 Hz, 1H), 6.914 (d, *J* = 8.7 Hz, 1H), 4.068(t, *J* = 12.9 Hz, 2H), 2.264 (s, 3H), 1.769-1.861(m, 2H), 1.609-1.695 (m, 6H), 1.424-1.7472 (m, 2H), 1.074-1.286 (m, 5H), 0.860-0.921 (m, 2H).

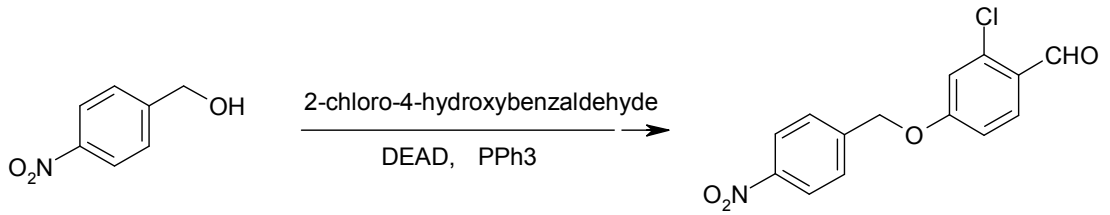
71b: 5-(4-(2-cyclohexylbutoxy)-3-methylbenzylidene)thiazolidine-2,4-dione



71a **71b**

71b: yield 87.5%; ^{1}H NMR (300 MHz, DMSO-d_6) δ7.787 (s, 1H), 7.349 (d, *J* = 8.7 Hz, 2H), 7.291 (s, 1H), 6.903(d, *J* = 8.7Hz, 2H), 4.045 (t, *J* = 12.9 Hz, 2H), 1.806-1.852 (m, 2H), 1.694-1.779 (m, 5H), 1.438-1.510 (m, 2H), 1.174-1.266 (m, 6H), 0.857-0.890 (m, 2H).

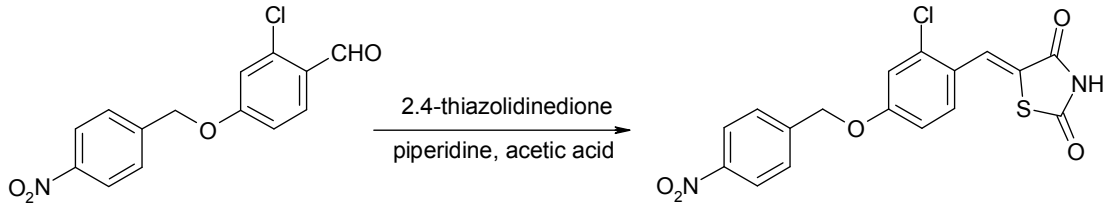
72a: 2-chloro-4-(4-nitrobenzyloxy)benzaldehyde



72a

72a: yield 69.4%; ^{1}H NMR (300 MHz, $CDCl_3$) δ10.349 (s, 1H), 7.937 (d, *J* = 13.2 Hz, 2H), 7.859 (d, *J* = 13.2 Hz, 1H), 7.397 (d, *J* = 13.2 Hz, 1H), 7.262 (d, *J* = 11.4 Hz, 1H), 7.075 (s, 1H) 7.061 (d, *J* = 13.2 Hz, 1H), 6.990 (d, *J* = 11.4 Hz, 1H), 5.180 (s, 2H).

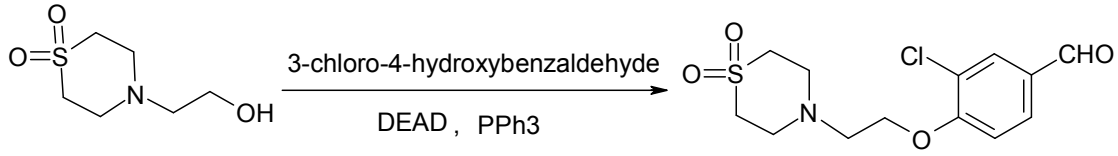
72b: 5-(2-chloro-4-(4-nitrobenzyloxy)benzylidene)thiazolidine-2,4-dione



72a **72b**

72b: yield 65.7%; ^{1}H NMR (300 MHz, DMSO-d_6) δ12.640(s, 1H), 7.887 (s, 1H), 7.704 (d, J = 13.2 Hz, 2H), 7.554 (d, J = 13.2 Hz, 2H), 7.510 (s, 1H) , 7.387 (d, J = 11.4 Hz, 1H), 7.223 (d, J = 11.4 Hz, 1H), 5.419 (s, 2H).

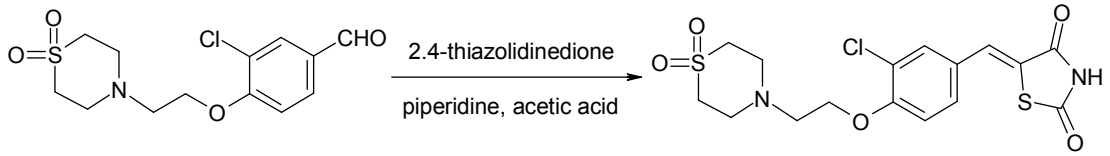
73a: 3-chloro-4-(2-Thiomorpholine 1,1-Dioxideethoxy)benzaldehyde



73a

73a: yield 88; ^{1}H NMR (300 MHz, $CDCl_3$) δ9.897 (s, 1H), 7.70 (s, 1H), 7.59 (d, J = 9.0 Hz, 1H), 6.99 (d, J = 9.0 Hz, 1H), 4.14 (t, J = 10.5 Hz, 2H), 3.149-3.27 (m, 8H), 3.04 (t, J = 10.5 Hz, 2H).

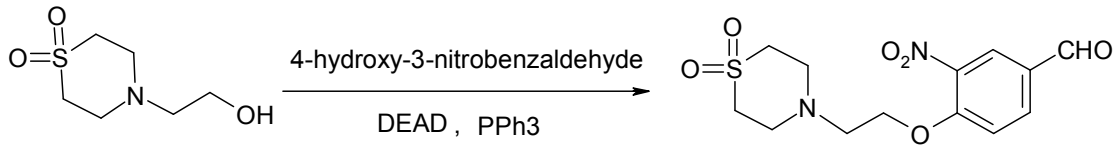
73b: 5-[3-chloro-4-(2-Thiomorpholine 1,1-Dioxideethoxy)benzylidene]-2,4-thiazolidinedione



73a **73b**

73b: yield 86%; ^{1}H NMR (300 MHz, DMSO-d_6) δ12.564 (s, 1H), 7.724 (s, 1H), 7.706 (s, 1H), 7.547 (d, J = 9.0 Hz, 1H), 7.11 (d, J = 9.0 Hz, 1H), 4.263 (t, J = 10.5 Hz, 2H), 3.031-3.119 (m, 8H), 2.990 (t, J = 10.5 Hz, 2H).

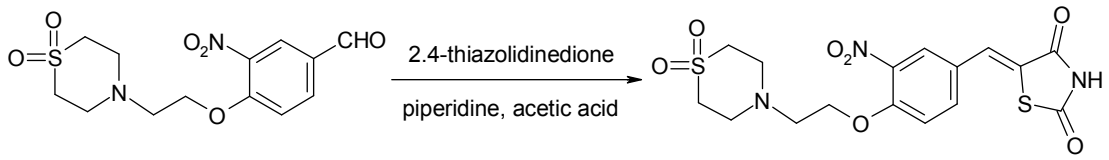
74a: 3-nitro-4-(2-Thiomorpholine1,1-Dioxideethoxy)benzaldehyde



74a

74a: yield 84%; ^{1}H NMR (300 MHz, $CDCl_3$) δ10.03 (s, 1H), 7.663 (d, J = 10.8 Hz, 1H), 7.396 (d, *J* = 10.8 Hz, 1H), 7.689 (s, 1H), 4.296 (t, *J* = 11.1 Hz, 2H), 2.966-3.011 (m, 8H), 2.847 (t, *J* = 11.1 Hz, 2H).

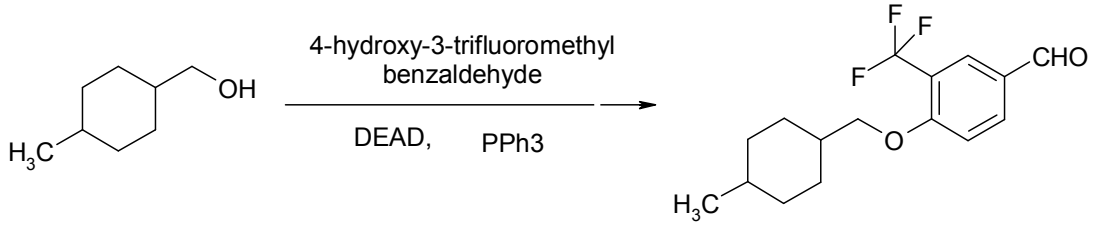
74b: 5-[3-nitro-4-(2-Thiomorpholine1,1-Dioxideethoxy)benzylidene]-2,4-thiazolidinedione



74a **74b**

74b: yield 67.7%; ^{1}H NMR (300 MHz, DMSO-d_6) δ12.630 (s, 1H), 8.148 (s, 1H), 7.860 (d, J = 10.8 Hz, 1H), 7.560 (d, *J* = 10.8 Hz, 1H), 7.782 (s, 1H), 4.360 (t, *J* = 11.1 Hz, 2H), 3.043-3.119 (m, 8H), 2.976 (t, *J* = 11.1 Hz, 2H).

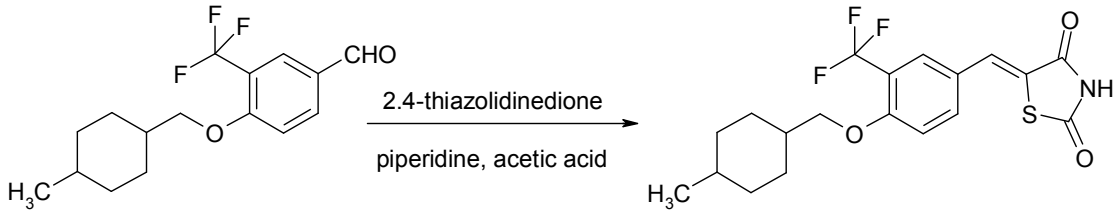
75a: 4-((4-metylcyclohexyl)methoxy)-3-(trifluromethyl)benzaldehyde



75a

75a: yield 83%; ^{1}H NMR (300 MHz, $CDCl_3$) δ10.012 (s, 1H), 7.744(s, 1H), 7.684 (d, *J* = 8.4 Hz, 1H), 7.036 (d, *J* = 8.4 Hz, 1H), 4.001 (d, *J* = 6.6 Hz, 1H), 3.912 (d, *J* = 6.6 Hz, 1H), 1.496-1.879 (m, 4H), 1.323-1.446 (m, 4H), 1.012-1.132 (m, 2H), 0.798 (d, *J* = 6.9 Hz, 3H).

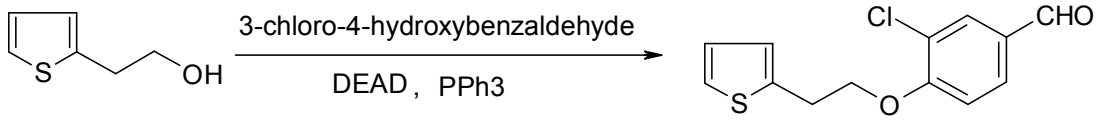
75b: 5-[4-((4-metylcyclohexyl)methoxy)-3-(trifluromethyl)benzylidene]thiazolidine-2,4-dione



75a **75b**

75b: yield 76.1%; ^{1}H NMR (300 MHz, DMSO-d_6) δ12.602 (s, 1H), 7.878 (s, 1H), 7.829(s, 1H), 7.805 (d, J = 8.4 Hz, 1H), 7.101 (d, J = 8.4 Hz, 1H), 4.117 (d, J = 6.6 Hz, 1H), 4.016 (d, J = 6.6 Hz, 1H), 1.685-1.907 (m, 4H), 1.454-1.523 (m, 4H), 1.083-1.122(m, 2H), 0.927 (d, J = 6.9 Hz, 3H).

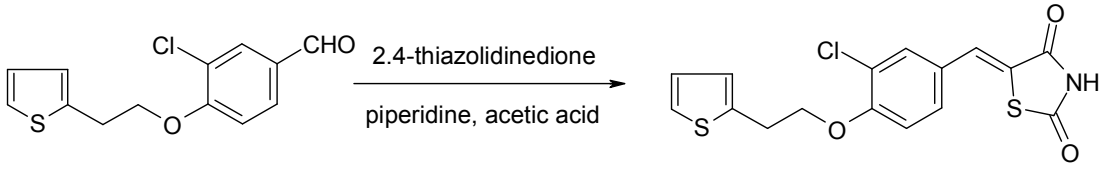
76a: 3-chloro-4-(2-(thiophen-2-yl)ethoxy)benzaldehyde



76a

76a: yield 84%; ^{1}H NMR (300 MHz, $CDCl_3$) δ9.988 (s, 1H), 7.526 (d, J = 2.4 Hz, 1H), 7.365 (d, J = 11.1 Hz, 1H), 7.231-7.363 (m, 2H), 6.989 (d, J = 3.3 Hz, 1H), 6.847 (d, J = 8.4 Hz, 1H), 4.263 (t, J = 12.6 Hz, 2H), 3.211 (t, J = 12.6 Hz, 2H).

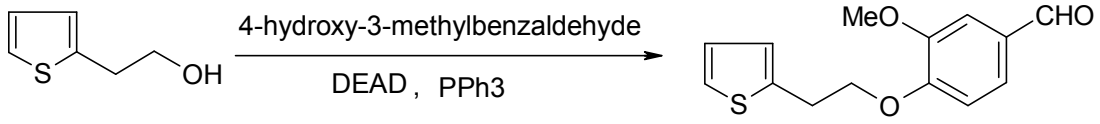
76b: 5-(3-chloro-4-(2-(thiophen-2-yl)ethoxy)benzylidene)thiazolidine-2,4-dione



76a **76b**

76b: yield 88.3%; ^{1}H NMR (300 MHz, DMSO-d_6) δ12.585 (s, 1H), 7.725 (s, 1H), 7.708 (d, J = 2.4 Hz, 1H), 7.536 (d, J = 11.1 Hz, 1H), 7.315-7.363 (m, 2H), 7.017 (d, J = 3.3 Hz, 1H), 6.978 (d, J = 8.4 Hz, 1H), 4.354 (t, J = 12.6 Hz, 2H), 3.322 (t, J = 12.6 Hz, 2H).

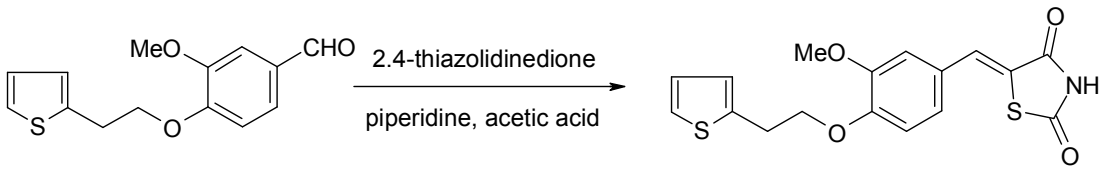
77a: 3-methoxy-4-(2-(thiophen-2-yl)ethoxy)benzaldehyde



77a

77a: yield 83%; ^{1}H NMR (300 MHz, $CDCl_3$) δ10.021 (s, 1H), 7.254 (d, *J* = 6.6 Hz, 1H), 7.139 (s, 1H), 6.977 (d, *J* = 14.4 Hz, 2H), 6,798-6.887 (m, 2H), 4.036 (t, *J* = 6.6 Hz, 2H), 3.653 (s, 3H), 3.133 (t, *J* = 6.6 Hz, 2H).

77b: 5-(3-methoxy-4-(2-(thiophen-2-yl)ethoxy)benzylidene)thiazolidine-2,4-dione

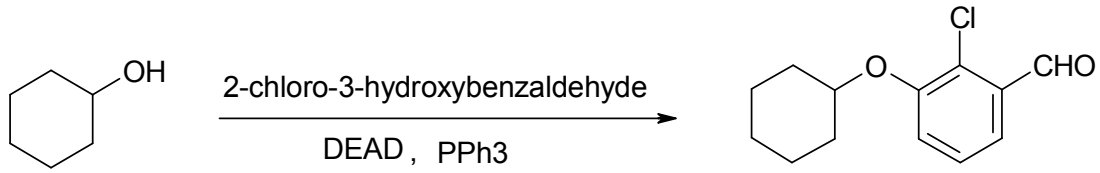


77a **77b**

77b: yield 88.4%; ^{1}H NMR (300 MHz, DMSO-d_6) δ12.438 (s, 1H), 7.722 (s, 1H), 7.357 (d, *J* = 6.6 Hz, 1H), 7.239 (s, 1H), 7.197 (d, *J* = 14.4 Hz, 2H), 6,946-6.994 (m, 2H), 4.265 (t, *J* = 6.6 Hz, 2H), 3.803 (s, 3H), 3.269 (t, *J* = 6.6 Hz, 2H).

Synthesis of compound 78 - 92

78a: 2-chloro-3-(cyclohexyloxy)benzaldehyde

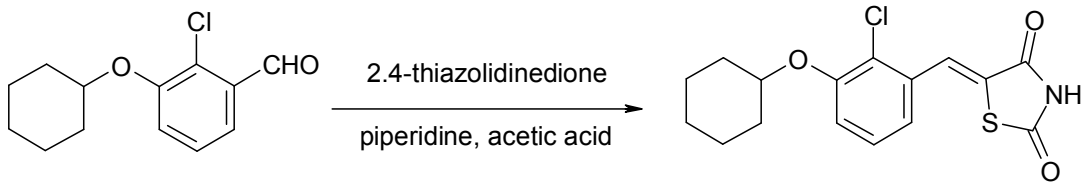


78a

78a: yield 71%; ^{1}H NMR (300 MHz, $CDCl_3$) δ10.525 (s, 1H), 7.524 (d, *J* = 9.3 Hz, 1H), 7.315 (m, 1H), 7.195 (d, *J* = 9.3 Hz, 1H), 4.310-4.389 (m, 1H), 1.933-2.046 (m, 2H), 1.658-1.765 (m,

4H), 1.216-1.487 (m, 2H), 0.690-0.896 (m, 2H).

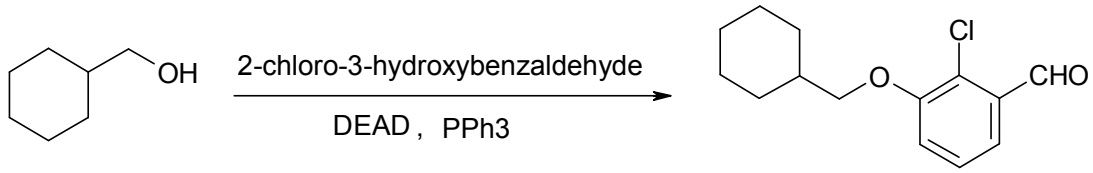
78b: 5-(2-chloro-3-(cyclohexyloxy)benzylidene)thiazolidine-2,4-dione



78a **78b**

78b: yield 78.9%; ^{1}H NMR (300 MHz, DMSO-d_6) δ12.587 (s, 1H), 7.724 (s, 1H), 7.524 (d, J = 9.3 Hz, 1H), 7.315 (t, 1H), 7.195 (d, J = 9.3 Hz, 1H), 4.310-4.389 (m, 1H), 1.933-2.044 (m, 2H), 1.734-1.822 (m, 2H), 1.491-1.674 (m, 2H), 1.208-1.446 (m, 2H), 0.860-0.946 (m, 2H).

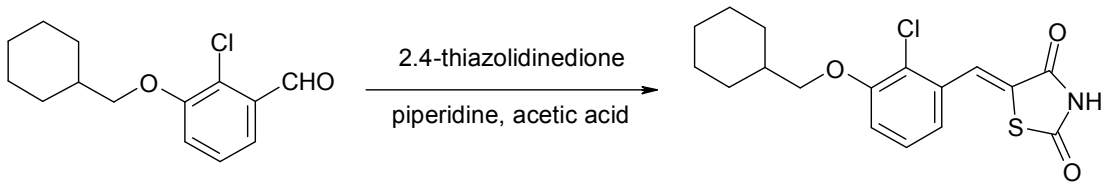
79a: 2-chloro-3-(cyclohexylmethoxy)benzaldehyde



79a

79a: yield 85.5%; ^{1}H NMR (300 MHz, $CDCl_3$) δ10.530 (s, 1H), 7.620 (d, J = 9.3 Hz, 1H), 7.273(m, 1H), 7.146 (d, J = 9.3 Hz, 1H), 3.862 (d, J = 6.0 Hz, 2H), 1.866-1.963 (m, 6H), 1.074-1.629 (m, 5H).

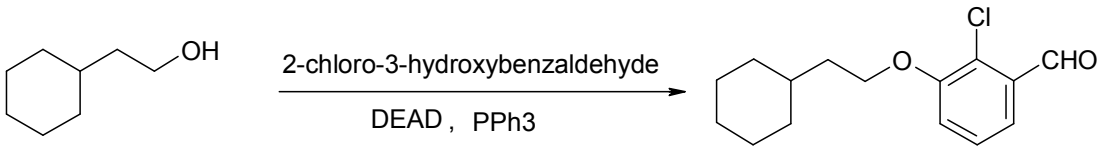
79b: 5-(2-chloro-3-(cyclohexylmethoxy)benzylidene)thiazolidine-2,4-dione



79a **79b**

79b: yield 76.3%; ^{1}H NMR (300 MHz, DMSO-d_6) δ7.721 (s, 1H), 7.514 (d, J = 9.3 Hz, 1H), 7.138-7.327(m, 1H), 7.142 (d, J = 9.3 Hz, 1H), 3.862 (d, J = 6.0 Hz, 2H), 1.7.3-1.933 (m, 6H), 1.088-1.579 (m, 5H).

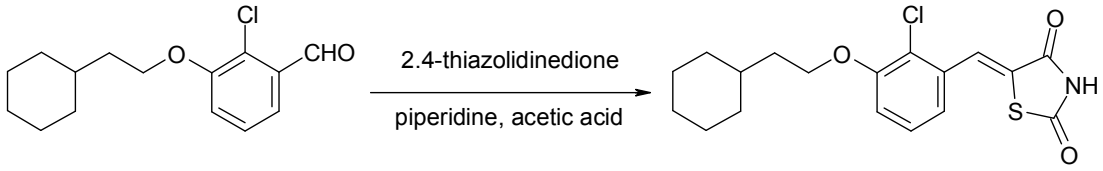
80a: 2-chloro-3-(2-cyclohexylethooxy)benzaldehyde



80a

80a: yield 73.6%; ^{1}H NMR (300 MHz, $CDCl_3$) δ10.532 (s, 1H), 7.582 (d, J = 9.6 Hz, 1H), 7.205-7.339 (m, 1H), 7.162 (d, J = 9.6 Hz, 1H), 4.125 (t, J = 13.2 Hz, 2H), 1.645-1.804 (m, 6H), 1.389-1.593 (m, 1H), 1.118-1.339 (m, 4H), 0.854-1.055 (m, 2H).

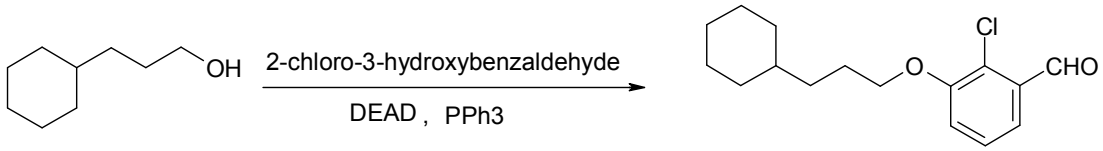
80b: 5-(2-chloro-3-(2-cyclohexylethoxy)benzylidene)thiazolidine-2,4-dione



80a **80b**

80b: yield 87%; ^{1}H NMR (300 MHz, DMSO-d_6) δ12.582 (s, 1H), 7.908 (s, 1H), 7.462 (t, J = 15.9 Hz, 1H), 7.283 (d, J = 7.8 Hz, 1H), 7.150 (d, J = 7.8 Hz, 1H), 4.140 (t, J = 12.9 Hz, 2H), 1.642-1.758 (m, 7H), 1.493 (m, 1H), 1.161-1.228 (m, 3H), 0.933-0.969 (m, 2H).

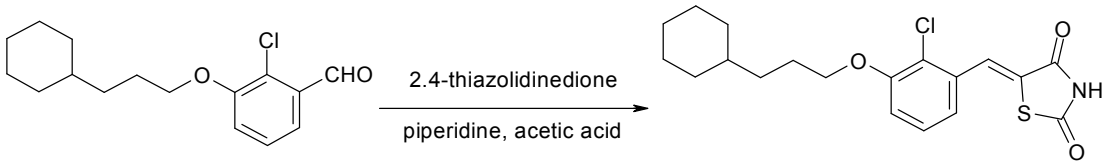
81a: 2-chloro-3-(cyclohexylpropoxy)benzaldehyde



81a

81a: yield 77.3%; ^{1}H NMR (300 MHz, $CDCl_3$) δ10.047 (s, 1H), 7.412 (d, *J* = 9.3 Hz, 1H), 7.132-7.275 (m, 1H), 7.044 (d, *J* = 9.3 Hz, 1H), 3.978 (t, *J* = 13.2 Hz, 2H), 1.625-1.862 (m, 2H), 1.425-1.582 (m, 5H), 0.998-1.256 (m, 6H), 0.747-0.869 (m, 2H).

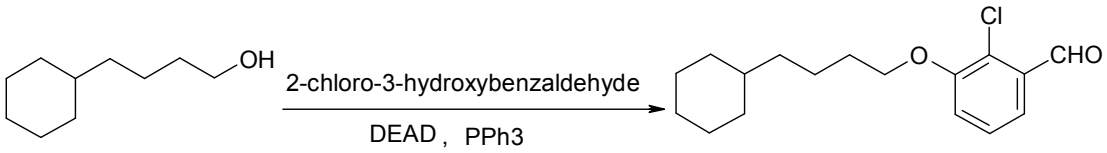
81b: 5-(2-chloro-3-(cyclohexylpropoxy)benzylidene)thiazolidine-2,4-dione



81a **81b**

81b: yield 74.1%; ^{1}H NMR (300 MHz, DMSO-d_6) δ7.943 (s, 1H), 7.521 (d, *J* = 9.3 Hz, 1H), 7.261-7.333 (m, 1H), 7.152 (d, *J* = 9.3 Hz, 1H), 4.045 (t, *J* = 13.2 Hz, 2H), 1.829-1.925 (m, 2H), 1.578-1.731 (m, 5H), 1.091-1.426 (m, 6H), 0.859-0.883 (m, 2H).

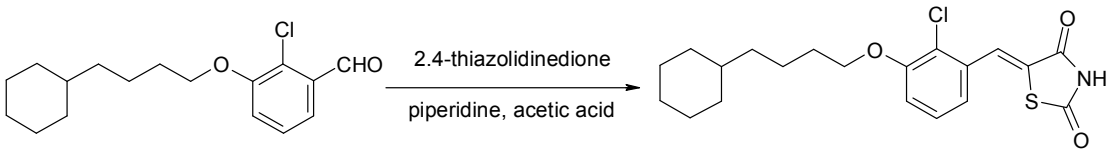
82a: 2-chloro-3-(cyclohexylbutoxy)benzaldehyde



82a

82a: yield 79.3%; ^{1}H NMR (300 MHz, $CDCl_3$) δ10.226 (s, 1H), 7.332 (d, *J* = 9.3 Hz, 1H), 7.398 (m, 1H), 7.114 (d, *J* = 9.3 Hz, 1H), 4.006 (t, *J* = 13.2 Hz, 2H), 1.810-1.8993 (m, 2H), 1.520-1.756(m, 5H), 1.144-1.499 (m, 8H), 0.900-0.999 (m, 2H).

82b: 5-(2-chloro-3-(cyclohexylbutoxy)benzylidene)thiazolidine-2,4-dione

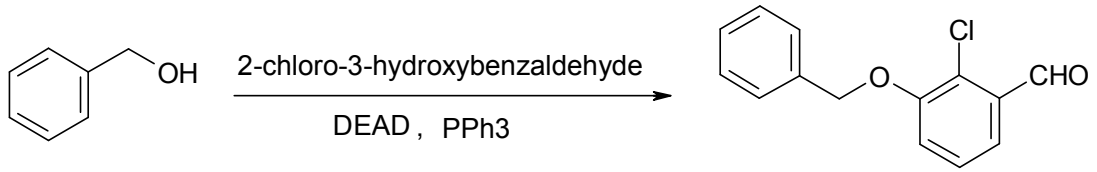


82a **82b**

82b: yield 83.6%; ^{1}H NMR (300 MHz, DMSO-d_6) δ7.894 (s, 1H), 7.496 (d, *J* = 9.3 Hz, 1H),

7.264-7.342 (m, 1H), 7.203 (d, *J* = 9.3 Hz, 1H), 4.103 (t, *J* = 13.2 Hz, 2H), 1.839-1.913 (m, 2H), 1.569-1.726 (m, 5H), 1.089-1.436 (m, 8H), 0.912-0.998 (m, 2H).

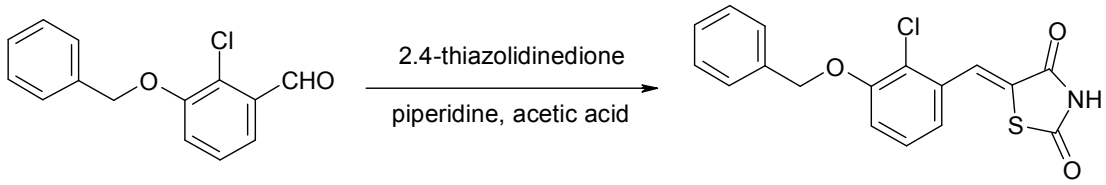
83a: 3-(benzyloxy)-2-chloroben zaldehyde



83a

83a: yield 74.1%; ^{1}H NMR (300 MHz, $CDCl_3$) δ7.753 (s, 1H), 7.498 (d, *J* = 7.8 Hz, 1H), 7.339-7.413 (m, 6H), 7.241 (d, *J* = 7.8 Hz, 1H), 5.243 (s, 2H).

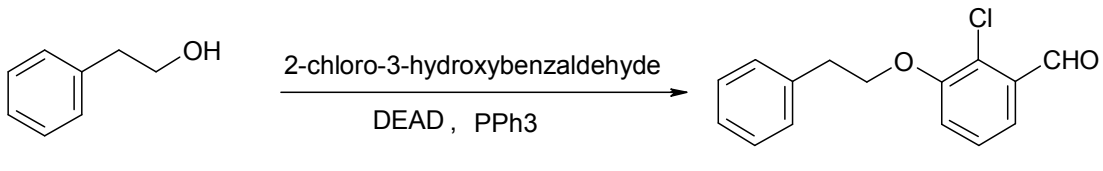
83b: 5-(3-(benzyloxy)-2-chlorobenzylidene)thiazolidine-2,4-dione



83a **83b**

83b: yield 75%; ^{1}H NMR (300 MHz, DMSO-d_6) δ7.753 (s, 1H), 7.498 (d, *J* = 7.8 Hz, 1H), 7.339-7.413 (m, 6H), 7.241 (d, *J* = 7.8 Hz, 1H), 5.243 (s, 2H).

84a: 2-chloro-3-phenethoxybenzaldehyde

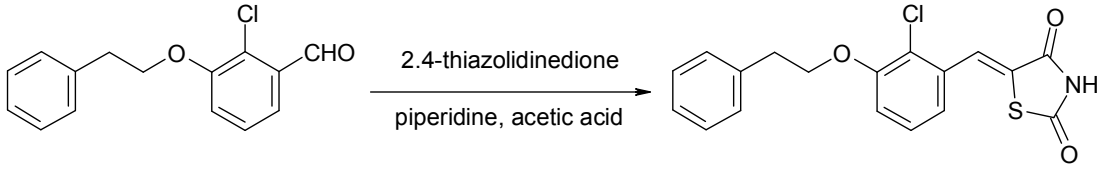


84a

84a: yield 75.1%; ^{1}H NMR (300 MHz, $CDCl_3$) δ10.151 (s, 1H), 7.299 (d, *J* = 7.8 Hz, 1H),

7.112-7.386 (m, 6H), 7.002 (d, *J* = 7.8 Hz, 1H), 4.321 (t, *J* = 13.5 Hz, 2H), 2.981 (t, *J* = 13.2 Hz, 2H).

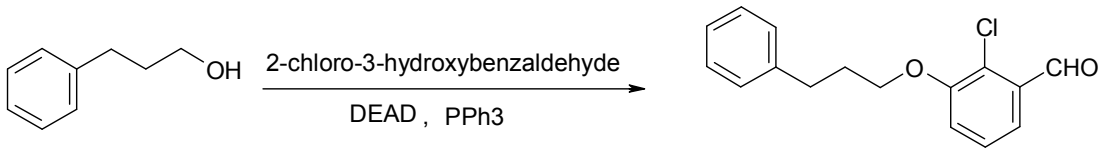
84b: 5-(2-chloro-3-phenethoxybenzylidene)thiazolidine-2,4-dione



84a **84b**

84b: yield 77.5%; ^{1}H NMR (300 MHz, DMSO-d_6) δ7.894 (s, 1H), 7.459 (d, *J* = 7.8 Hz, 1H), 7.141-7.495 (m, 6H), 7.164 (d, *J* = 7.8 Hz, 1H), 4.328 (t, *J* = 13.5 Hz, 2H), 3.107 (t, *J* = 13.2 Hz, 2H).

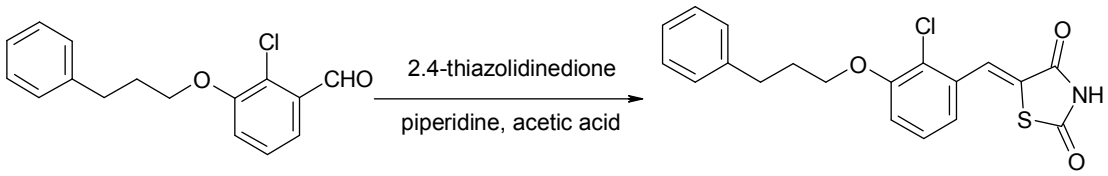
85a: 2-chloro-3-(3-phenylpropoxy)benzaldehyde



85a

85a: yield 64.6%; ^{1}H NMR (300 MHz, $CDCl_3$) δ10.120 (s, 1H), 7.337 (t, *J* = 7.8 Hz, 1H), 7.106 – 7.211 (m, 7H), 4.025 (t, *J* = 12.3 Hz, 2H), 2.685 (t, *J* = 12.5 Hz, 2H), 2.001 (t, *J* = 13.2 Hz, 2H).

85b: 5-(2-chloro-3-(3-phenylpropoxy)benzylidene)thiazolidine-2,4-dione

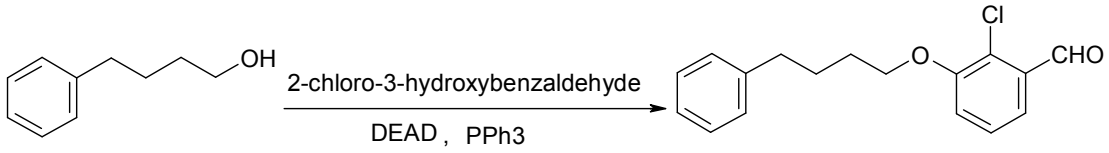


85a **85b**

85b: yield 82.4%; ^{1}H NMR (300 MHz, DMSO-d_6) δ7.927 (s, 1H), 7.464 (t, *J* = 7.8 Hz, 1H),

7.151 – 7.312 (m, 7H), 4.109 (t, *J* = 12.3 Hz, 2H), 2.813 (t, *J* = 12.5 Hz, 2H), 2.084 (t, *J* = 13.2 Hz, 2H).

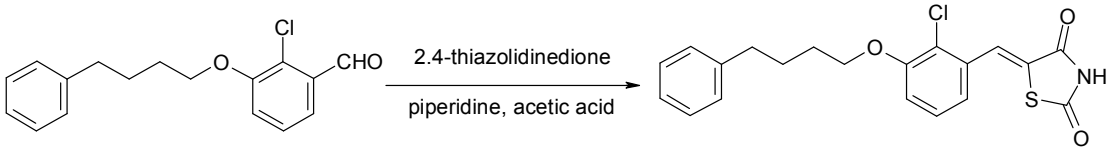
86a: 2-chloro-3-(4-phenylbutoxy)ben zaldehyde



86a

86a: yield 72.9%; ^{1}H NMR (300 MHz, $CDCl_3$) δ10.144 (s, 1H), 7.274 (t, *J* = 8.1 Hz, 1H), 7.011-7.233 (m, 7H), 4.011 (t, *J* = 5.1 Hz, 2H), 2.458 (t, *J* = 5.3 Hz, 2H), 2.042 (t, *J* = 2.7 Hz, 4H).

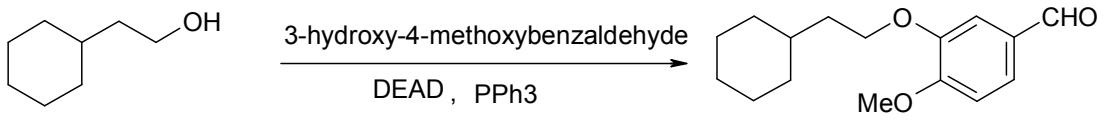
86b: 5-(2-chloro-3-(4-phenylbutoxy)benzylidene)thiazolidine-2,4-dione



86a **86b**

86b: yield 82.1%; ^{1}H NMR (300 MHz, DMSO-d_6) δ12.719 (s, 1H), 7.932 (s, 1H), 7.474 (t, *J* = 8.1 Hz, 1H), 7.151-7.303 (m, 7H), 4.145 (t, *J* = 5.1 Hz, 2H), 2.658 (t, *J* = 5.3 Hz, 2H), 2.084 (t, *J* = 2.7 Hz, 4H).

87a: 3-(2-cyclohexyleyhoxy)-4-methoxybenzaldehyde (87a)

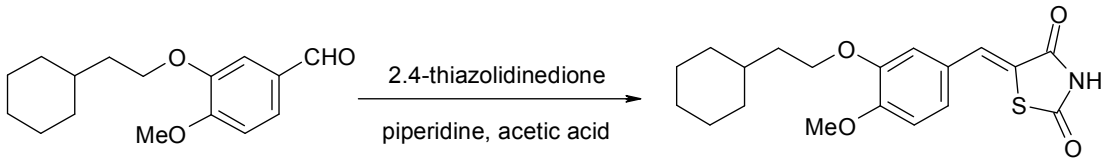


87a

87a: yield 82.1%; ^{1}H NMR (300 MHz, $CDCl_3$) δ9.847 (s, 1H), 7.460 (d, *J* = 9.5 Hz, 1H), 7.427 (s, 1H), 6.987 (d, *J* = 9.5 Hz, 1H), 4.136 (t, *J* = 13.5 Hz, 2H), 3.686 (s, 3H), 1.528-1.743 (m, 7H),

1.445-1.505 (m, 1H), 1.157-1.439 (m, 3H), 0.939-1.058 (m, 2H).

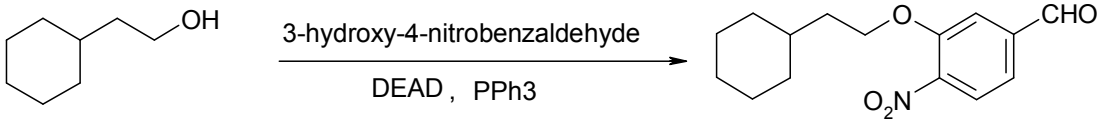
87b: 5-(3-(2-cyclohexylethoxy)-4-methoxybenzylidene)thiazolidine-2,4-dione



87a **87b**

87b: yield 87.2%; ^{1}H NMR (300 MHz, DMSO-d_6) δ12.436 (s, 1H), 8.165 (s, 1H), 7.941 (d, J = 9.5 Hz, 1H), 7.661 (s, 1H), 7.273 (d, J = 9.5 Hz, 1H), 4.233 (t, J = 13.5 Hz, 2H), 3.864 (s, 3H), 1.682-1.759 (m, 7H), 1.442-1.586 (m, 1H), 1.182-1.242 (m, 3H), 0.896-0.926 (m, 2H).

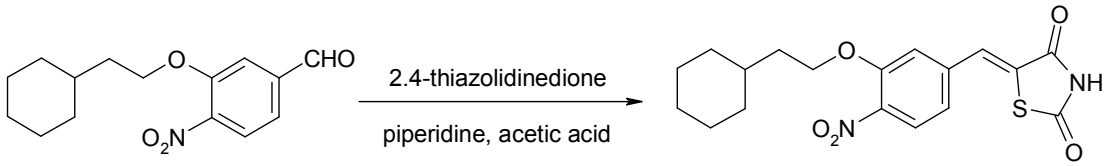
88a: 3-(2-cyclohexylethoxy)-4-nitrobenzaldehyde



88a

88a: yield 82.4%; ^{1}H NMR (300 MHz, $CDCl_3$) δ10.041 (s, 1H), 7.909 (d, J = 8.4 Hz, 1H), 7.574 (s, 1H), 7.500 (s, J = 8.4 Hz, 1H), 4.239 (t, J = 13.5 Hz, 2H), 1.549-1.765 (m, 7H), 1.334-1.501 (m, 1H), 1.019-1.305 (m, 3H), 0.924-0.993 (m, 2H).

88b: 5-(3-(2-cyclohexylethoxy)-4-nitrobenzylidene)thiazolidine-2,4-dione

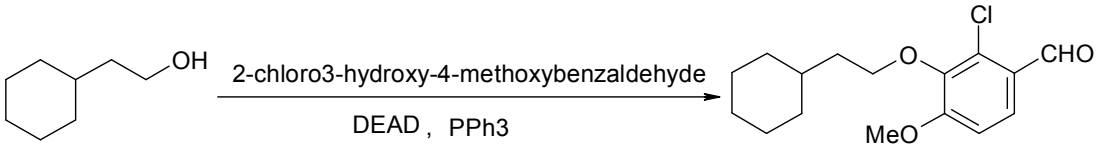


88a **88b**

88b: yield 87%; ^{1}H NMR (300 MHz, DMSO-d_6) δ12.644 (s, 1H), 8.003 (d, J = 8.4 Hz, 1H), 7.799 (s, 1H), 7.611 (s, 1H), 7.273 (s, J = 8.4 Hz, 1H), 4.255 (t, J = 13.5 Hz, 2H), 1.618-1.746 (m,

7H), 1.401-1.546 (m, 1H), 1.144-1.323 (m, 3H), 0.928-0.1.006 (m, 2H).

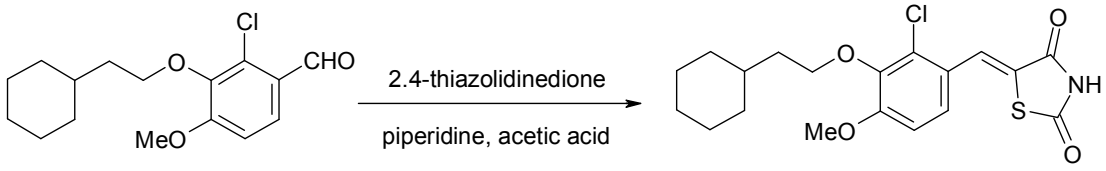
89a: 2-chloro-3-(2-cyclohexylethoxy)-4-methoxybenzaldehyde



89a

89a: yield 88.3%; ^{1}H NMR (300 MHz, $CDCl_3$) δ10.346 (s, 1H), 7.734 (s, J = 8.7 Hz, 1H), 6.926 (s, J = 8.7 Hz, 1H), 4.067 (t, J = 12.6 Hz, 2H), 3.92 (s, 3H), 1.610-1.77 (m, 8H), 1.109-1.352 (m, 3H), 0.901-1.028 (m, 2H).

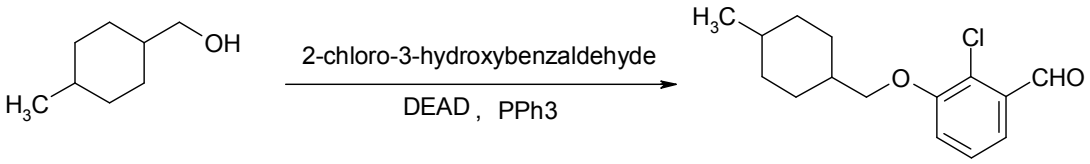
89b: 5-(2-chloro-3-(2-cyclohexylethoxy)-4-methoxybenzylidene)thiazolidine-2,4-dione



89a **89b**

89b: yield 78.1%; ^{1}H NMR (300 MHz, DMSO-d_6) δ12.743 (s, 1H), 7.319 (s, J = 8.7 Hz, 1H), 7.247 (s, J = 8.7 Hz, 1H), 4.007 (t, J = 12.6 Hz, 2H), 3.890 (s, 3H), 1.516-1.764 (m, 8H), 1.109-1.245 (m, 3H), 0.894-0.970 (m, 2H).

90a: 2-chloro-3-[(4-methylcyclohexyl)methoxy]benzaldehyde (90a)

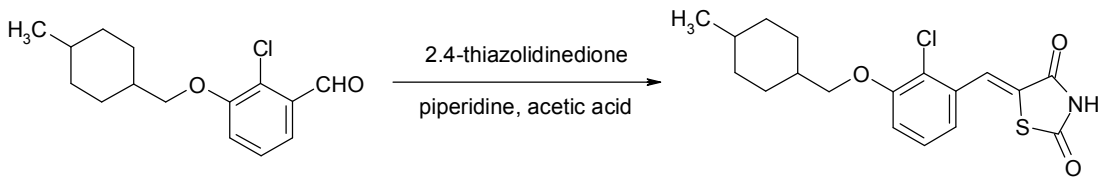


90a

90a: yield 84.6%; ^{1}H NMR (300 MHz, $CDCl_3$) δ10.103 (s, 1H), 7.147 (m, 1H), 7.003 (d, J = 9.3 Hz, 1H), 6.912 (d, J = 9.3 Hz, 1H), 3.798 (d, J = 7.2 Hz, 2H), 1.989-2.042 (m, 1H), 1.369-

1.598 (m, 5H), 1.096-1.290 (m, 2H), 0.987 (d, *J* = 6.9 Hz, 1H), 0.748-0.897 (m, 2H).

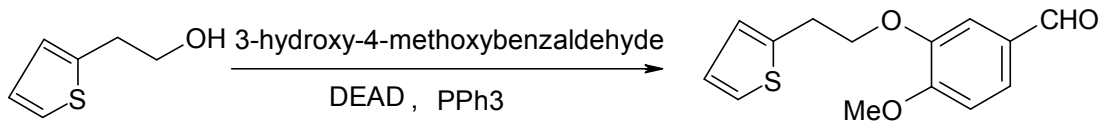
90b: 5-{2-chloro-3-[(4-methylcyclohexyl)methoxy]benzylidene}-1,3-thiazolidine-2,4-dione



90a **90b**

90b: yield 81.2%; ^{1}H NMR (300 MHz, DMSO-d_6)) δ8.242 (s, 1H), 7.262 (m, 1H), 7.111 (d, *J* = 9.3 Hz, 1H), 7.025 (d, *J* = 9.3 Hz, 1H), 3.961 (d, *J* = 7.2 Hz, 2H), 2.038-2.076 (m, 1H), 1.456-1.810 (m, 5H), 1.233-1.339 (m, 2H), 0.954 (d, *J* = 6.9 Hz, 1H), 0.900-1.416 (m, 2H).

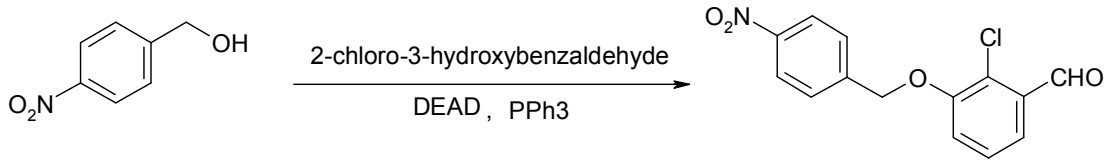
91a: 4-methoxy-3-(2-(thiophen-2-yl)ethoxy)benzaldehyde (91a)



91a

91a: yield 79.2%; ^{1}H NMR (300 MHz, $CDCl_3$) δ10.006 (s, 1H), 7.325 (d, *J* = 6.3 Hz, 1H), 7.198 (d, *J* = 1.8 Hz, 1H), 7.097 (d, *J* = 1.8 Hz, 1H), 7.011 (s, 1H), 6,847-6.896 (m, 2H), 4.014 (t, *J* = 13.2 Hz, 2H), 3.745 (s, 3H), 3.069 (t, *J* = 13.2 Hz, 2H).

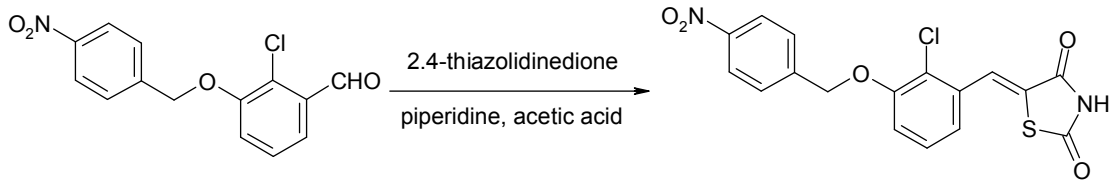
92a: 2-chloro-3-(4-nitrobenzyloxy)benzaldehyde (92a)



92a

92a: yield 82.1%; ^{1}H NMR (300 MHz, $CDCl_3$) δ8.405 (s, 1H), 8.300 (d, *J* = 9 Hz, 2H), 7.763 (d, *J* = 9 Hz, 2H), 7.451 (t , *J* = 8.1 Hz, 1H), 7.249 (t, *J* = 7.5 Hz, 2H), 5.419 (s, 2H).

92b: 5-(2-chloro-3-(4-nitrobenzyloxy)benzylidene)thiazolidine-2,4-dione

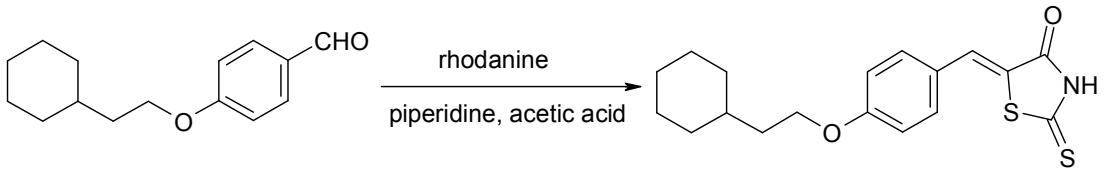


92a **92b**

92b: yield 78.4%; ^{1}H NMR (300 MHz, DMSO-d_6) δ10.379 (s, 1H), 8.304 (d, J = 9 Hz, 2H), 7.770 (d, J = 9 Hz, 2H), 7.536 (m, 1H), 7.469 (t, J = 7.5 Hz, 2H), 5.419 (s, 2H).

Synthesis of compounds 93 - 98

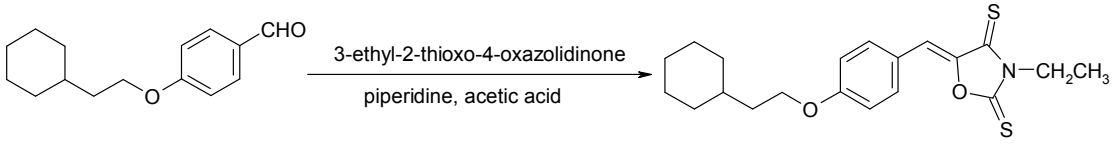
93: 5-(4-(2-cyclohexylethoxy)benzylidene)-4-thioxothiazolidindin-2-one



3a **93**

To a solution of **4-(2-cyclohexylethoxy)benzaldehyde** (1 g, 4.3 mmol) and rhodanine (504 mg, 4.3 mmol) in toluene (20 mL) was added piperidine (0.21 mL, 2.15 mmol), acetic acid (0.14 mL, 2.15 mmol). The procedure was described as the preparation of **3b** to afford **93** (1.15 g, 81%) as yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ7.758 (s, 1H) 7.499 (d, J = 14.7 Hz, 2H), 6.970 (d, J = 14.7Hz, 2H), 4.036 (t, J =11.7 Hz, 2H), 3.575 (s, 1H), 1.704 (t, J = 11.7 Hz, 2H), 1.565-1.756 (m, 5H), 1.434-1.528 (m, 1H), 1.103-1.260 (m, 3H), 0.907-1.029 (m, 2H).

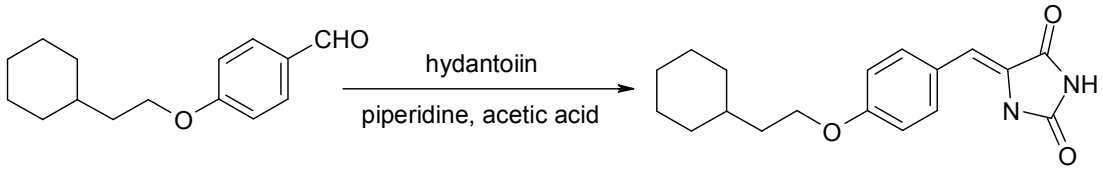
94: 3-(4-(2-cyclohexylethoxy)benzylidene)-3-ethyloxazolidine-2,4-dione



3a **94**

94: yield 84%; ^{1}H NMR (300 MHz, $CDCl_3$) δ7.806 (d, *J* = 11.7 Hz, 2H), 6.969 (d, *J* = 11.7 Hz, 2H), 6.714 (s, 1H), 4.076 (t, *J* = 13.5 Hz, 2H), 4.006 (q, *J*= 14.7 Hz, 2H), 1.714 (t, *J* = 13.5 Hz, 2H), 1.568-1.786 (m, 4H), 1.568-1.462 (m, 1H), 1.354 (t, *J* = 14.7 Hz, 3H), 1.106-1.269 (m, 4H), 0.910-1.033 (m, 2H).

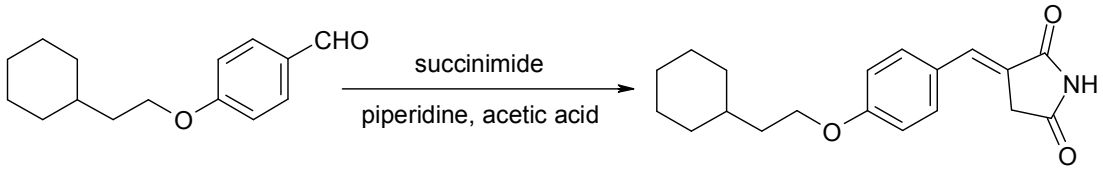
95: 5-(4-(2-cyclohexylethoxy)benzylidene)imidazolidine-2,4-dione



3a **95**

95: yield 83%; ^{1}H NMR (300 MHz, DMSO-d_6) δ11.213 (s, 1H), 10.374 (s, 1H), 7.517 (d, *J* = 7.8 Hz, 2H), 6.884 (d, *J* = 7.8 Hz, 2H), 6.315 (s, 1H), 3.935 (t, *J* = 12.6 Hz, 2H), 1.655 (t, *J* = 12.6 Hz, 2H), 1.577-1.922 (m, 4H), 1.028-1.269 (m, 5H), 0.787-0.862 (s, 2H).

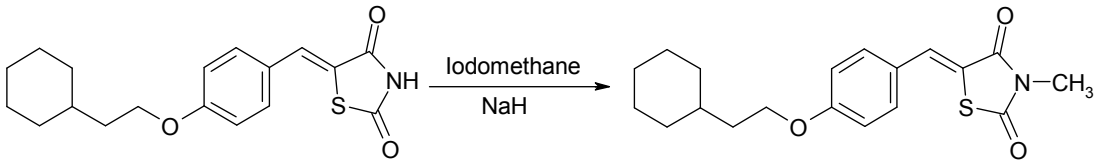
96: 3-(4-(2-cyclohexylethoxy)benzylidene)pyrrolidine-2,5-dione



3a **96**

96: yield 84%; ^{1}H NMR (300 MHz, $CDCl_3$) δ8.306 (s, 1H), 7.296 (s, 1H), 7.055 (d, *J* = 11.7 Hz, 2H), 6.838 (d, *J* = 11.7 Hz, 2H), 3.992 (t, *J* = 13.2 Hz, 2H), 3.854 (s, 2H), 1.627 (t, *J* = 13.2 Hz, 2H), 1.523-1.772 (m, 6H), 1.430-1.513 (m, 1H), 1.134-1.271 (m, 2H), 0.904-1.012 (m, 2H).

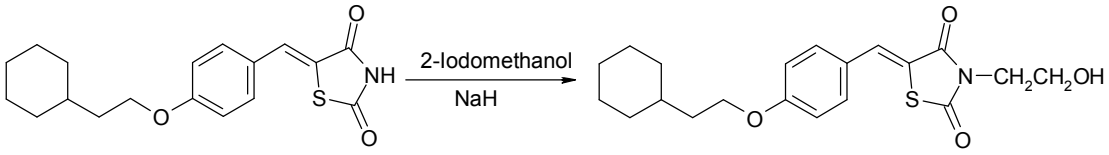
97: 5-[4-(2-cyclohexylethoxy)benzylidene]-3-methyl-1,3-thiazolidine-2,4-dione



3b **97**

Sodium hydride (40.56 mg, 1.01mol, 60% dispersion in oil) was added to a solution of **3b** (160 mg, 0.48 mmol) in THF (20 mL) at 0℃over 10 min with stirring under nitrogen. The mixture was then stiired for 10 min. A solution of Iodomethane (205.54 mg, 1.45 mmol) in THF (5 mL) was added slowly. The mixture was then striied for 3 h, after which the reaction mixture was extracted with ethyl acetate and washed with water. The organic layer was dried used magnesium sulfate anhydrous, filtered and evaporated. The residual oil was purified by chromatography over silica gel (elution with hexane/ethyl acetate, 10 : 1) to afford 142 mg of **97** (85%) as white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ7.866 (s, 1H), 7.483 (d, *J* = 8.7 Hz, 2H), 6.992 (d, *J* = 8.7 Hz, 2H), 4.075 (t, *J* = 13.2 Hz, 2H), 3.244 (s, 3H), 1.668-1.782 (m, 4H), 1.446-1.539 (m, 1H), 1.105-1.255 (m, 4H), 0.832-1.047 (m, 4H).

98: 5-[4-(2-cyclohexylethoxy)benzylidene]-3-(hydroxyethyl)-1,3-thiazolidine-2,4-dione



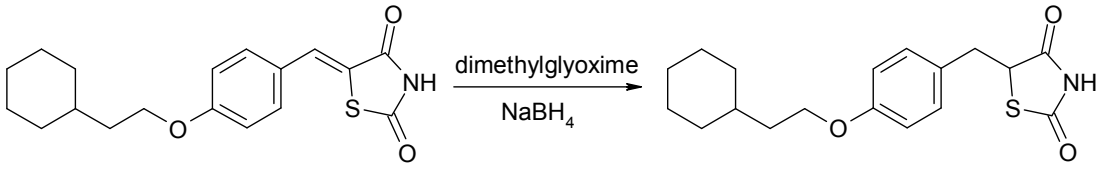
3b **98**

Sodium hydride (24.14 mg, 1.0 mmol, 60% dispersion in oil) was added to a solution of TD9 (200 mg, 0.60 mmol) in DMF (20 mL) at room temperature with stirring under nitrogen. The mixture was then stiired for 10 min. A solution of 2-Iodoethanol (123.81 mg, 0.72 mmol) in DMF (5 mL) was added slowly and was striied at 60℃ for 48 h. The procedure was described as the preparation of **97** to give **98** (82%); ^{1}H NMR (300 MHz, $CDCl_3$) δ7.878 (s, 1H), 7.485 (d, *J* = 14.4 Hz, 2H), 7.007 (d, *J* = 14.4 Hz, 2H), 4.078 (t, *J* = 13.2 Hz, 2H), 4.001 (t, *J* = 10.2 Hz, 2H), 3.891 (t, *J* = 10.2 Hz, 2H), 2.049 (m, 1H), 1.670-1.782 (m, 7H), 1.471-1.529 (m,

1H), 1.178-1.284 (m, 3H), 0.956-1.034 (m, 2H).

Synthesis of compounds 99 - 106

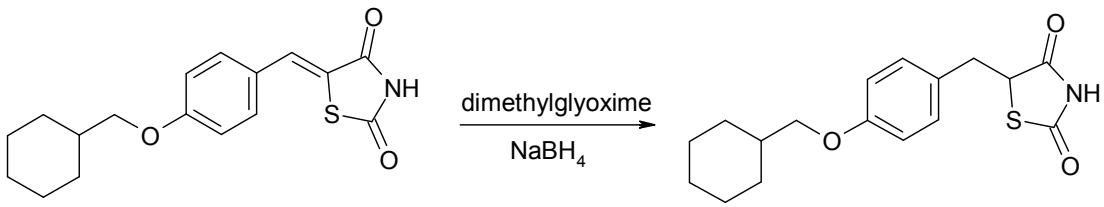
99: 5-(4-(2-cyclohexylethoxy)benzyl) thiazolidine-2,4-dione



3b **99**

To a stirring solution of $CoCl_2 \cdot 6H_2O$ (4.5 mg, 0.015 mmol) and dimethylglyoxime (70.1 mg, 0.6 mmol) in H_2O (10 mL) was added 1.0 N NaOH (4 drops) followed by $NaBH_4$ (384.6 mg, 10 mmol) and the mixture was cooled to 0℃. A solution of the **3b** (1 g, 3.02 mmol) in THF-DMF (2 : 1, 15 mL) was added over 20 min. The mixture was stirred 18 h at room temperature. Acetic acid was added until the PH of the mixture was approximately 6. The mixture was then diluted with H_2O and extracted with ethyl acetate and water. The organic layer was washed several times with water and dried used magnesium sulfate anhydrous, filtered and evaporated. The residual oil was purified by chromatography over silica gel (elution with hexane/ethyl acetate, 20 : 1) to afford **99** as white solid (0.8 g, 79%); ^{1}H NMR (300 MHz, DMSO-d_6) δ11.998 (s, 1H), 7.135 (d, J = 7.5 Hz, 2H), 6.861 (d, J = 7.5 Hz, 2H), 4.870 (dd, J = 3.3, 4.8 Hz, 1H), 3.966 (t, J = 12.9 Hz, 2H), 3.250 (dd, J = 4.5, 10.2 Hz, 1H), 3.07 (dd, J = 8.7, 5.1 Hz, 1H), 1.548-1.615 (m, 7H), 1.433-1.548 (m, 1H), 1.097-1.261 (m, 3H), 0.869-0.977 (m, 2H).

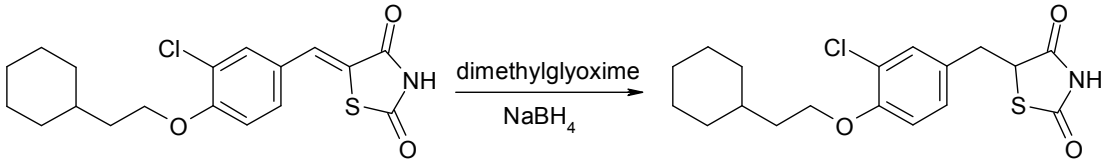
100: 5-(4-(cyclohexylmethoxy)benzyl)thiazolidine-2,4-dione



2b **100**

100: yield 85.4%; ^{1}H NMR (300 MHz, $CDCl_3$) δ7.810 (s, 1H), 7.145 (d, *J* = 8.7 Hz, 2H), 6.854 (d, *J* = 8.7 Hz, 2H), 4.528 (dd, *J* = 3.6, 6.0 Hz, 1H), 3.740 (d, *J* = 6.6 Hz, 2H), 3.486 (dd, *J* = 4.2, 10.2 Hz, 1H), 3.138 (dd, *J* = 9.6, 4.8 Hz, 1H), 1.604-1.882 (m, 6H), 1.142-1.426 (m, 3H), 0.976-1.313 (m, 2H).

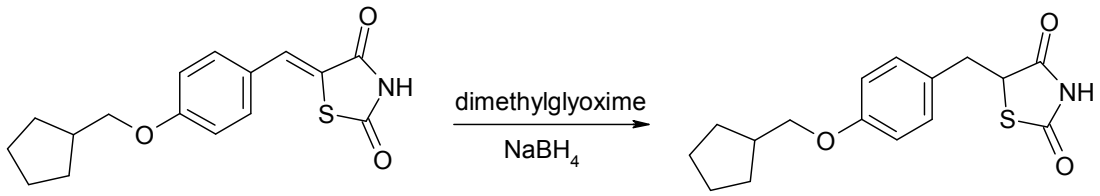
101: 5-(3-chloro-4-(2-cyclohexylethoxy)benzyl)thiazolidine-2,4-dione



43b **101**

101: yield 81.5%; ^{1}H NMR (300 MHz, $CDCl_3$) δ7.900 (s, 1H), 7.242 (s, 1H), 7.078 (d, *J* = 10.8 Hz, 1H), 6.913 (d, *J* = 10.8 Hz, 1H), 4.523 (dd, *J* = 3.9, 5.1 Hz, 1H), 4.068 (t, *J* = 13.5 Hz, 2H), 3.447 (dd, *J* = 4.2, 10.2 Hz, 1H), 3.134 (dd, *J* = 9.3, 4.8 Hz, 1H), 1.689-1.793 (m, 7H), 1.504-1.572 (m, 1H), 1.144-1.329 (m, 3H), 0.926-1.037 (m, 2H).

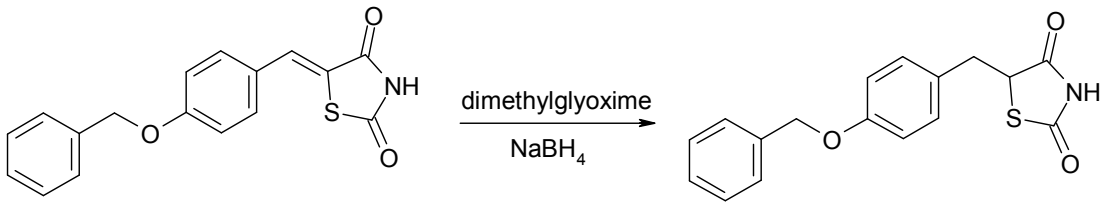
102: 5-(4-(cyclopentylmethoxy)benzyl)thiazolidine-2,4-dione



22b **102**

102: yield 78.6%; ^{1}H NMR (300 MHz, $CDCl_3$) δ7.742 (s, 1H), 7.146 (d, *J* = 8.7 Hz, 2H), 6.874 (d, *J* = 8.7 Hz, 2H), 4.531 (dd, *J* = 4.2, 5.4 Hz, 1H), 3.819 (d, *J* = 6.9 Hz, 2H), 3.469 (dd, *J* = 3.9, 10.5 Hz, 1H), 3.145 (dd, *J* = 9.3, 4.5 Hz, 1H), 2.302-2.402 (m, 1H), 1.799-1.867 (m, 2H), 1.565-1.646 (m, 4H), 1.319-1.384 (m, 2H).

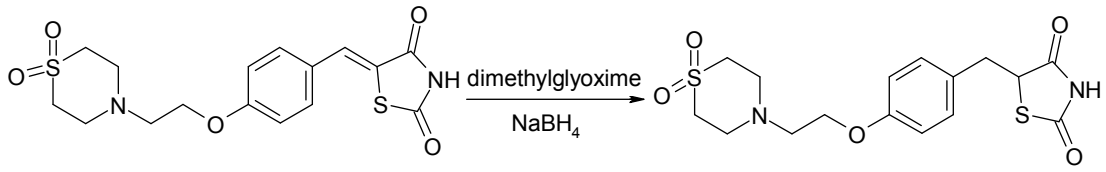
103: 5-(4-(benzyloxy)benzyl)thiazolidine-2,4-dione



30b **103**

103: yield 82.5%; ^{1}H NMR (300 MHz, $CDCl_3$) δ7.444 (s, 1H), 7.308-7.418 (m, 5H), 7.167 (d, *J* = 8.7 Hz, 2H), 6.947 (d, *J* = 8.7 Hz, 2H), 5.052 (s, 2H), 4.533 (dd, *J* = 3.9, 5.7 Hz, 1H), 3.487 (dd, *J* = 4.2, 10.2 Hz, 1H), 3.156 (dd, *J* = 9.0, 4.8 Hz, 1H).

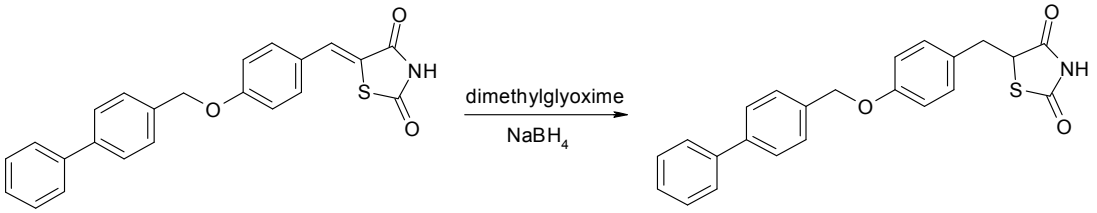
104: 5-(4-(2-Thiomorpholine 1,1-Dioxideethoxy)benzyl)-2,4-thiazolidinedione



6b **104**

104: yield 77.6%; ^{1}H NMR (300 MHz, $CDCl_3$) δ7.728 (s, 1H), 7.238 (s, 1H), 7.568 (d, *J* = 9.3 Hz, 2H), 6.893 (d, *J* = 9.3 Hz, 2H), 4.887 (dd, *J* = 4.2, 4.8 Hz, 1H), 4.163 (t, *J* = 11.4 Hz, 2H), 4.069 (t, *J* = 11.4 Hz, 2H), 3.095 (m, 8H), 2.957 (m, 2H).

105: 5-(4-(biphenyl-4-ylmethoxy)benzyl)thiazolidine-2,4-dione

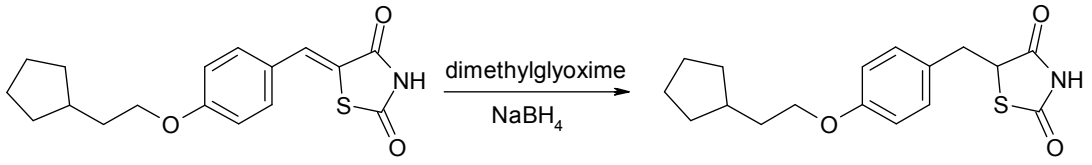


36b **105**

105: yield 80.5%; ^{1}H NMR (300 MHz, $CDCl_3$) δ7.727 (s, 1H), 7.661-7.703 (m, 4H), 7.435-7.578 (m, 4H), 7.205-7.359 (m, 1H), 7.205 (d, *J* = 8.7 Hz, 2H), 6.952 (d, *J* = 8.7 Hz, 2H), 5.112 (s, 2H), 4.894 (dd, *J* = 4.2, 5.6 Hz, 1H), 3.381 (dd, *J* = 4.2, 10.2 Hz, 1H), 3.089 (dd, *J* = 8.7, 4.6 Hz,

1H).

106: 5-(4-(2-cyclopentylethoxy)benzyl)thiazolidine-2,4-dione

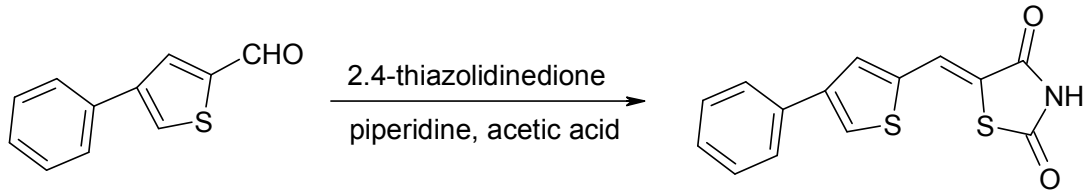


23b **106**

106: yield 81.6%; ^{1}H NMR (300 MHz, $CDCl_3$) δ7.926 (s, 1H), 7.148 (d, *J* = 8.4 Hz, 2H), 6.86 (d, *J* = 8.4 Hz, 2H), 4.529 (dd, *J* = 3.6, 5.4 Hz, 1H), 3.98 (t, *J* = 13.5 Hz, 2H), 3.485 (dd, *J* = 3.9, 10.2 Hz, 1H), 3.143 (dd, *J* = 9.6, 4.5 Hz, 1H), 1.810-1.845 (m, 1H), 1.764-1.787 (m, 4H), 1.510-1.623 (m, 4H), 1.125-1.192 (m, 2H).

Synthesis of compound 107 - 109

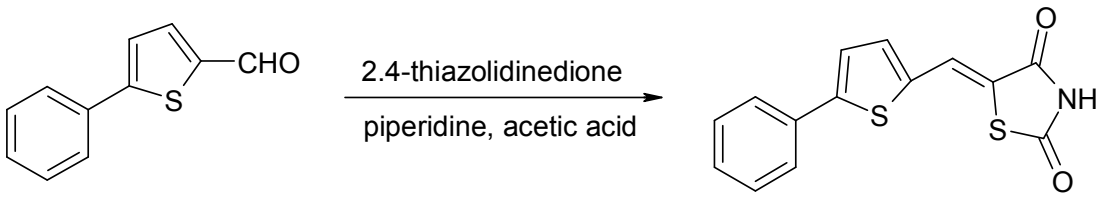
107: 5-((4-phenylthiophen-2-yl)methylene)thiazolidine-2,4-dione



107

To a solution of 4-phenylthiophene-2-carboxaldehyde (1 g, 4.3 mmol) and 2,4-thiazolidinedione (504 mg, 4.3 mmol) in toluene (20 mL) was added piperidine (0.21 ml, 2.15 mmol), acetic acid (0.14 ml, 2.15 mmol) subsequently, the mixture was boiled under reflux in a Dean-Stark water trap overnight. Then the mixture was cooled and filtered, the precipitate washed with ether or hexane and dried in the oven to give **107** (1.19 g, 83%); ^{1}H NMR (300 MHz, DMSO-d_6) δ12.606 (s, 1H), 8.312 (s, 1H), 8.086 (d, *J* = 9.6 Hz, 2H), 7.738 (d, *J* = 9.6 Hz, 2H), 7.47 (m, 2H), 7.313-7,362 (m, 1H).

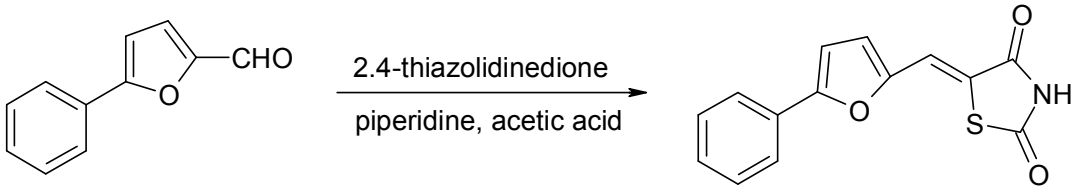
108: 5-[(5-phenylthiophen-2-yl)methylidene]-1,3-thiazolidine-2,4-dione



108

108: yield 84.3%; ^{1}H NMR (300 MHz, DMSO-d_6) δ12.560 (s, 1H), 8.026 (s, 1H), 7.770 (d, J = 8.7 Hz, 2H), 7.719 (q, J = 11.7 Hz, 2H), 7.462 (t, J = 14.7 Hz, 2H), 7.359-7.392 (m, 1H).

109: 5-[(5-phenylfuran-2-yl)methylidene]-1,3-thiazolidine-2,4-dione



109

109: yield 86.1%; ^{1}H NMR (300 MHz, DMSO-d_6) δ12.465 (s, 1H), 8.271 (s, 1H), 7.835 (d, J = 1.2 Hz, 2H), 7.807 (s, 1H), 7.551 (t, J = 15.3 Hz, 2H), 7.423 (t, J = 15.0 Hz, 1H), 7.284 (d, J = 3.6 Hz, 1H), 7.234 (d, J = 3.6 Hz, 1H).

4. Conclusion

PGE_2 has been implicated in a wide variety of physiological and pathological processes. PGE_2 is short-lived in vivo since it is rapidly metabolized by first oxidation to 15-ketoprostaglandins catalyzed by cytosolic enzyme 15-PGDH. Various pharmacological agents of diverse structures have been reported for their inhibition of 15-PGDH. Among these compounds, only 2-hydroxy-5-(3, 5-dimethoxycarbonyl-benzoyl)benzene acetic acid, a sulfasalazine analoge, was found to inhibit the enzyme at nanomolar range. Inhibition appears to be noncompetitive with respect to both prostaglandin substrate and NAD^+. However, this compound is of azo nature and may rapidly undergo decomposition following absorption. TDs compound **CT-8** is chemically stable. Thiazolidinediones have been used in clinical trials as antidiabetic agents. The use of TDs as chemopreventive agent in animal model is currently under investigation. Recently, knockout mice deficient in 15-PGDH have been generated. It has been shown that metabolism of PGE_2 by 15-PGDH is essential for remodeling the ductus arteriosus. Therefore, inhibitors of 15-PGDH may be useful in the clinical management of ductus-dependent congenital heart defects in which elevated PGE_2 levels are deemded to be investigators, more physiological and pathological roles of 15-PGDH will be uncovered. Inhibitors of 15-PGDH will be valuable for the therapeutic management of disease in which elevated prostaglandin levels are needed.

In conclusion, series of TDs were designed, synthesized and evaluated for their 15-PGDH inhibitory activities. We introduced $-CH_2$ group between cyclohexyl ring and ether linkage of compound **CT-8**. The number of $-CH_2$ was increased and followed by the optimal for inhibitory

activity observed at two -CH_2 linkage. Replacement of the cyclohexyl ring with a benzene ring decreased significantly the inhibitory potency. Replacement of cyclohexane by the 5-member ring resulted in a significant increase in its 15-PGDH inhibitory potency. Substitutions on the central aromatic ring of CT-8 with either electron withdrawing or donating group resulted in increasing of the 15-PGDH inhibitory activity. The olefinic bond between central aromatic ring and 2,4-thiazolidinedione ring appears to orient the molecule more favorably toward the binging site in this enzyme. It was also interesting to discover that the amine group of thiazolidine-2, 4-dione plays an important role in the inhibitory potency. 109 thiazolidinedione derivatives we synthesized and the compound **43b** 5-(3-chloro-4-(2-cyclohexylethoxy)benzylidene)thiazolidine-2,4-dione was the most potent inhibitor that was effective in the nanomolar range.

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^{1}H NMR Spectra

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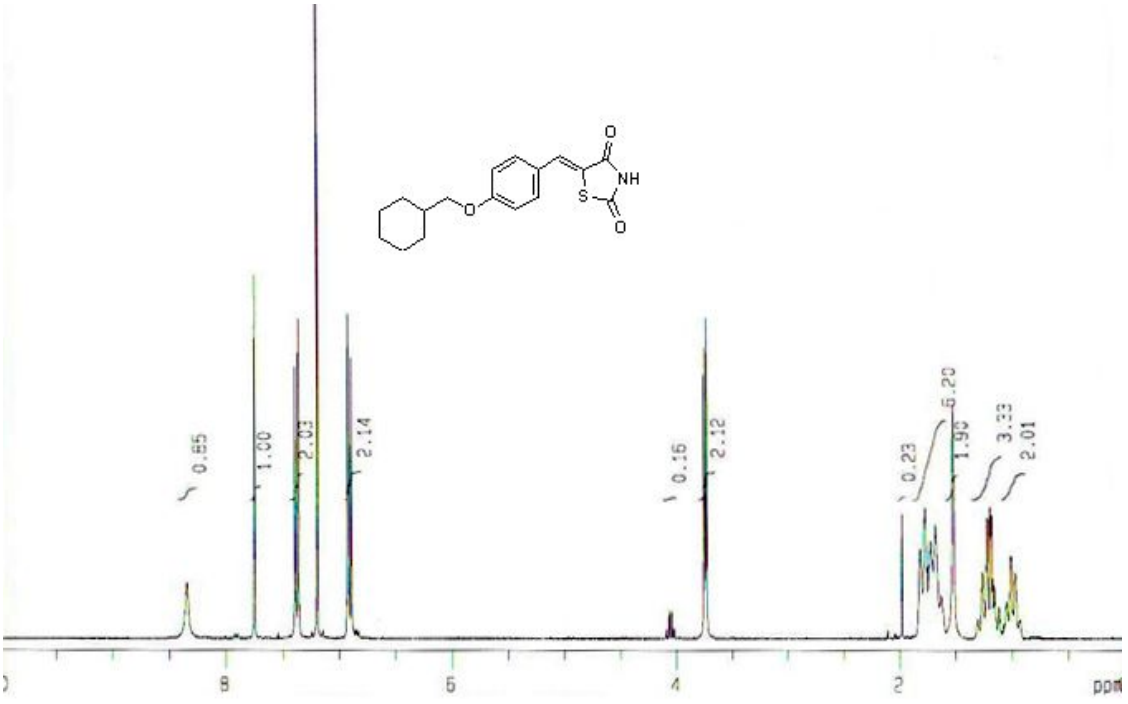

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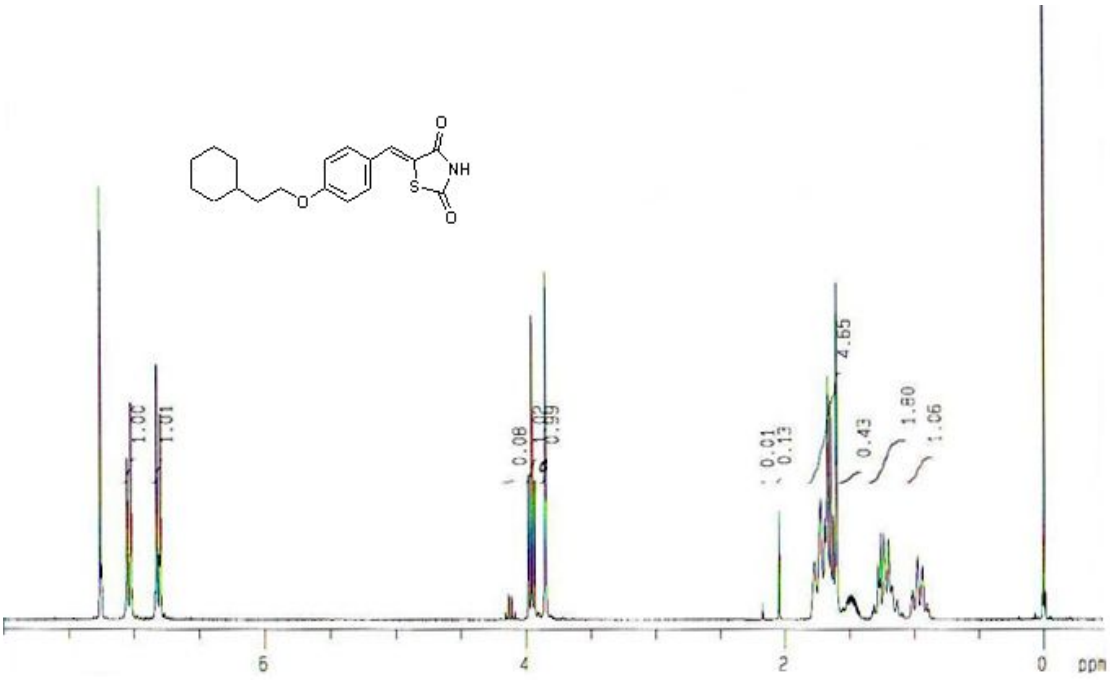

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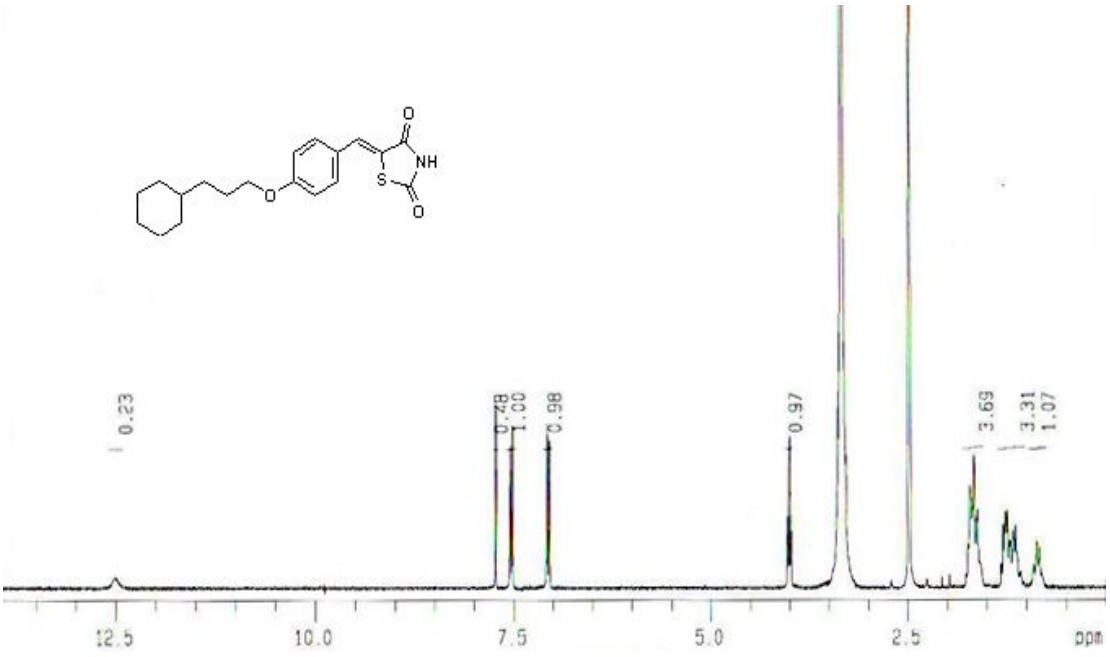

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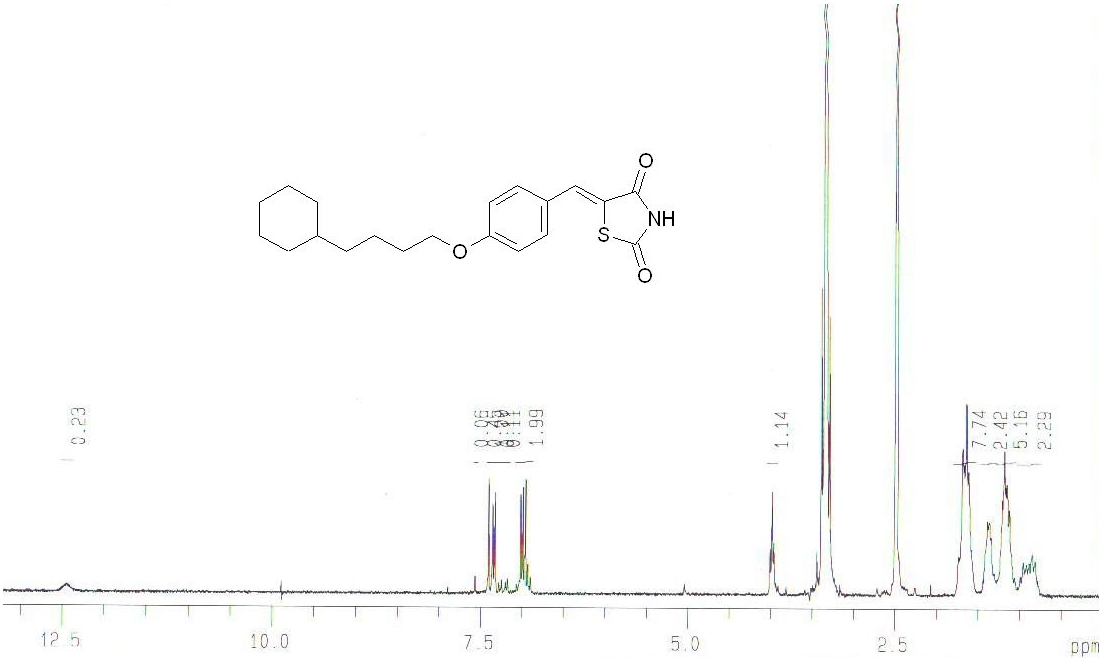

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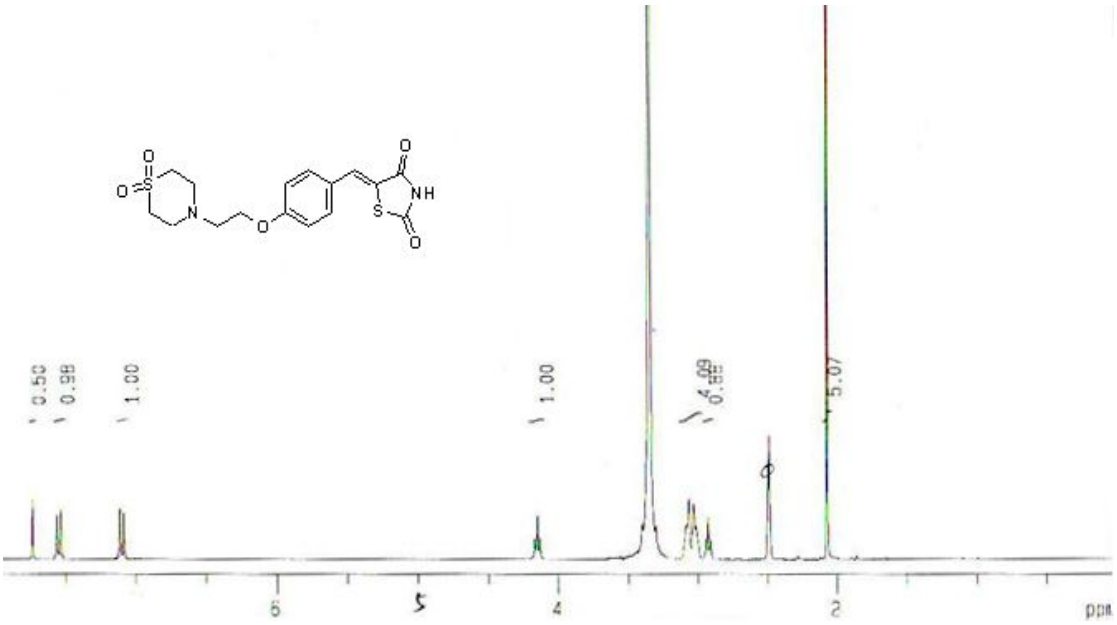

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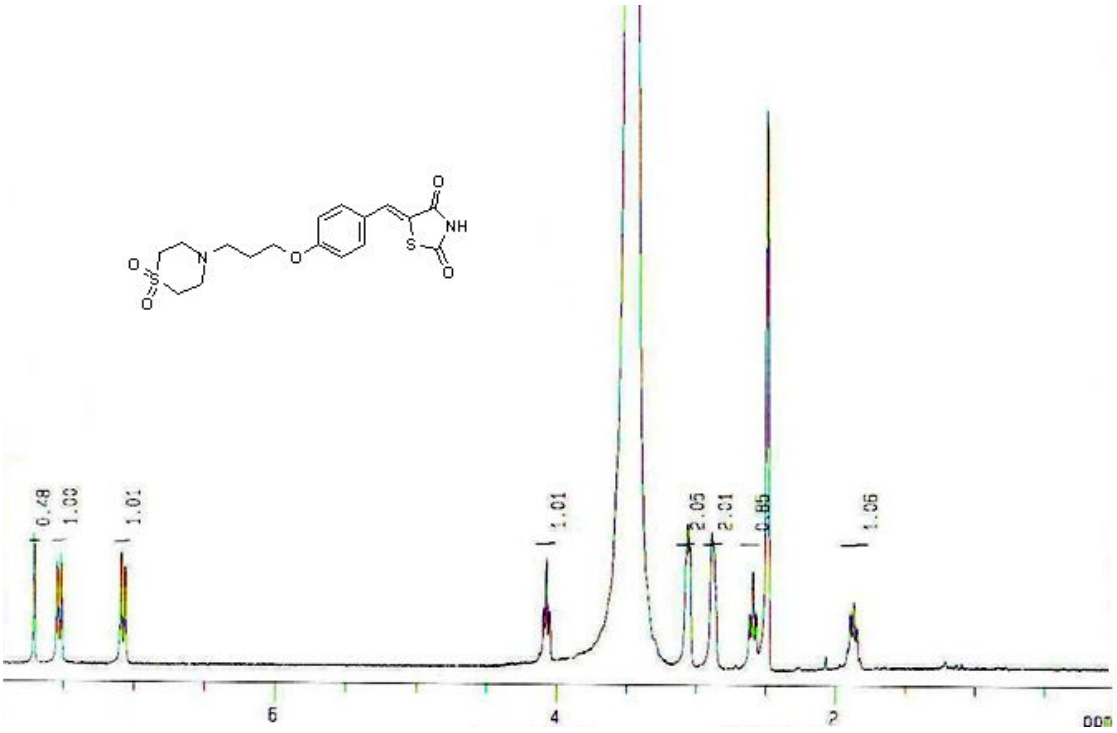

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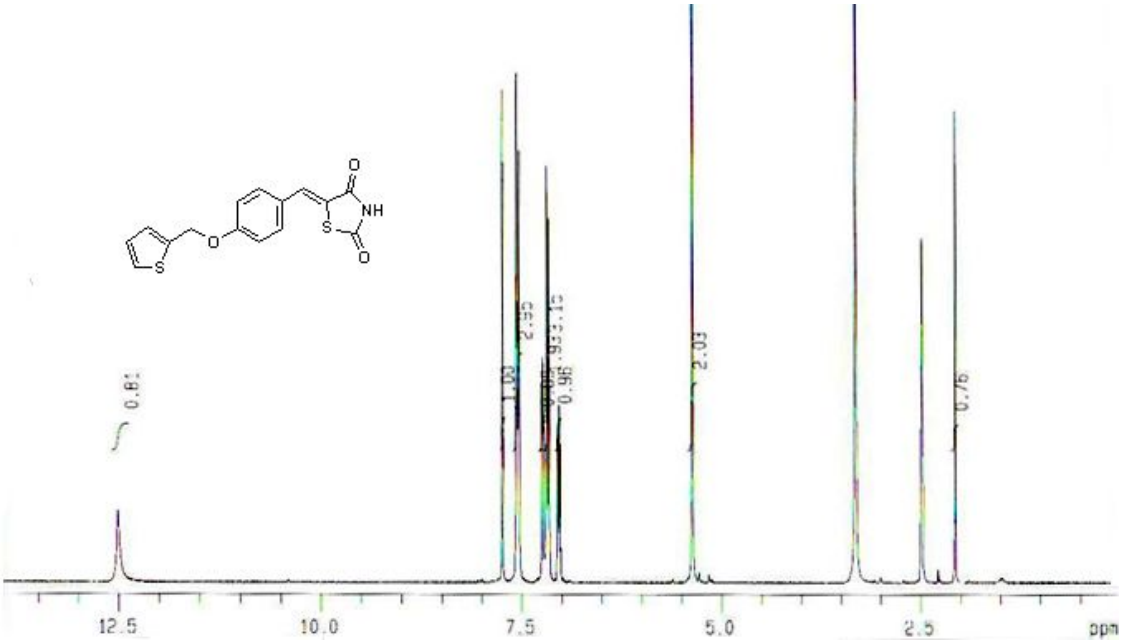

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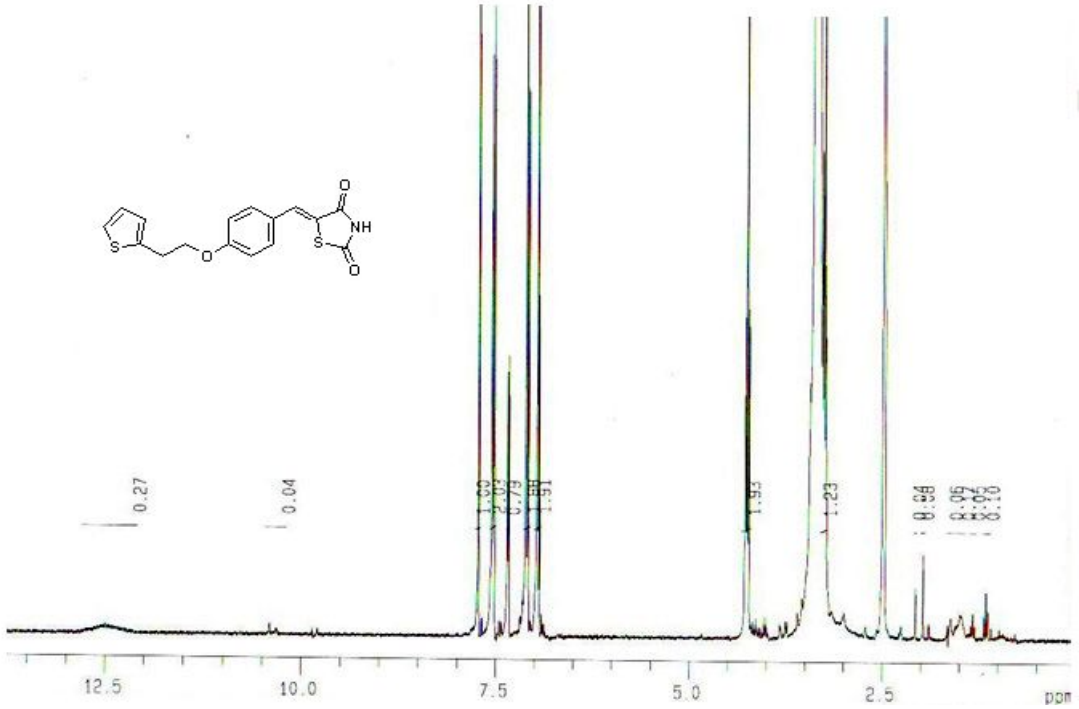
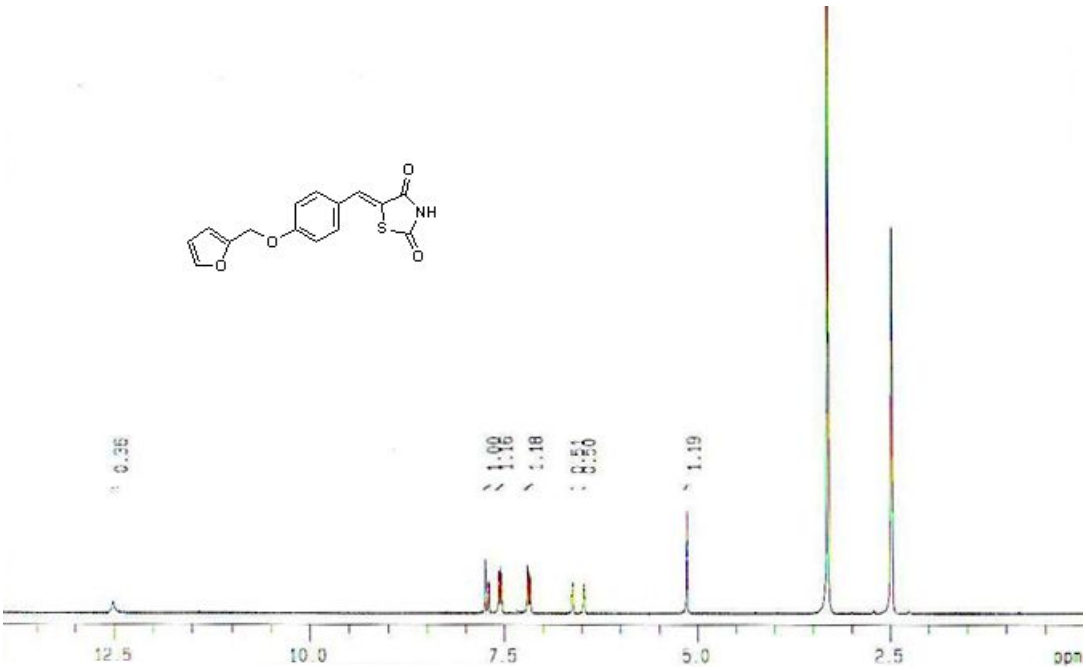
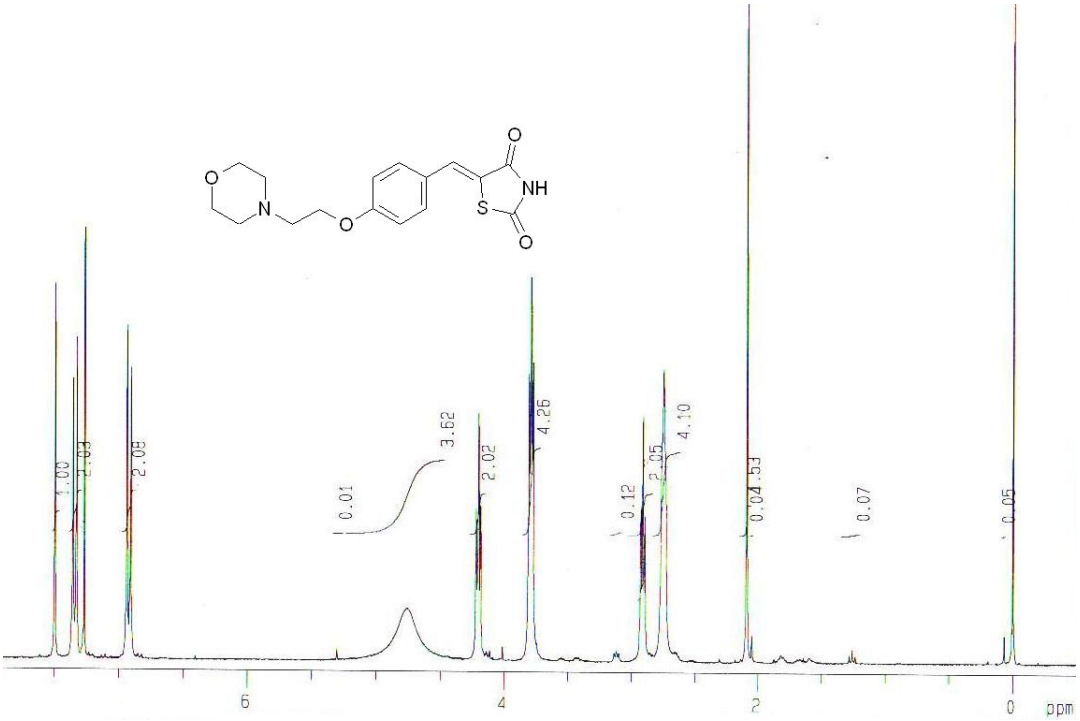


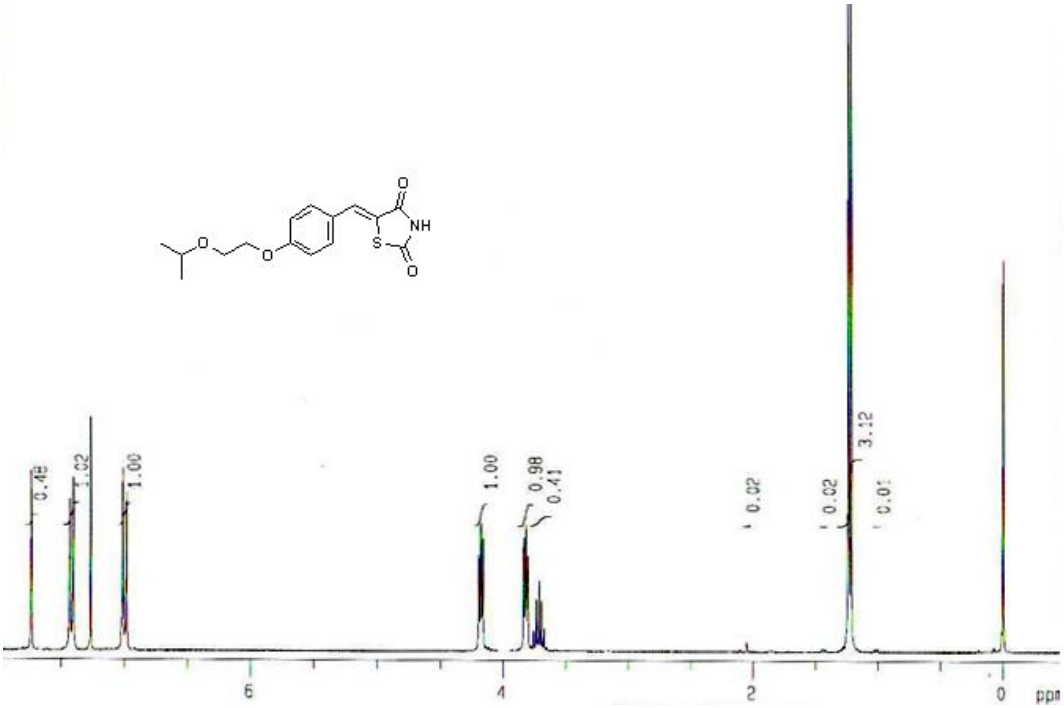
5-(4-(2-(Thiophen-2-yl)ethoxy)benzylidene)thiazolidine-2,4-dione (9b)



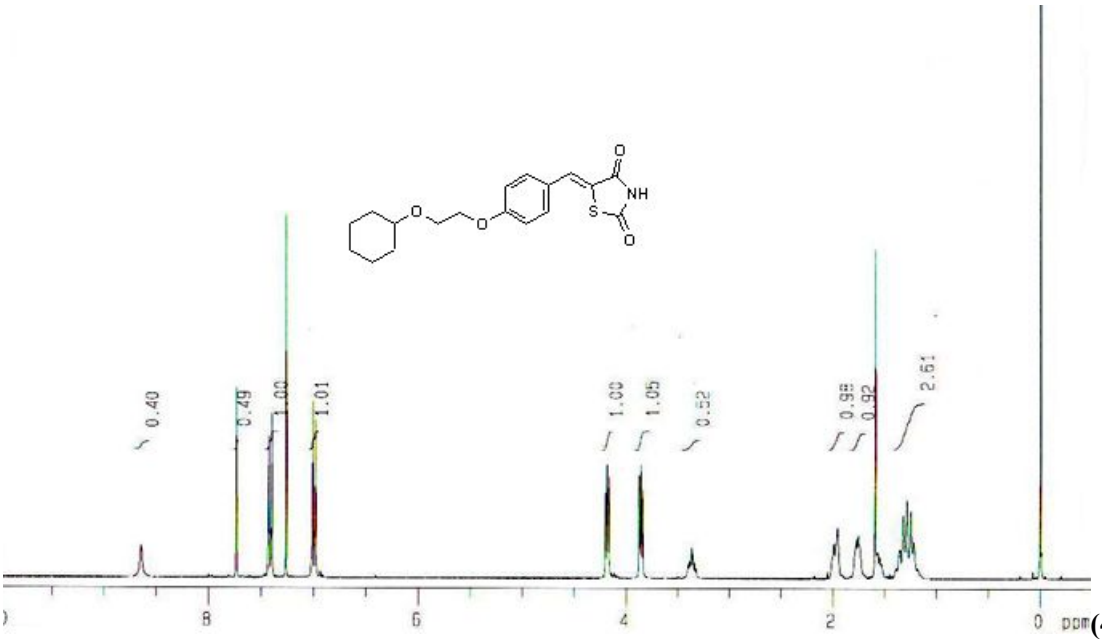
5-[4-(furan-2-ylmethoxy) benzylidene] thiazolidine-2,4-dione (10b)



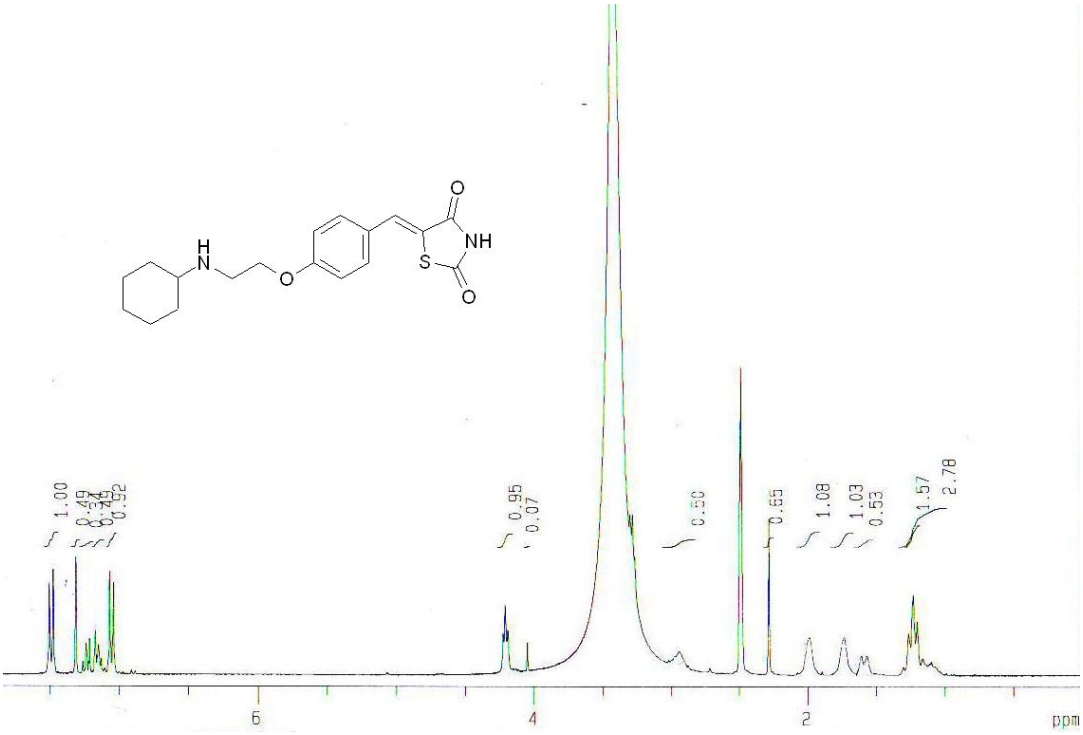
5-[4-(Thiophen-3-ylmethoxy)benzylidene]thiazolidine-2,4-dione (11b)



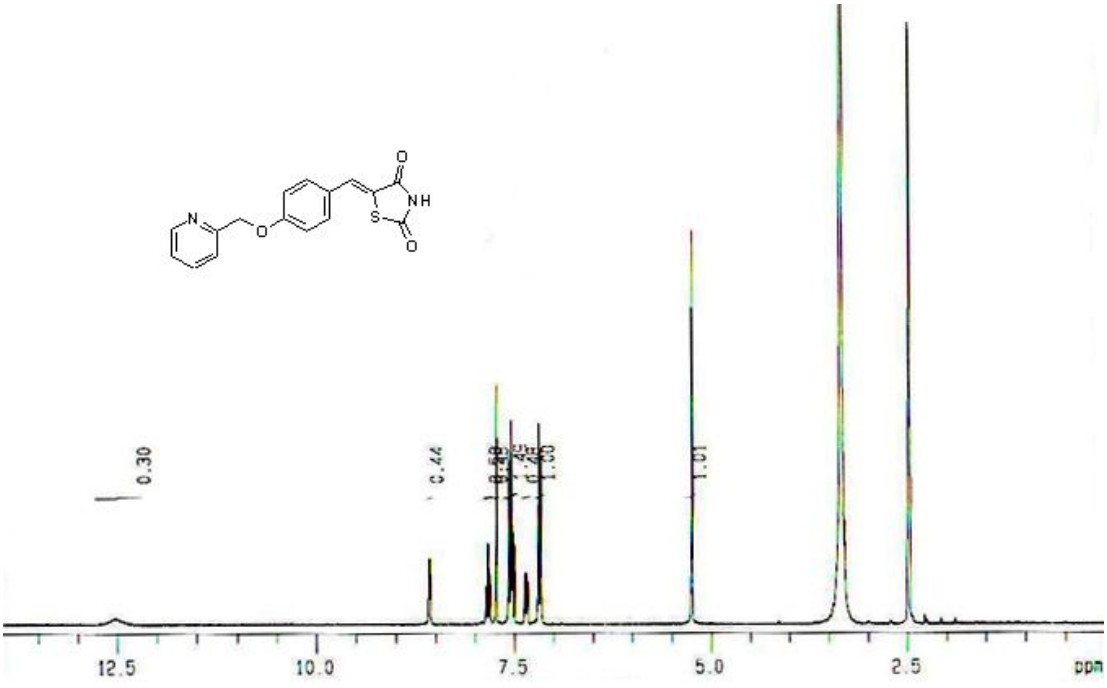
5-(4-(2-Isopropoxyethoxy)benzylidene)thiazolidine-2,4-dione (14b)



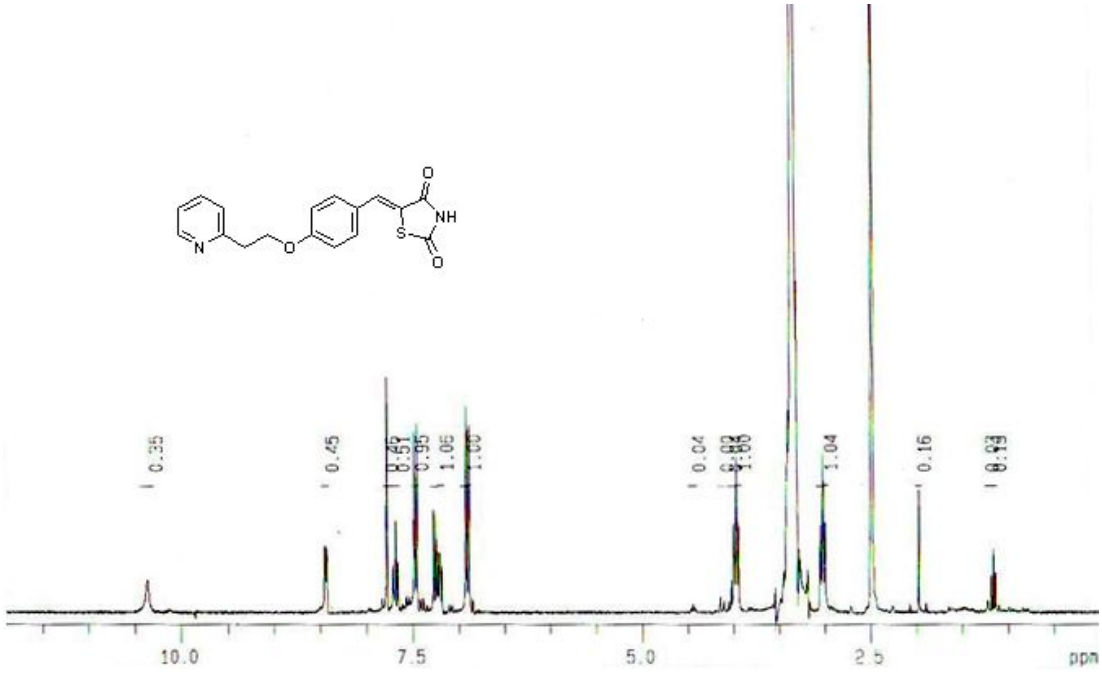
(4-(2-(Cyclohexyloxy)ethoxy)benzylidene)thiazolidine-2,4-dione (15b)



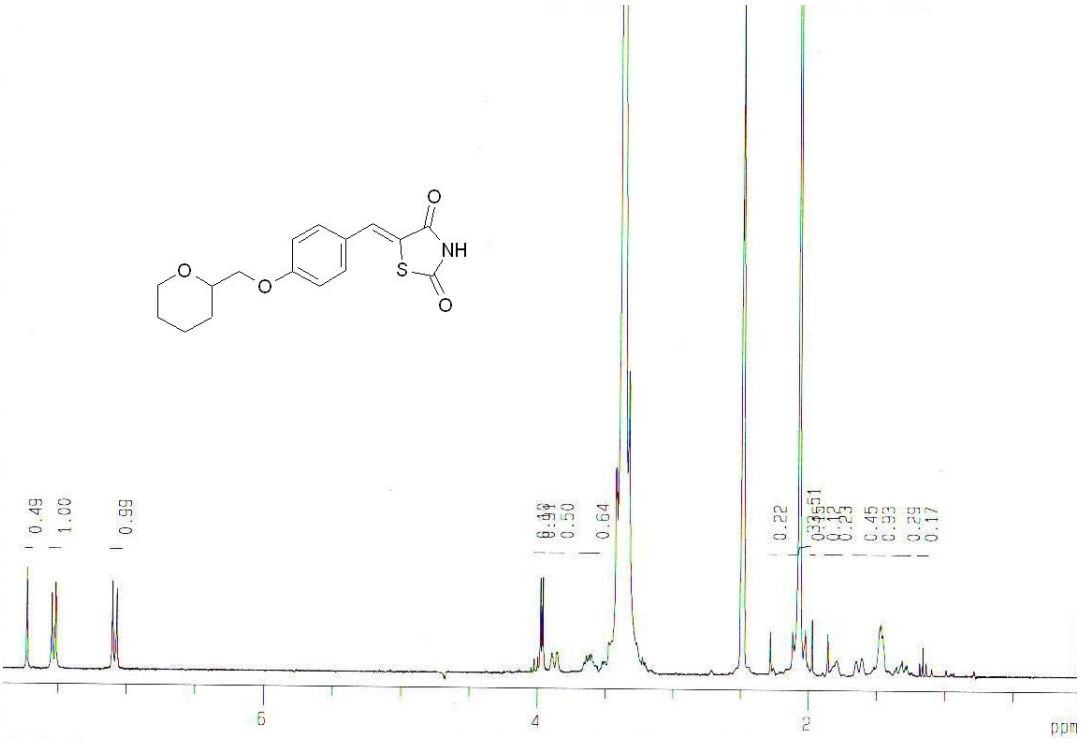
5-(4-(2-(Cyclohexylamino)ethoxy)benzylidene)thiazolidine-2,4-dione (16b)



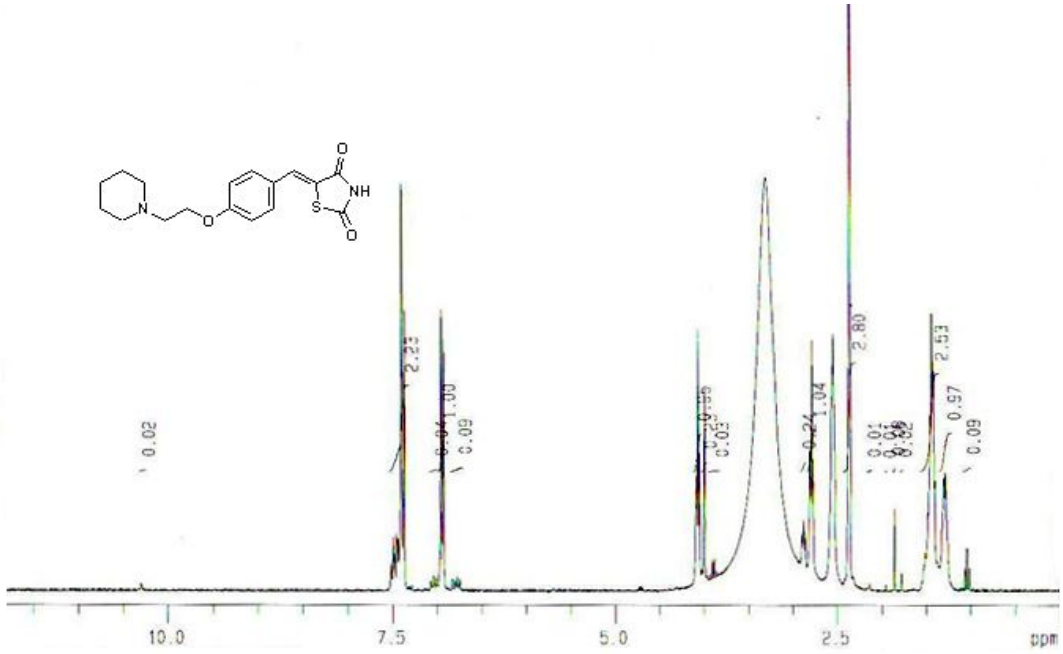
5-(4-(piridin-2-ylmethoxy)benzylidene)thiazolidine-2,4-dione (17b)



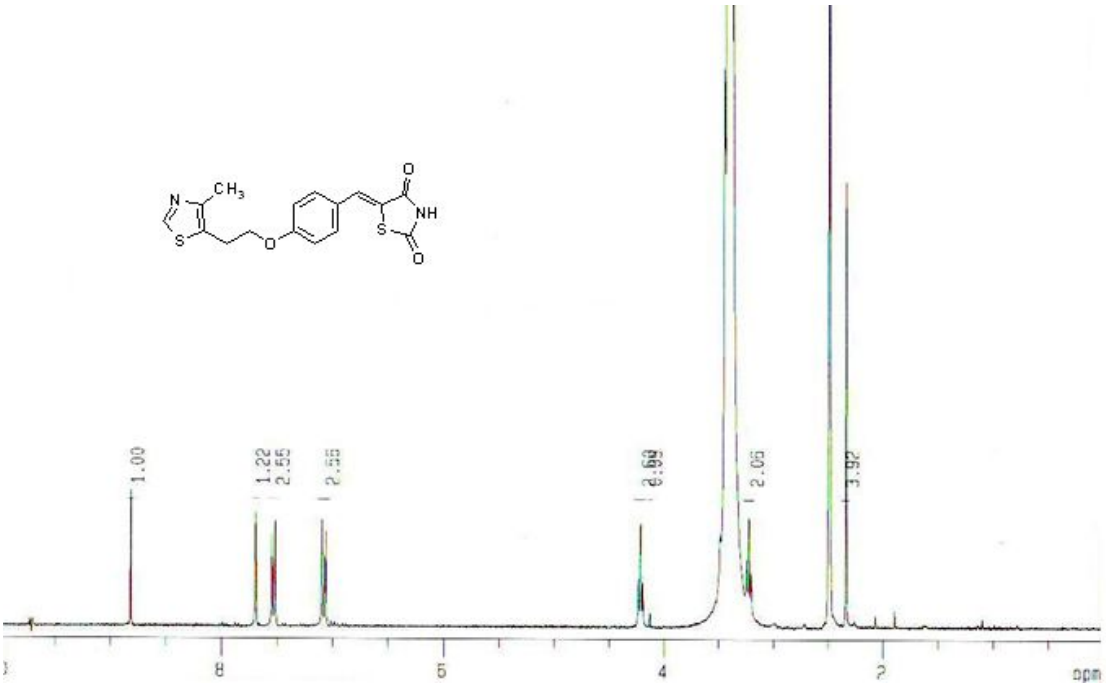
5-(4-(2-(Pyridin-2-yl)ethoxy)benzylidene)thiazolidine-2,4-dione (18b)



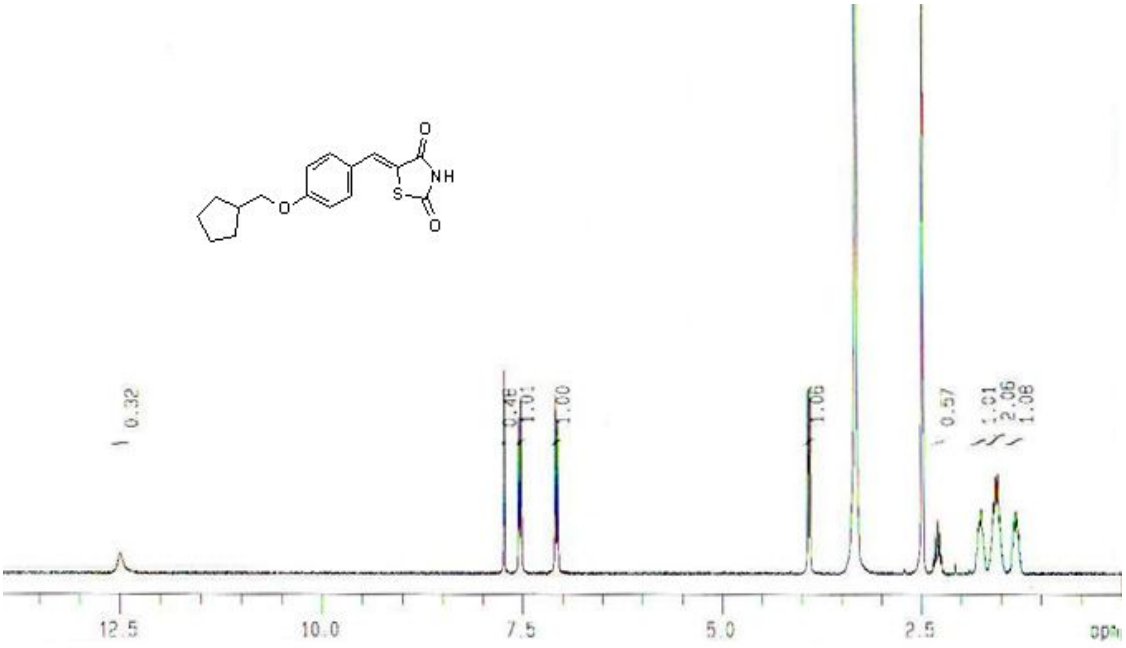
5-(4-(tetrahydropyran-2-methoxy)thiazolidine)-2,4-dione (19b)



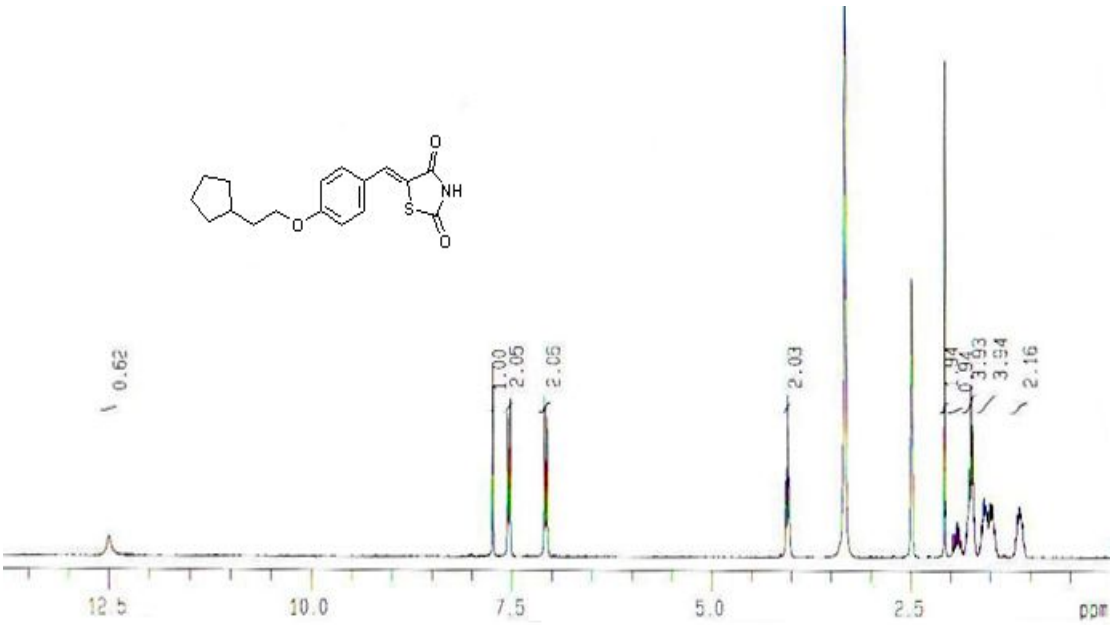
5-[4-(2-(piperidin-1-yl)ethoxy)benzylidene]thiazolidine-2,4-dione (20b)



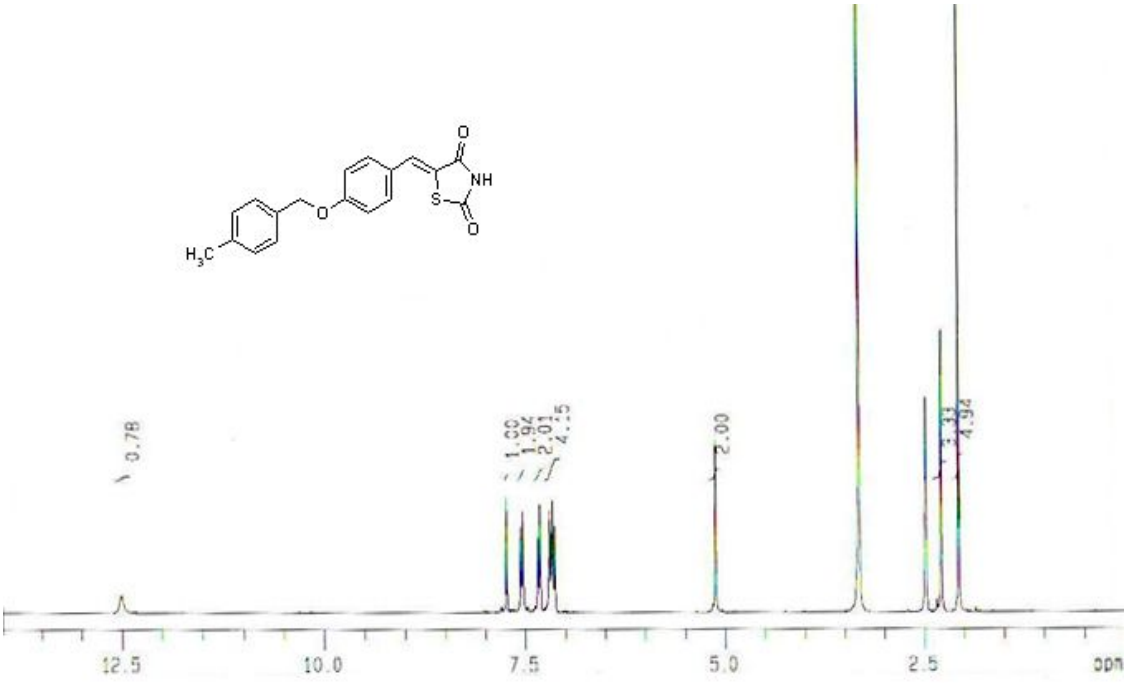
5-(4-(2-(4-methylthiazol-5-yl)ethoxy)benzylidene)thiazolidine-2,4-dione (21b)



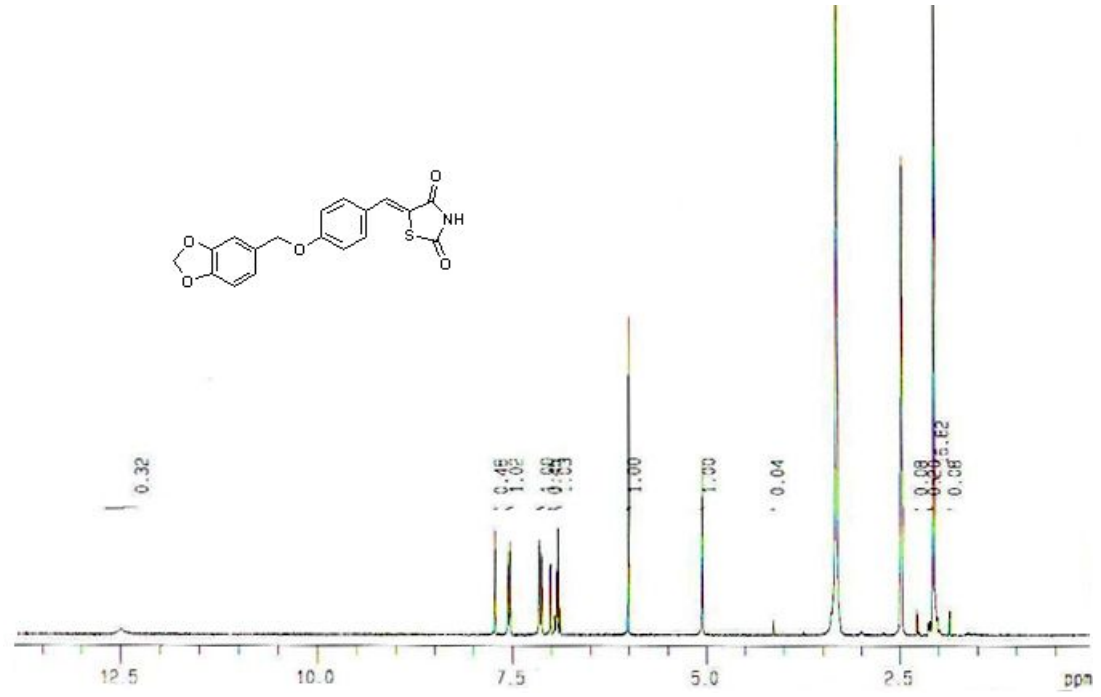
5-(4-(cyclopentylmethoxy)benzylidene)thiazolidine-2,4-dione (22b)



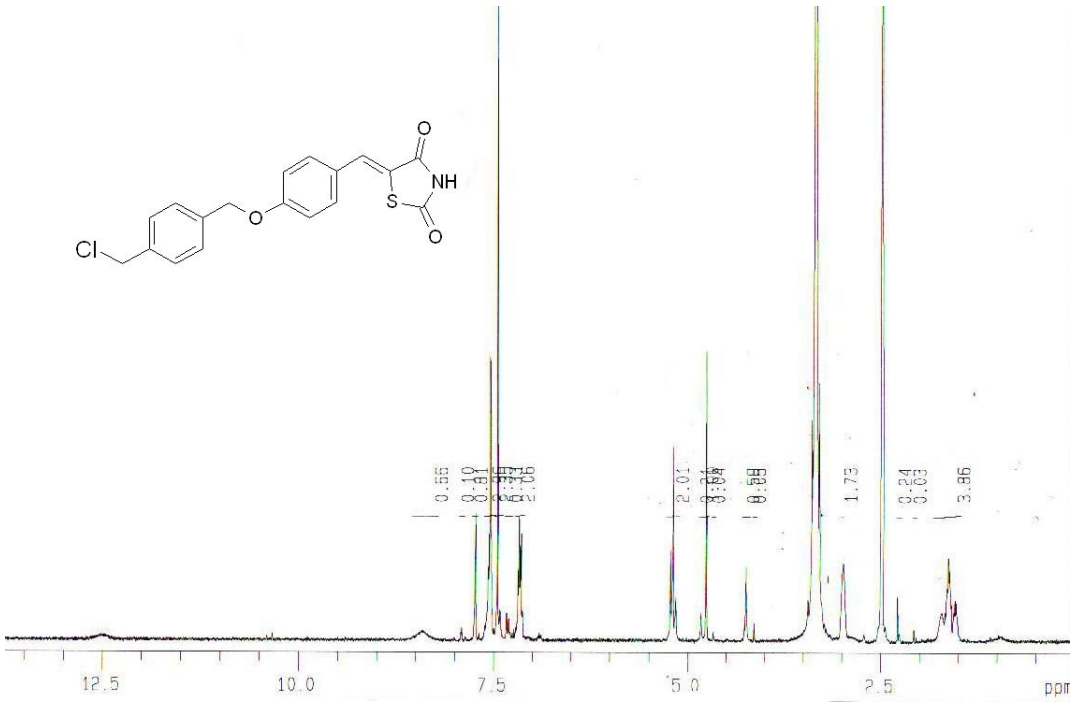
5-(4-(2-cyclopentylethoxy)benzylidene)thiazolidine-2,4-dione (23b)



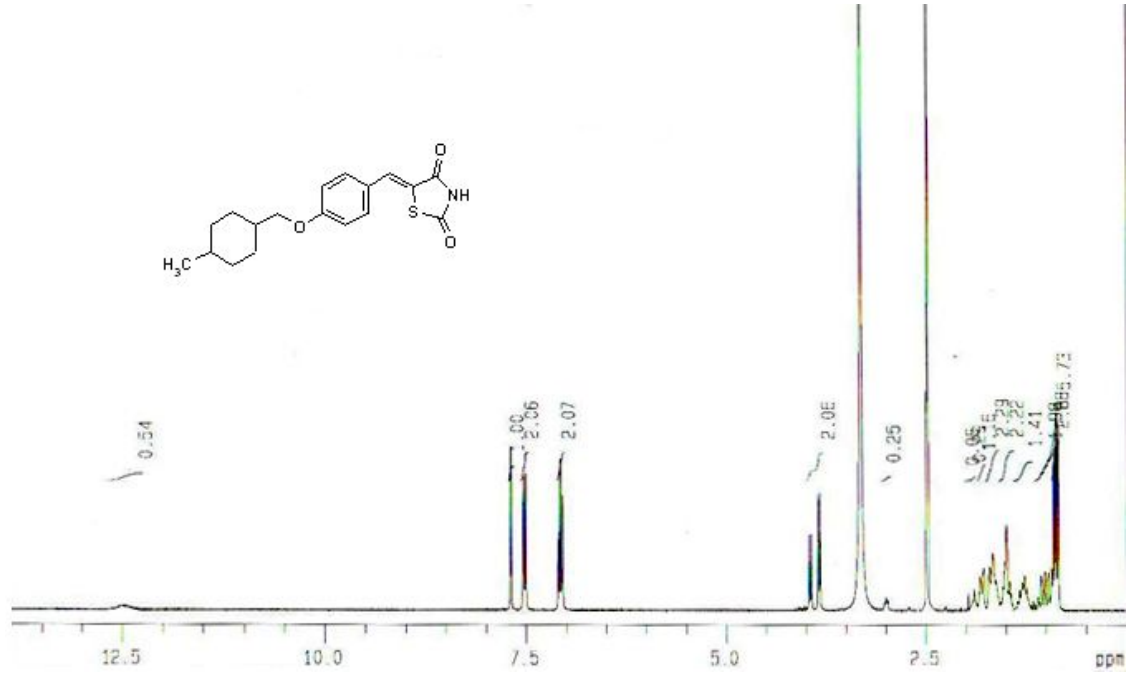
5-(4-(4-metylbenzyloxy)benzylidene)thiazolidine-2,4-dione (25b)



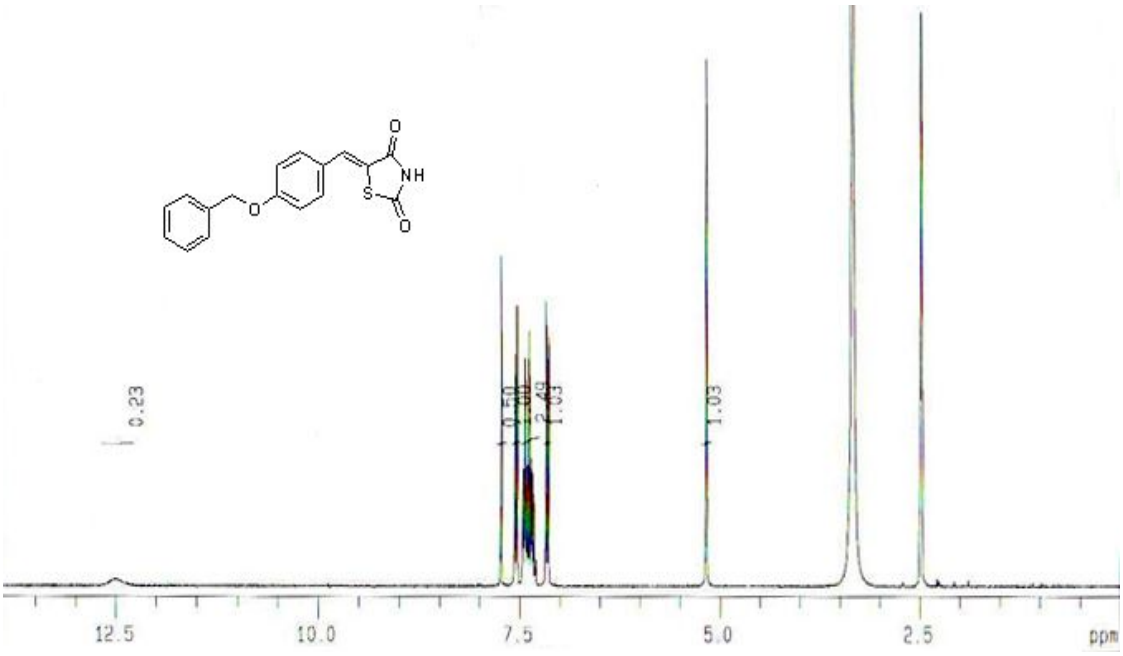
5-[4-(benzo[d][1,3]dioxol-5-ylmethoxy)benzylidene]thiazolidine-2,4-dione (26b)



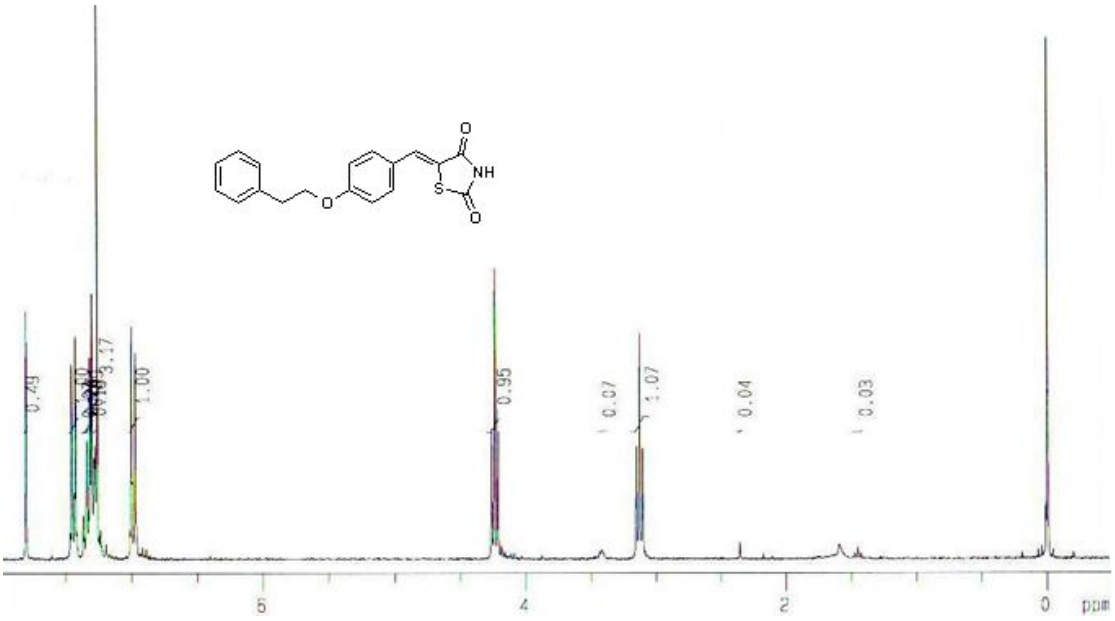
5-[4-(4-(chlorometyl)benzyloxy)benzylidene]thiazolidine-2,4-dione (27b)



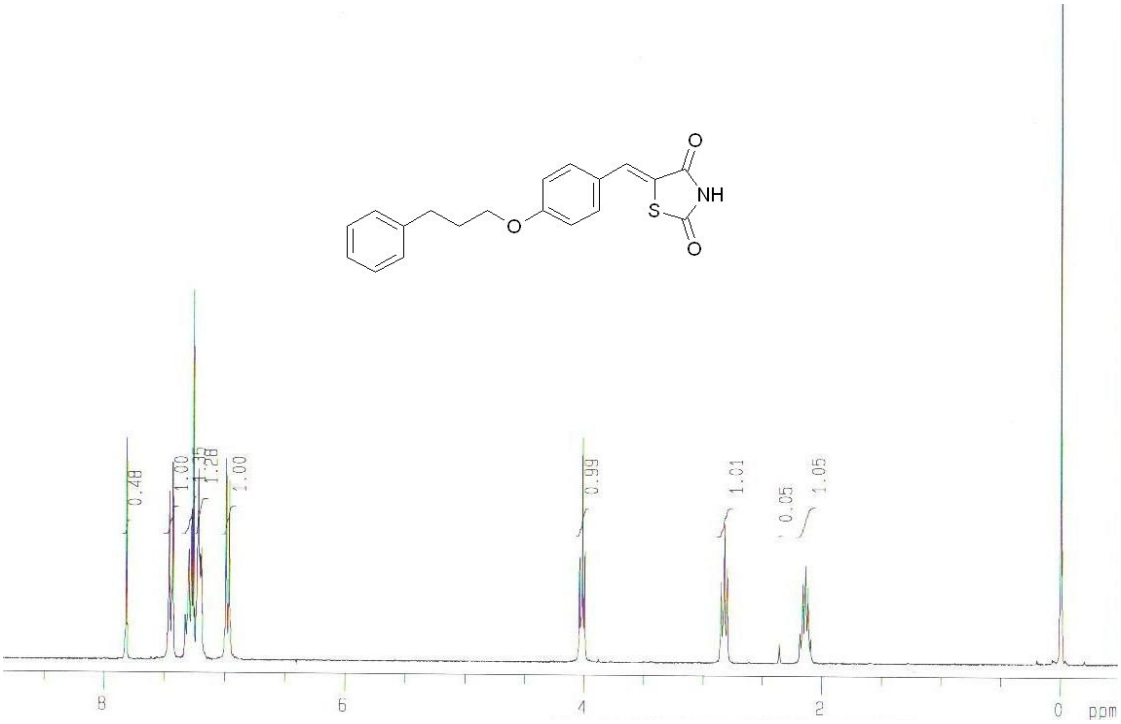
5-[4-((4-metylcyclohexyl)methoxy)benzylidene]thiazolidine-2,4-dione (28b)



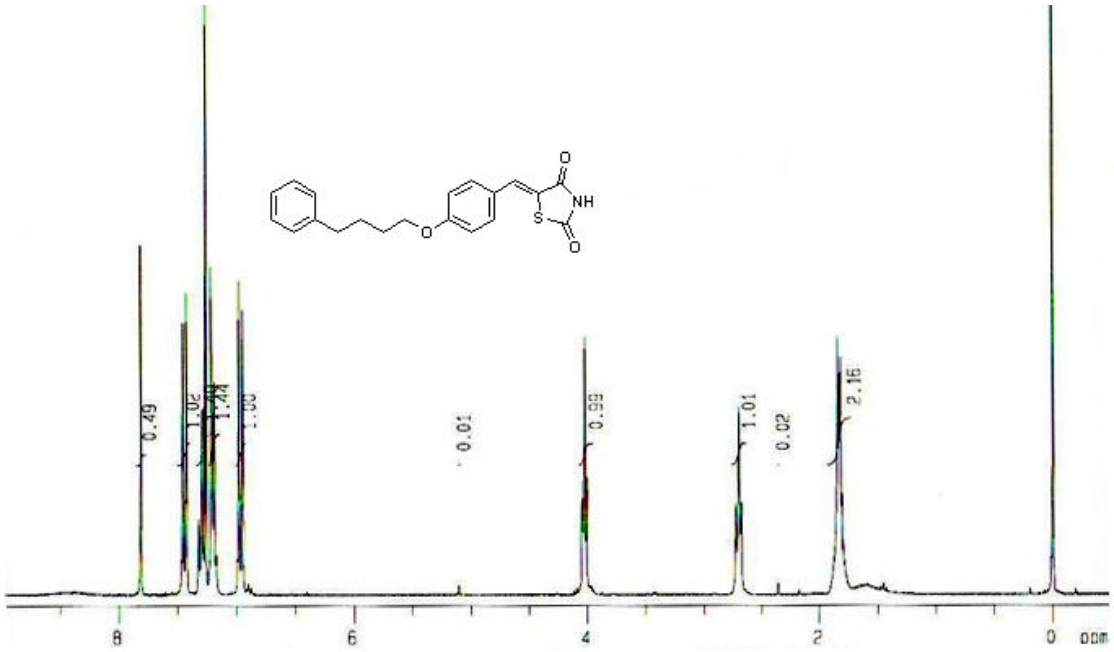
5-(4-(benzyloxy)benzylidene)thiazolidine-2,4-dione (30b)



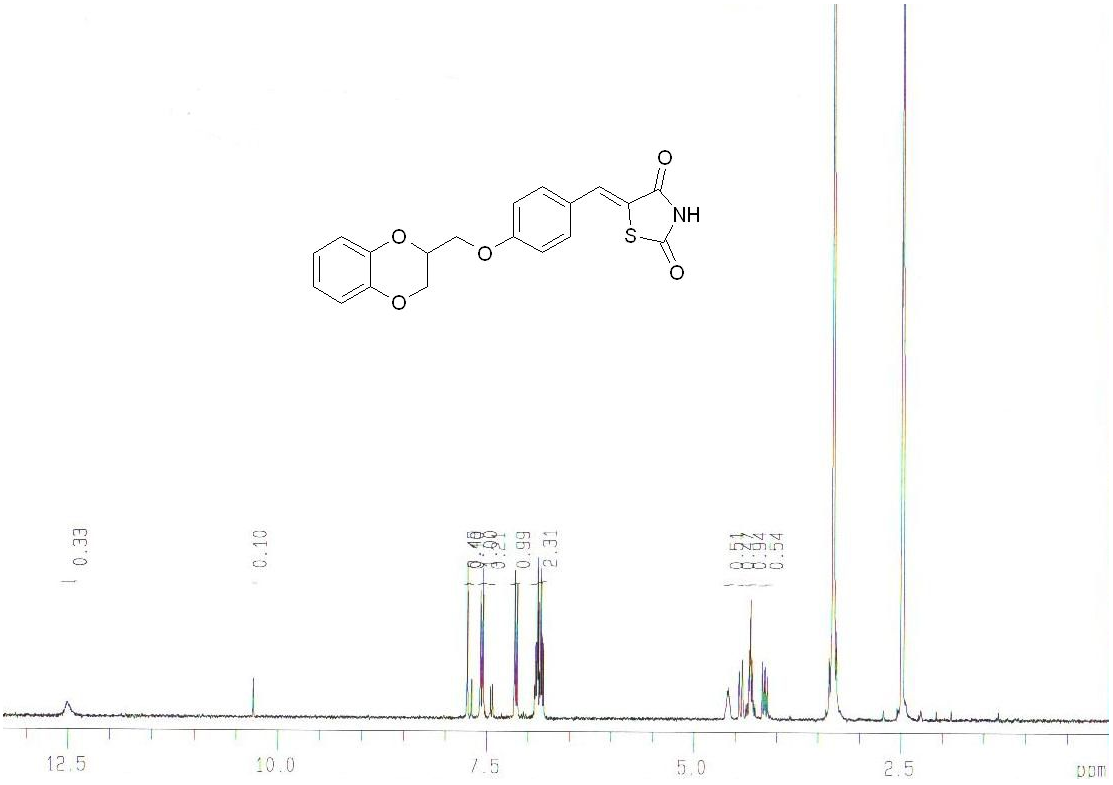
5-[4-(2-phenylethoxy)benzylidene]-1,3-thiazolidine-2,4-dione (31b)



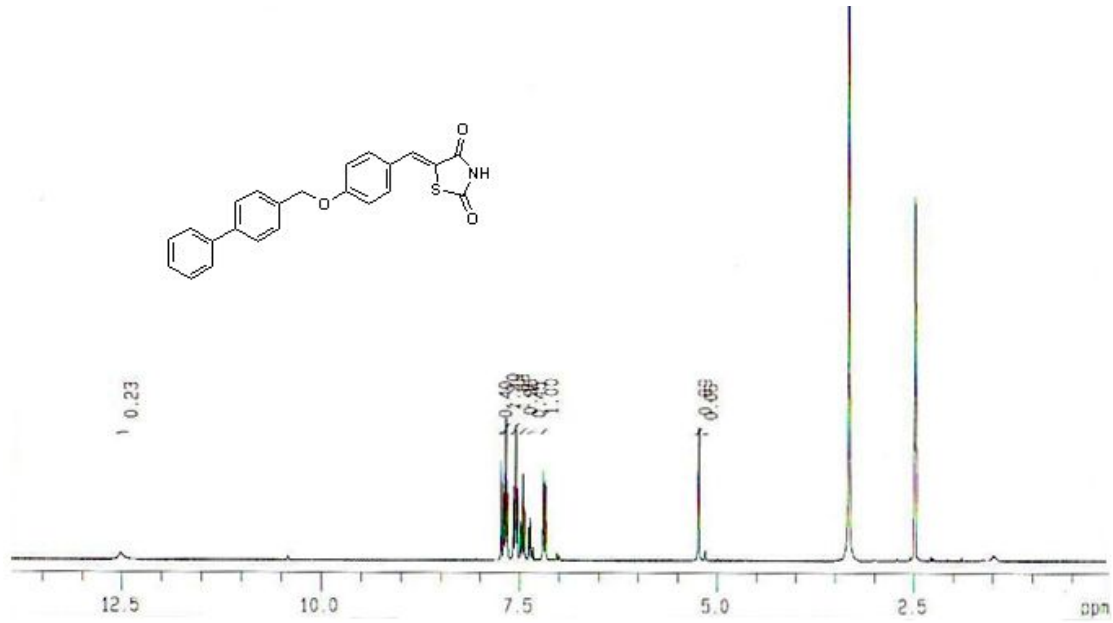
5-[4-(2-phenylpropoxy)benzylidene]-1,3-thiazolidine-2,4-dione (32b)



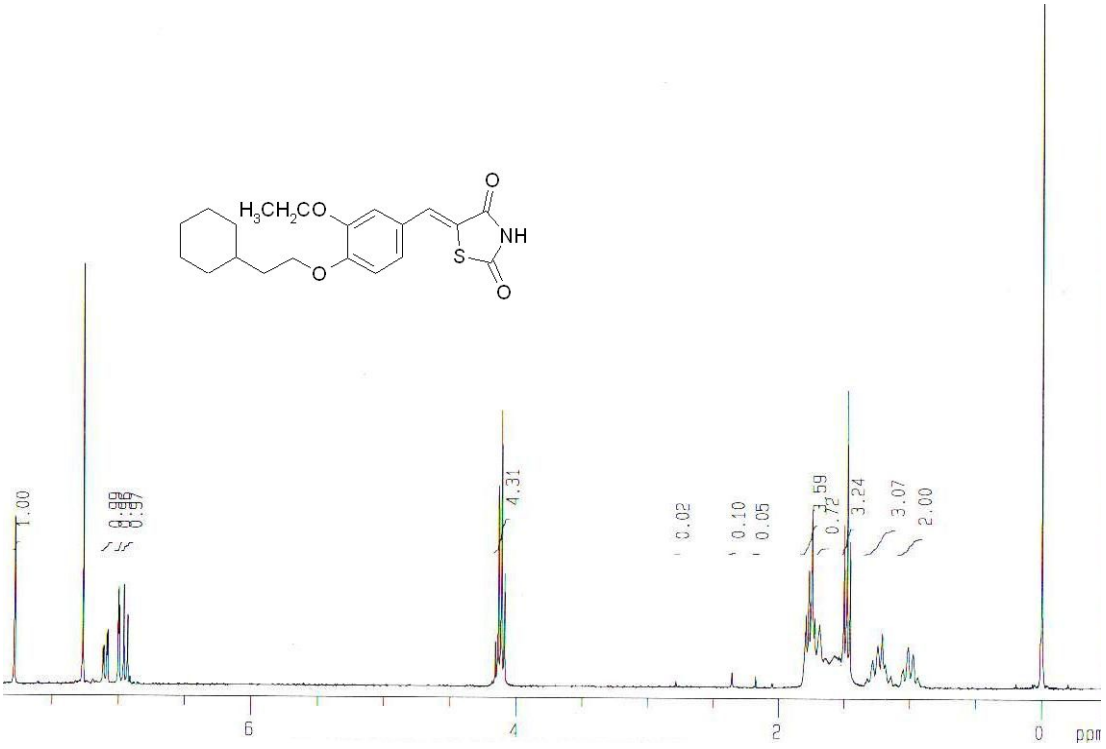
5-[4-(2-phenylbutoxy)benzylidene]-1,3-thiazolidine-2,4-dione (33b)



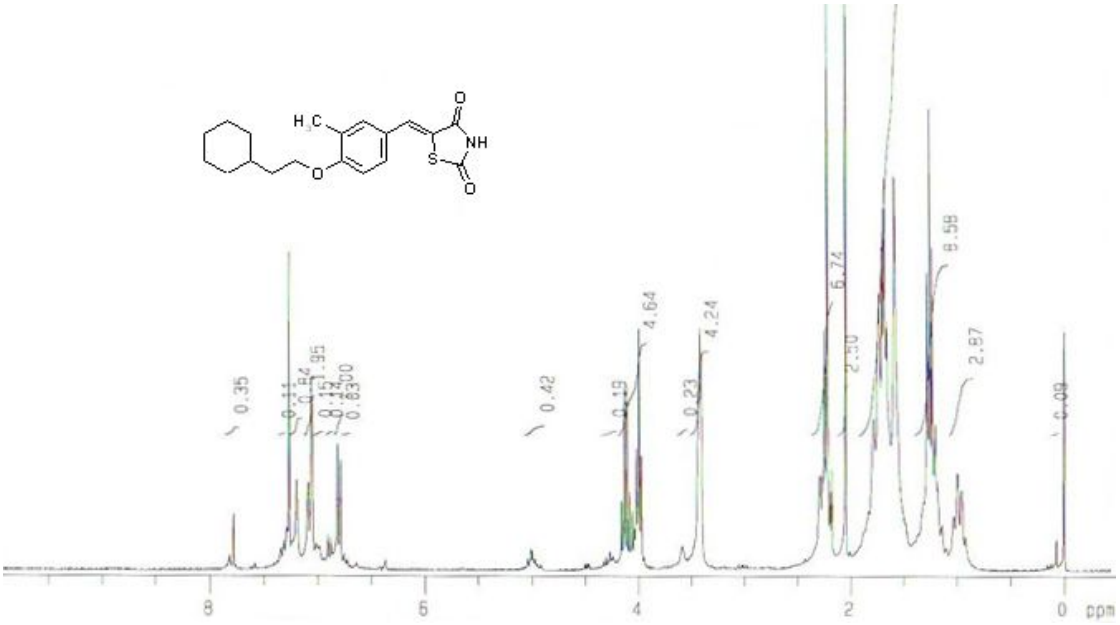
5-(4-((2,3-Dihydrobenzo[b][1,4]dioxin-2-yl)methoxy)benzylidene)thiazolidine-2,4-dione (34b)



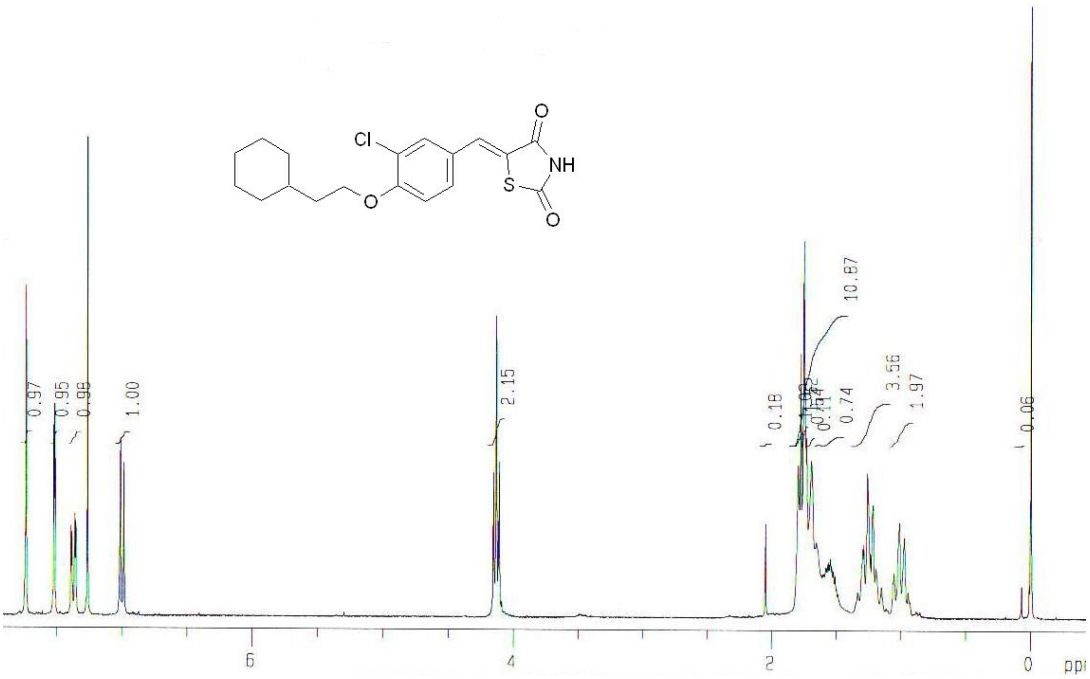
5-(4-(Biphenyl-4-ylmethoxy)benzylidene)thiazolidine-2,4-dione (36b)



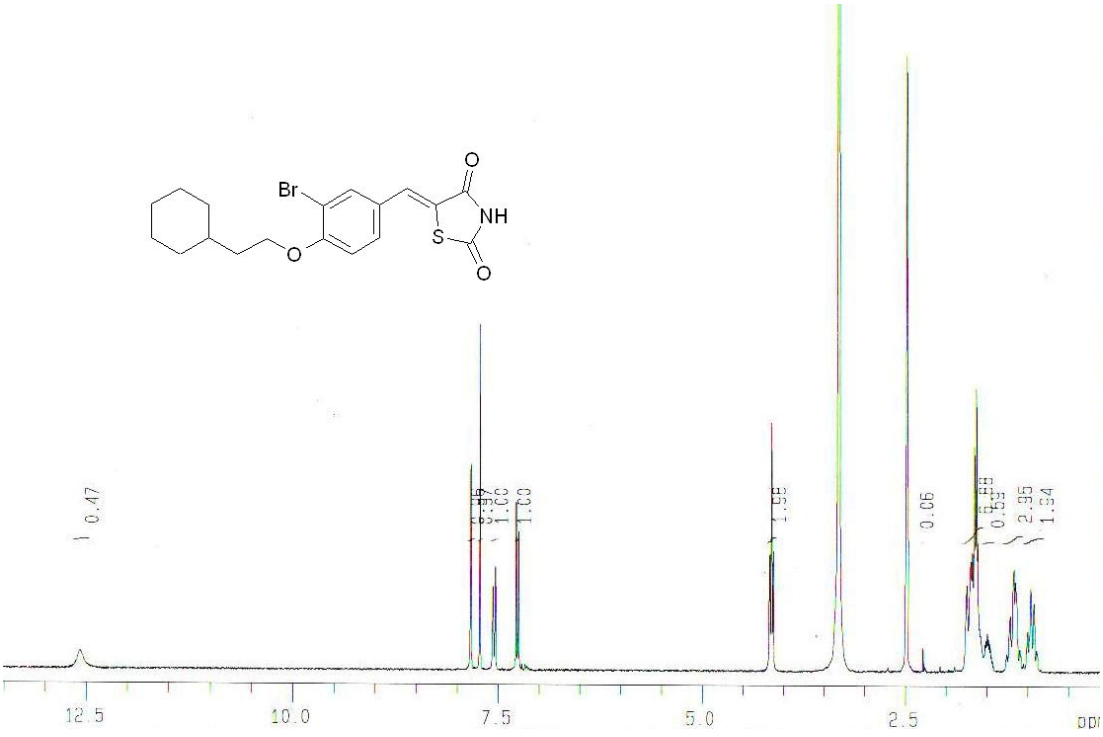
5-(4-(2-cyclohexylethoxy)-3-ethoxybenzylidene)thiazolidine-2,4-dione (39b)



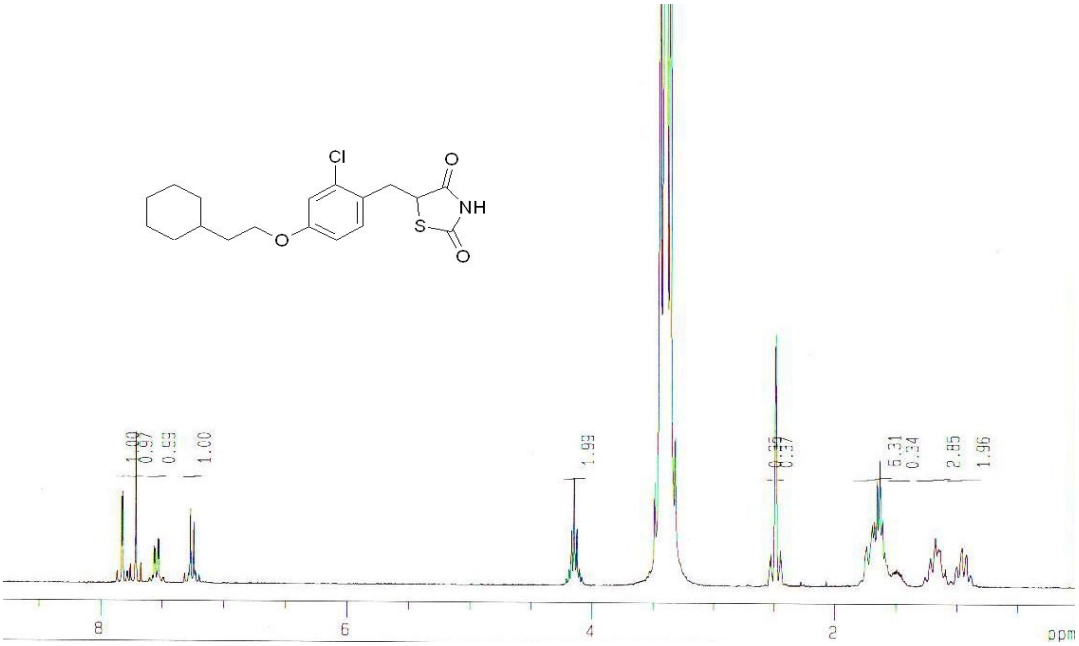
5-(4-(2-cyclohexylethoxy)-3-methylbenzylidene)thiazolidine-2,4-dione (40b)



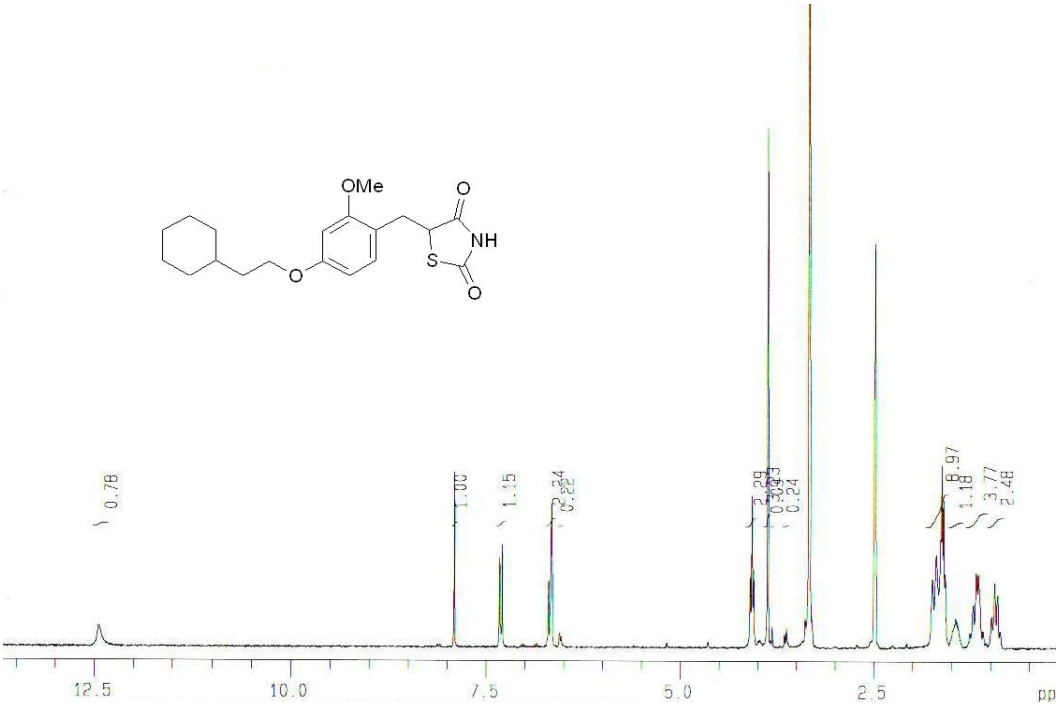
5-(3-chloro-4-(2-cyclohexylethoxy)benzylidene)thiazolidine-2,4-dione (43b)



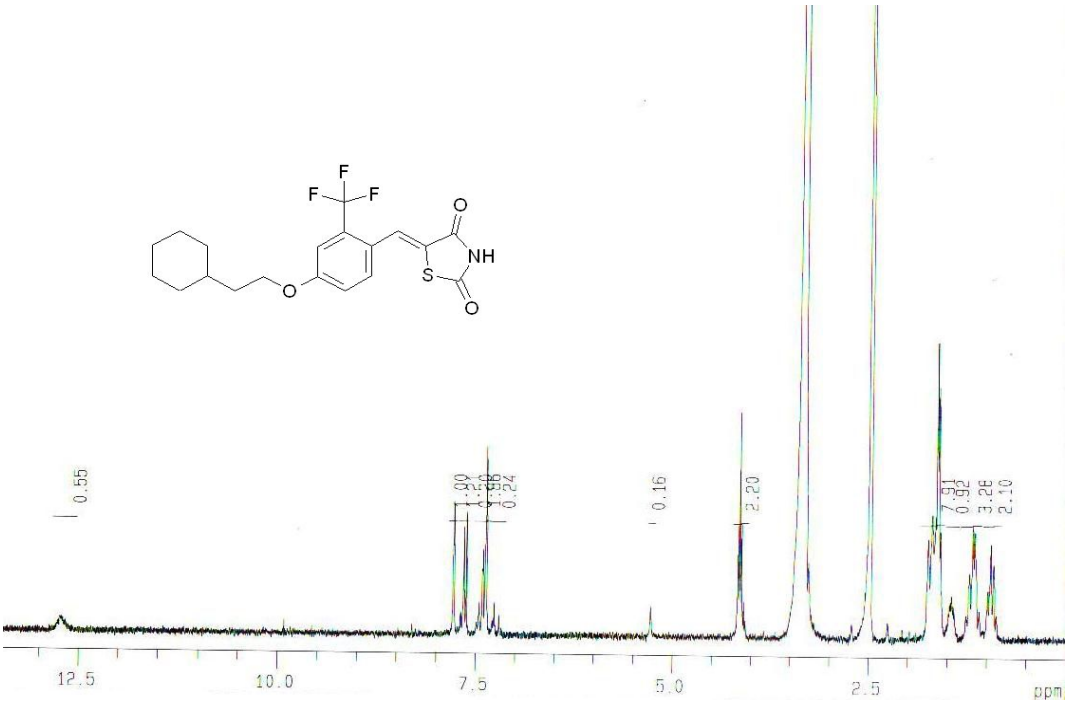
5-(3-bromo-4-(2-cyclohexylethoxy)benzylidene)thiazolidine-2,4-dione (44b)



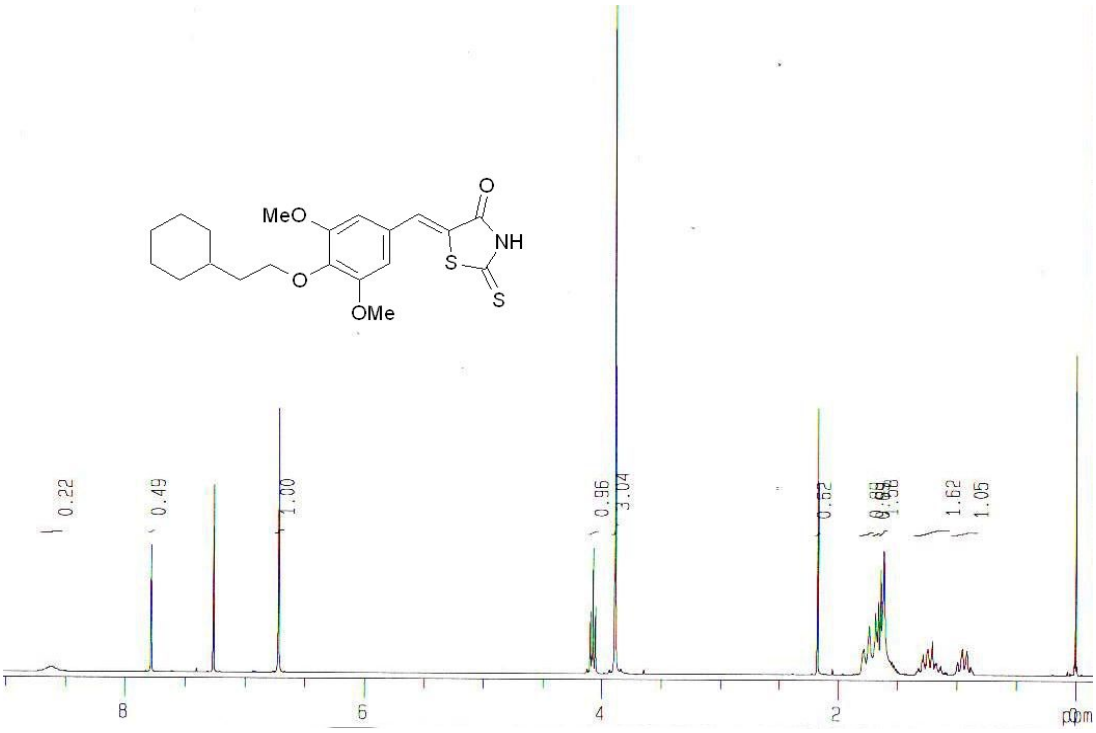
5-(2-chloro-4-(2-cyclohexylethoxy)benzylidene)thiazolidine-2,4-dione (45b)



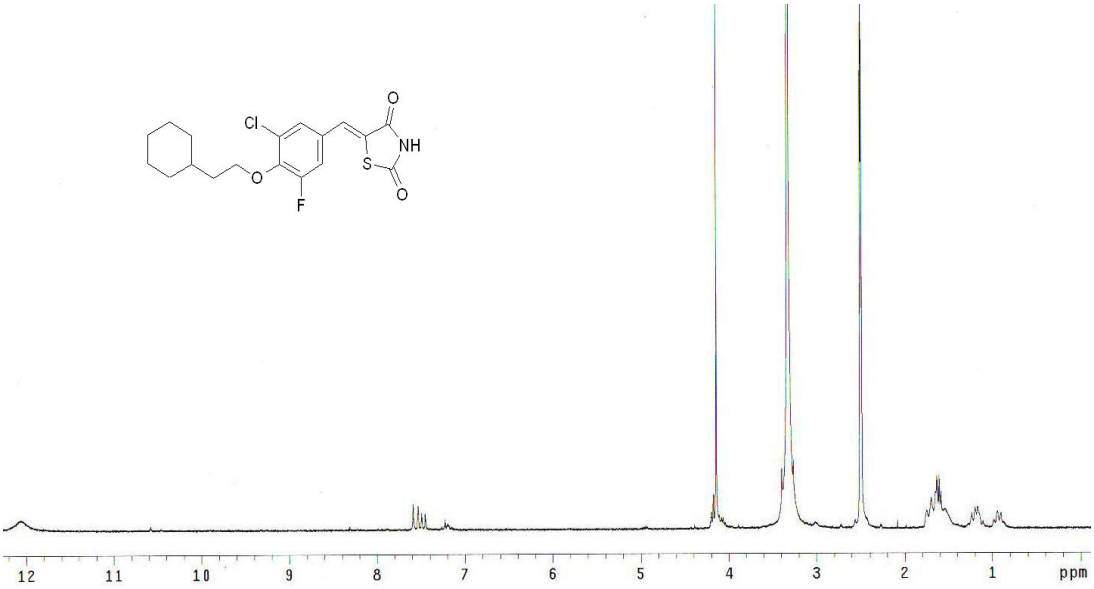
5-(4-(2-cyclohexylethoxy)-2-methoxybenzylidene)thiazolidine-2,4-dione (46b)



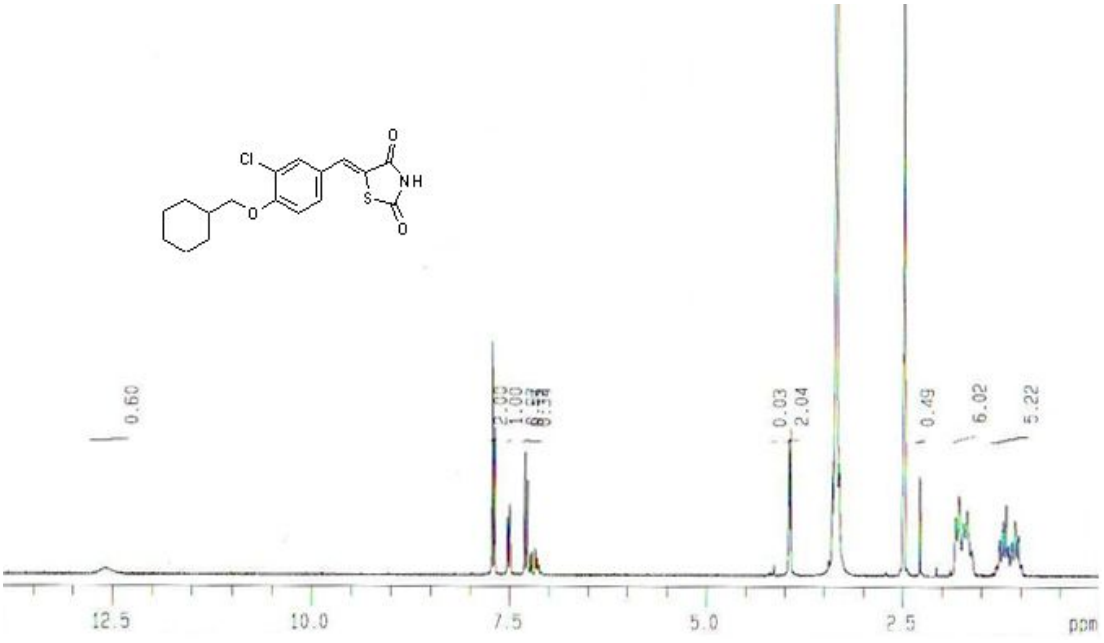
5-(4-(2-cyclohexylethoxy)-2-(trifluromethyl)benzylidene)thiazolidine-2,4-dione (47b)



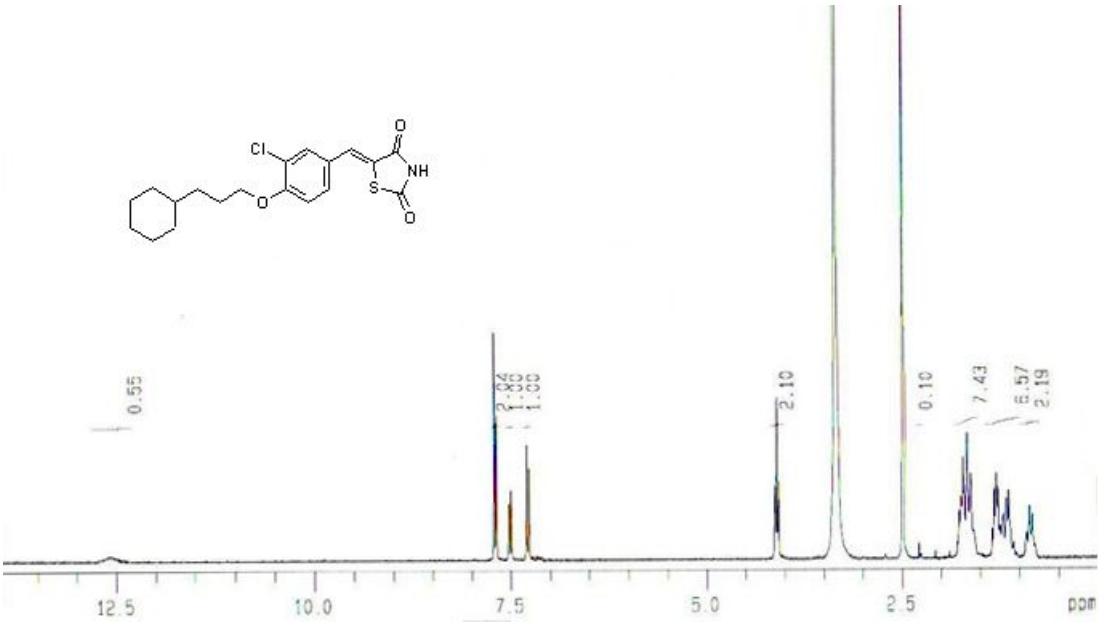
5-(4-(2-cyclohexylethoxy)-3,5-dimethoxybenzylidene)thiazolidine-2,4-dione (48b)



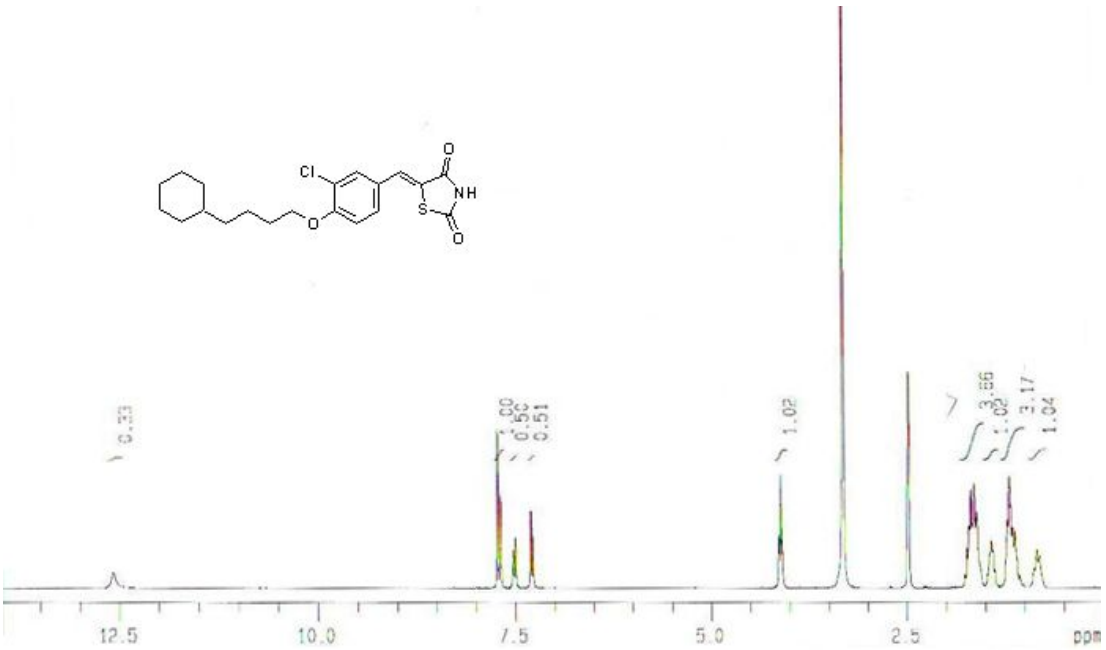
5-(3-chloro-5-fluoro-4-(2-cyclohexylethoxy)benzylidene)thiazolidine-2,4-dione (50b)



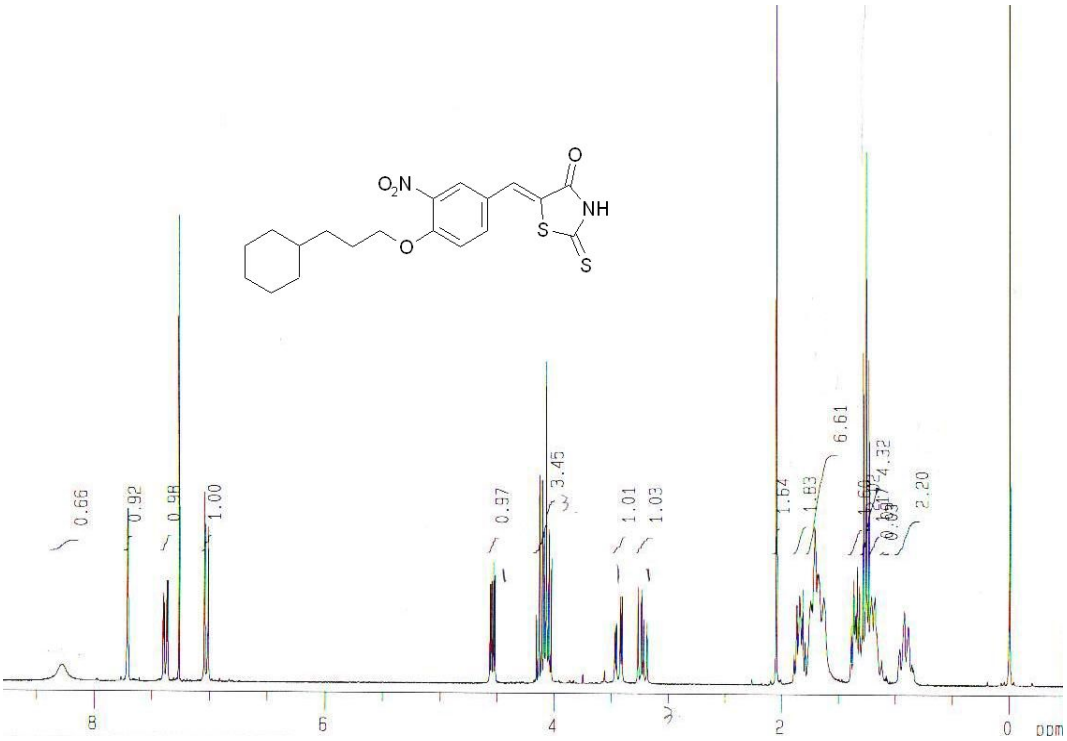
5-(3-chloro-4-(cyclohexylmethoxy)benzylidene)thiazolidine-2,4-dione (52b)



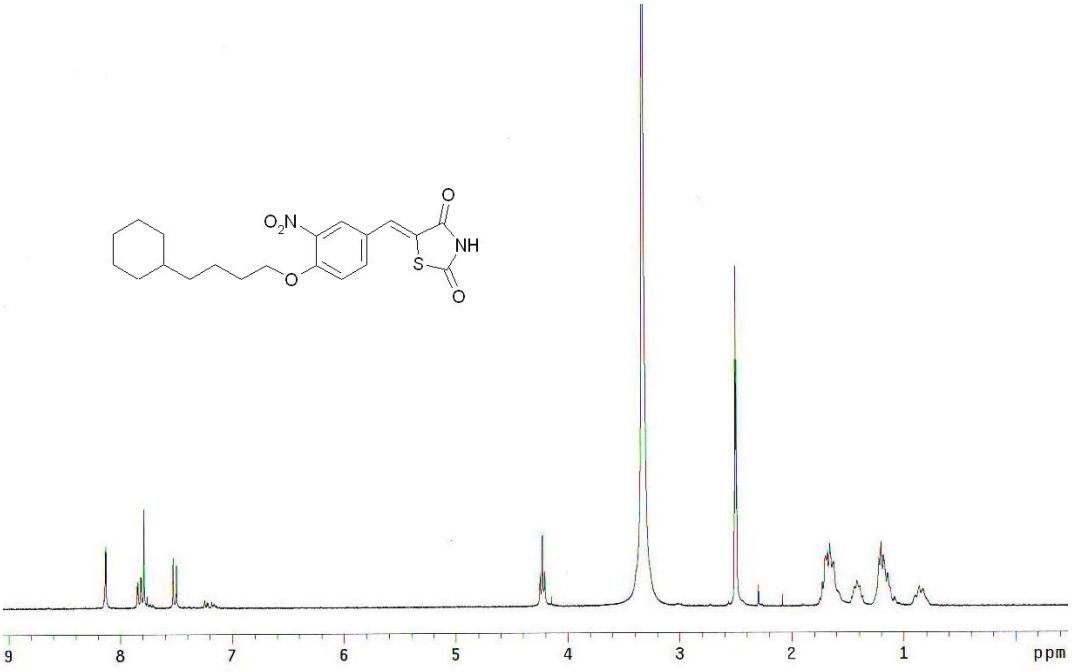
5-(3-chloro-4-(cyclohexylpropoxy)benzylidene)thiazolidine-2,4-dione (53b)



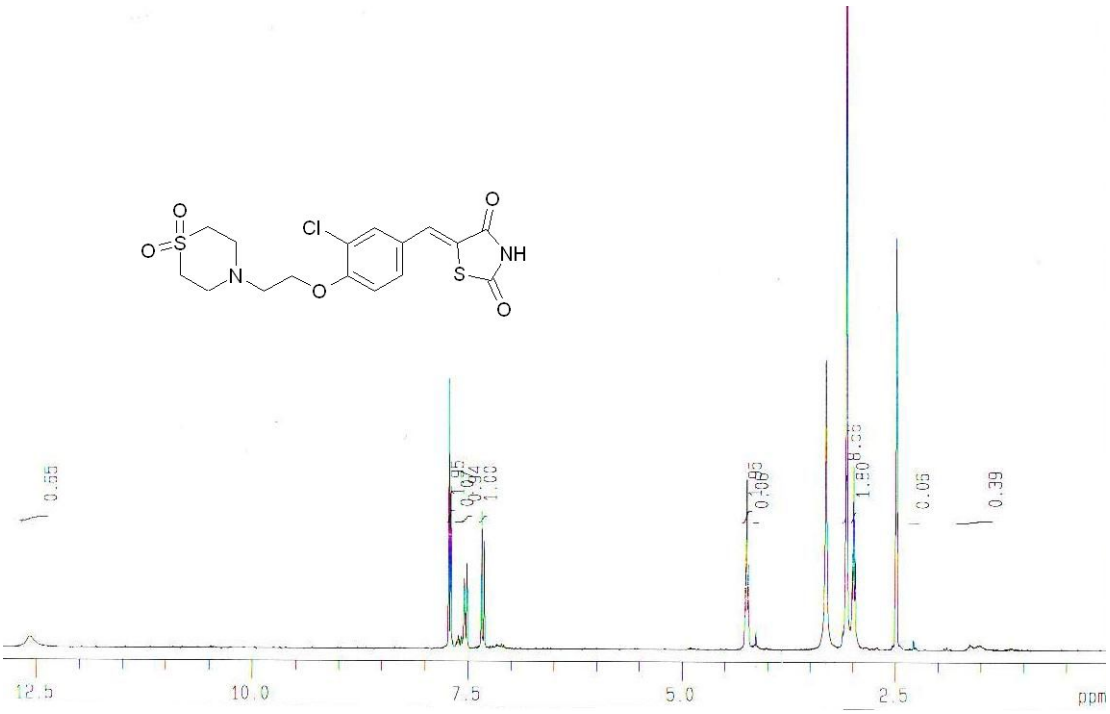
5-(3-chloro-4-(cyclohexylbutoxy)benzylidene)thiazolidine-2,4-dione (54b)



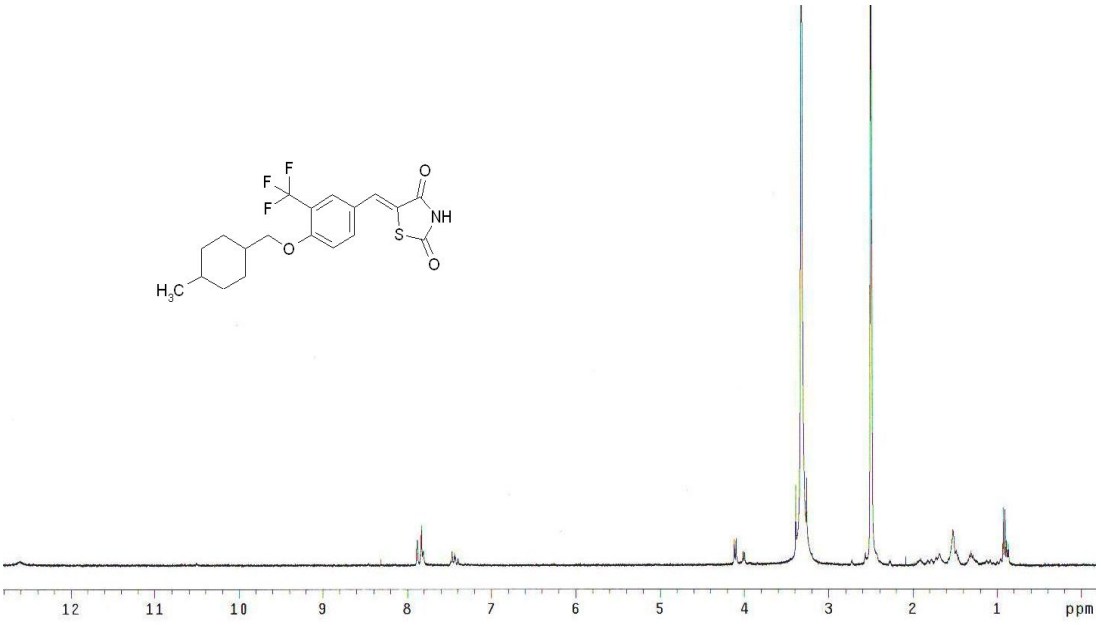
5-(4-(3-cyclohexylpropoxy)-3-nitrobenzylidene)thiazolidine-2,4-dione (67b)



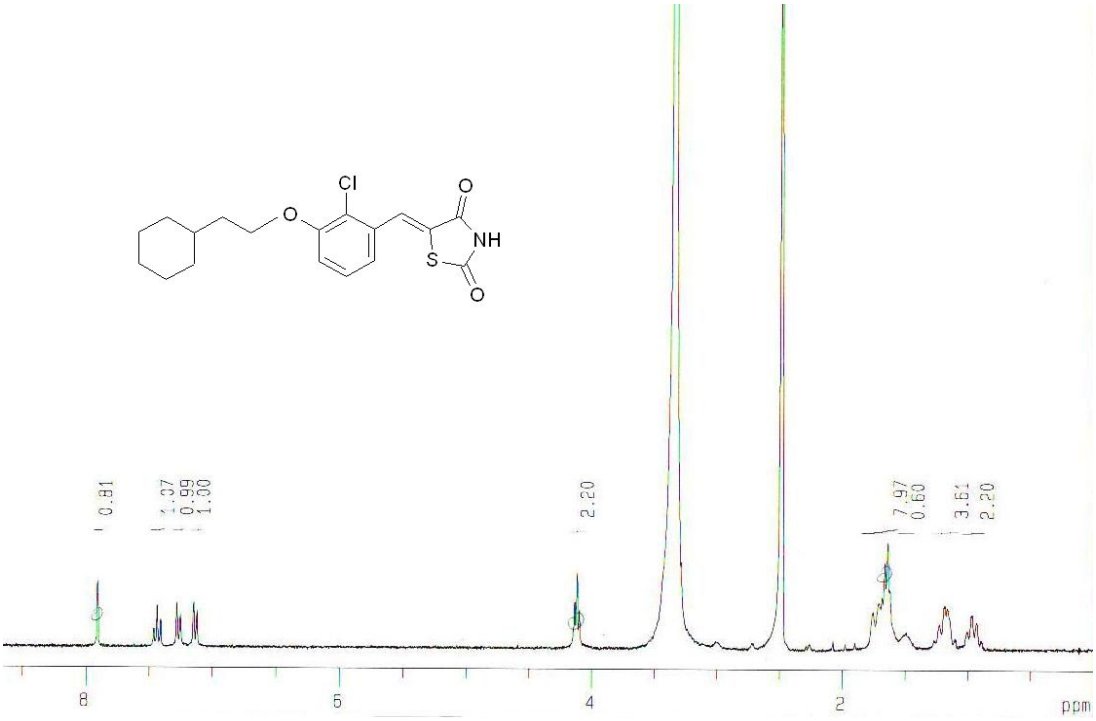
5-(4-(2-cyclohexylbutoxy)-3-nitrobenzylidene)thiazolidine-2,4-dione (68b)



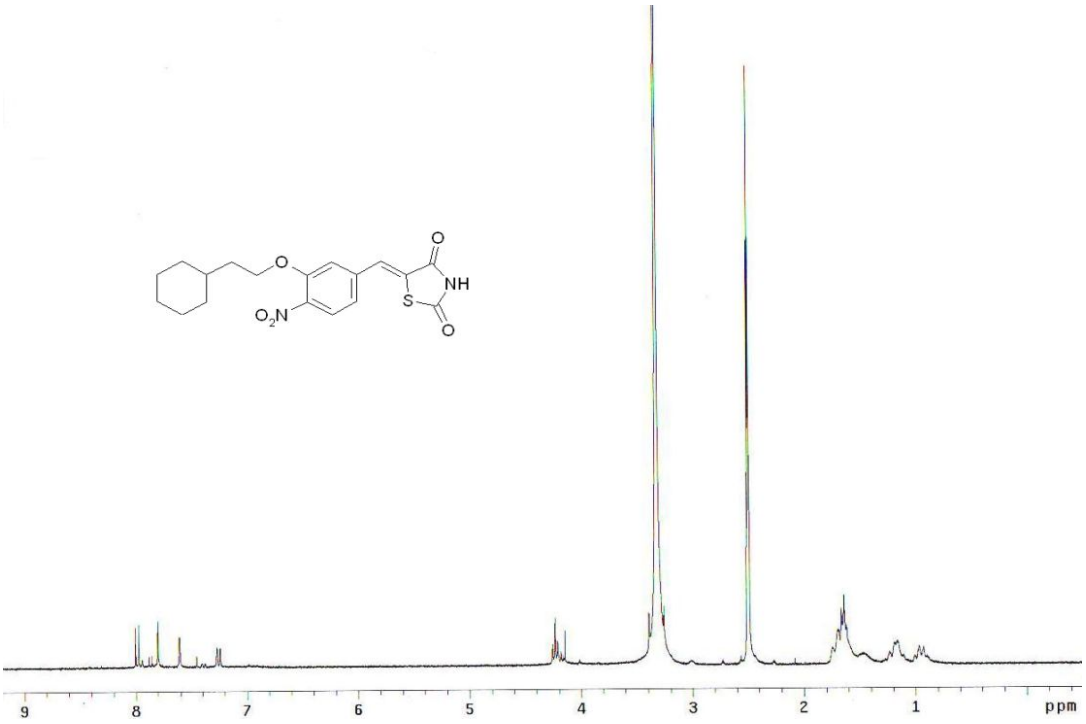
5-[3-chloro-4-(2-Thiomorpholine 1,1-Dioxideethoxy)benzylidene]-2,4-thiazolidinedione (73b)



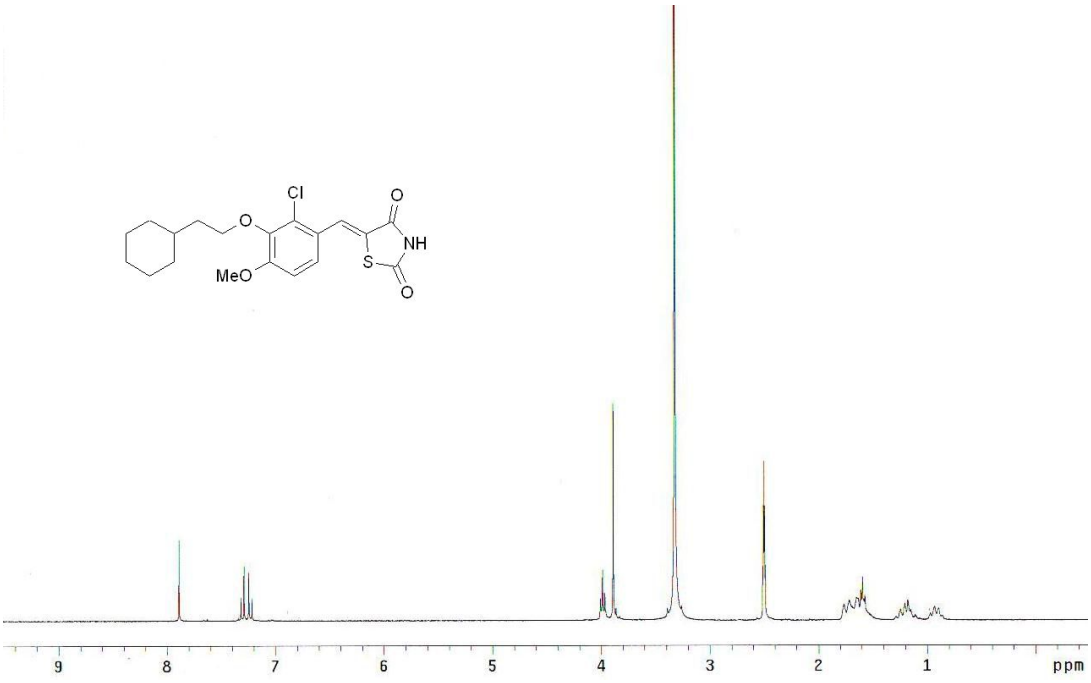
5-[4-((4-metylcyclohexyl)methoxy)-3-(trifluromethyl)benzylidene]thiazolidine-2,4-dione (75b)



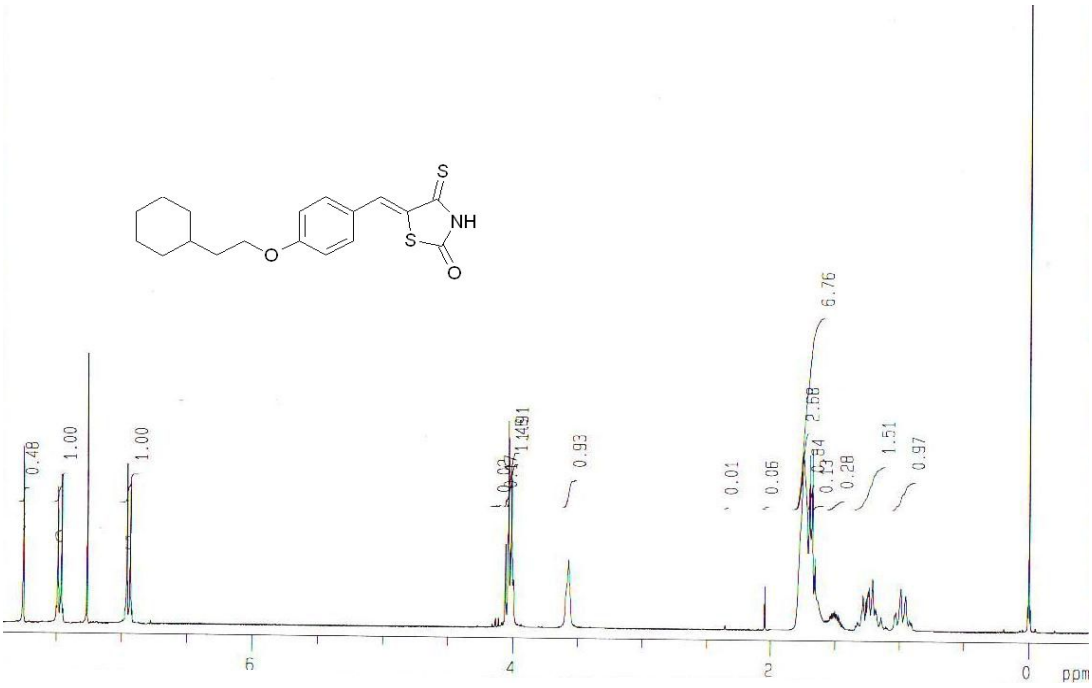
5-(2-chloro-3-(2-cyclohexylethoxy)benzylidene)thiazolidine-2,4-dione (80b)



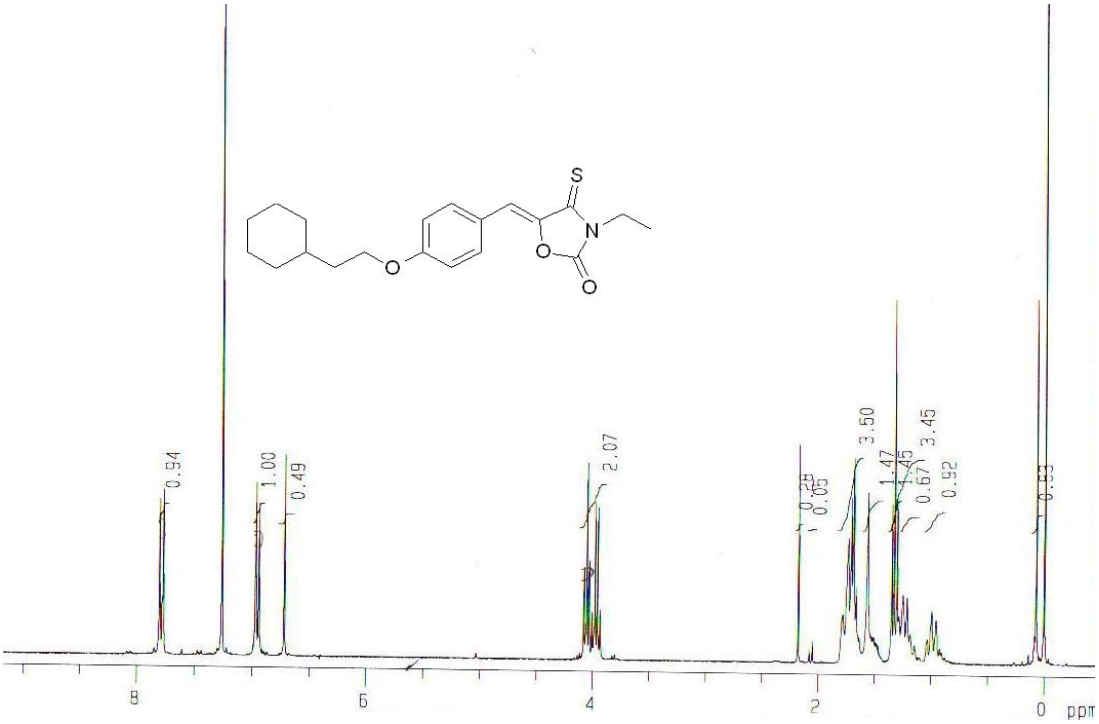
5-(3-(2-cyclohexylethoxy)-4-nitrobenzylidene)thiazolidine-2,4-dione (88b)



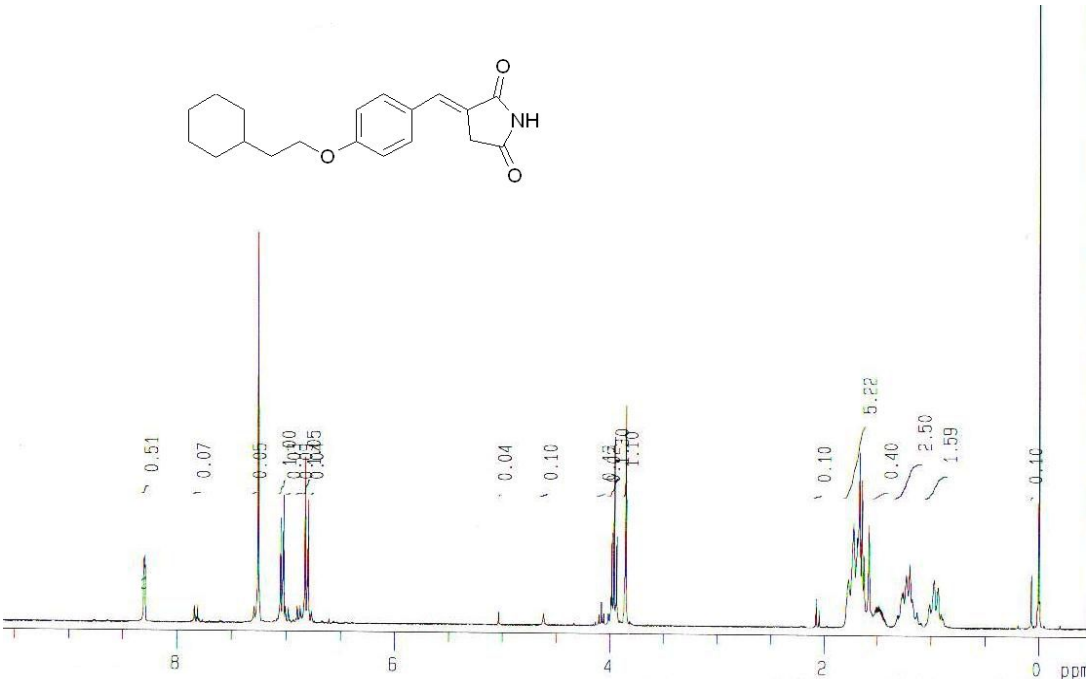
5-(2-chloro-3-(2-cyclohexylethoxy)-4-methoxybenzylidene)thiazolidine-2,4-dione (89b)



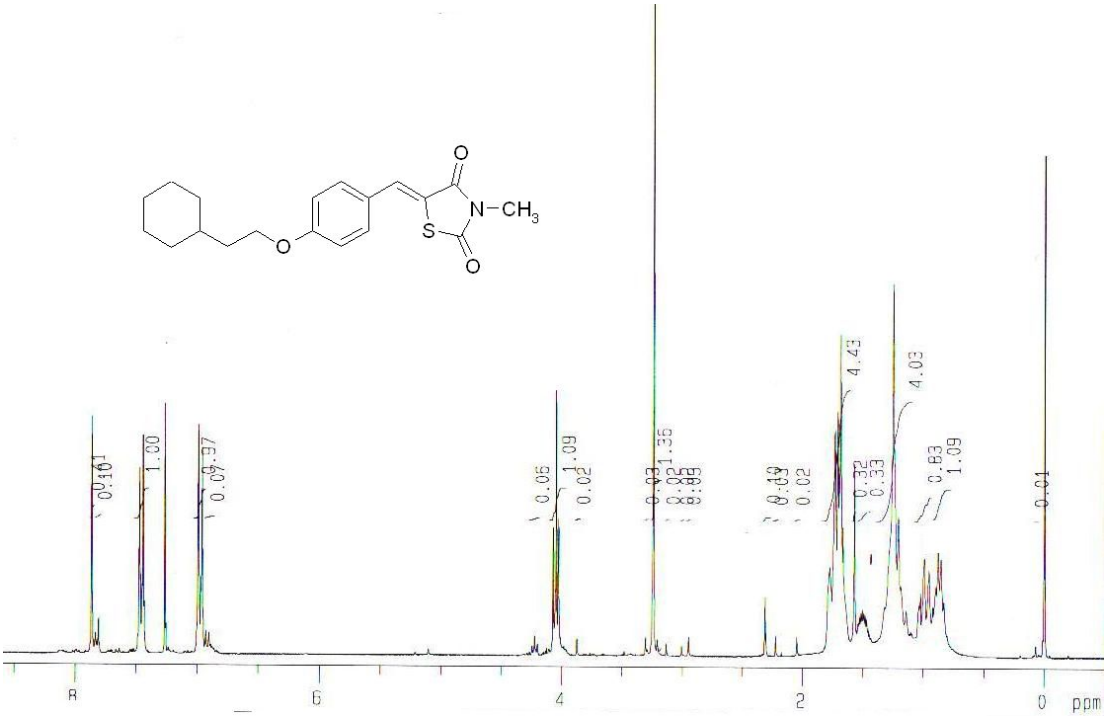
5-(4-(2-cyclohexylethoxy)benzylidene)-4-thioxothiazolidindin-2-one (93)



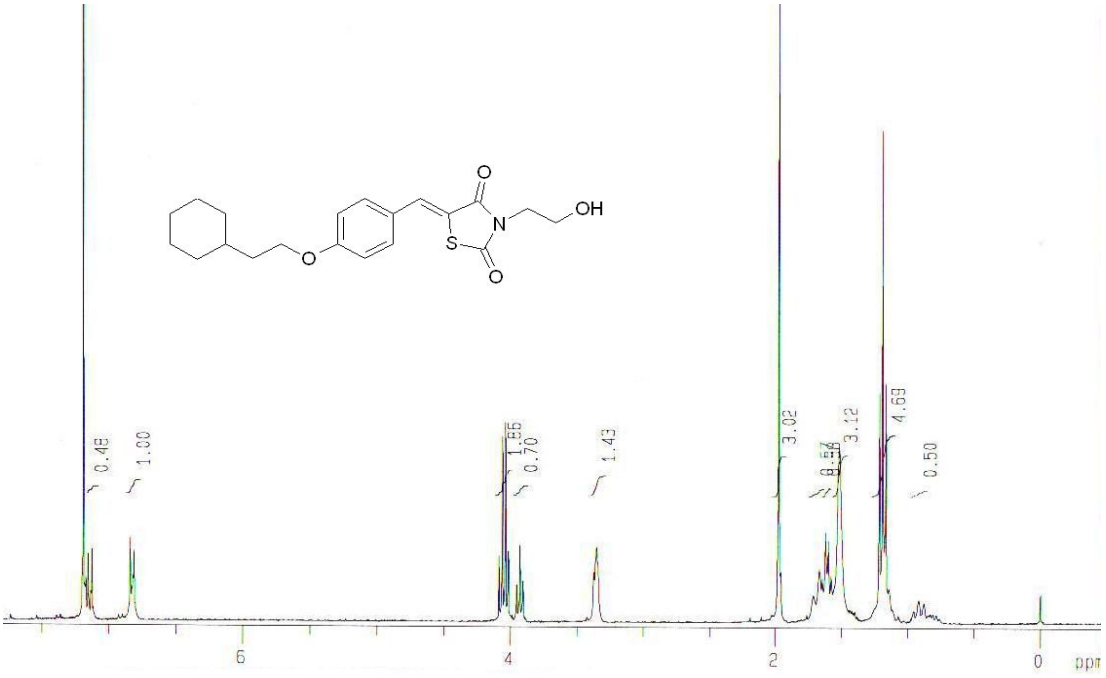
3-(4-(2-cyclohexylethoxy)benzylidene)-3-ethyloxazolidine-2,4-dione (94)



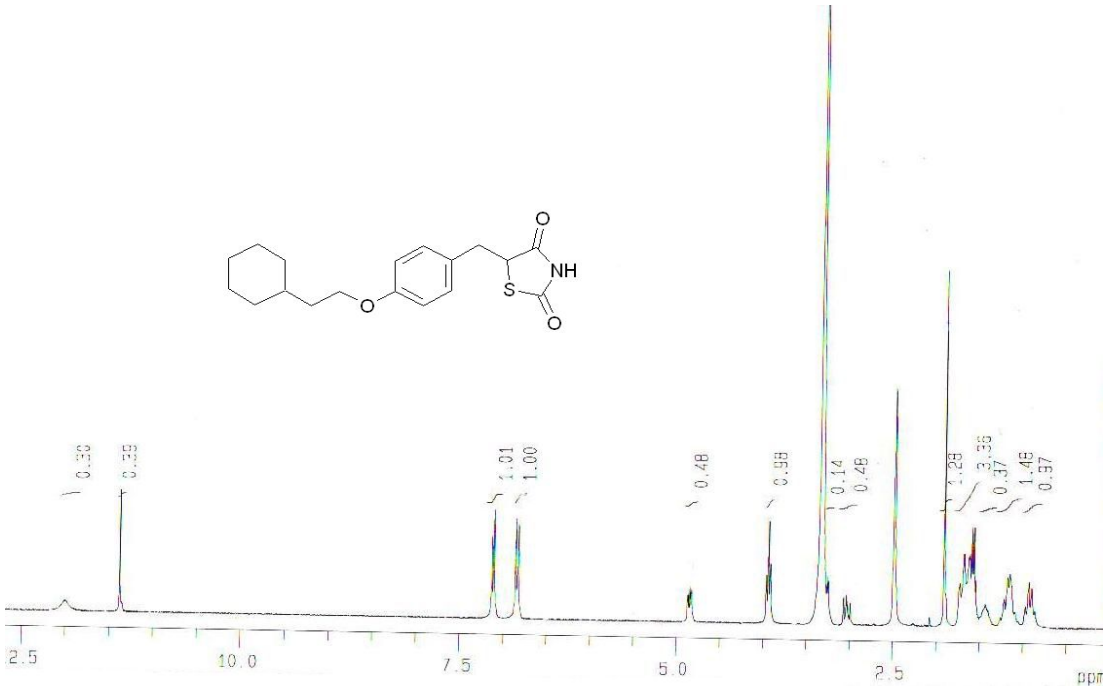
3-(4-(2-cyclohexylethoxy)benzylidene)pyrrolidine-2,5-dione (96)



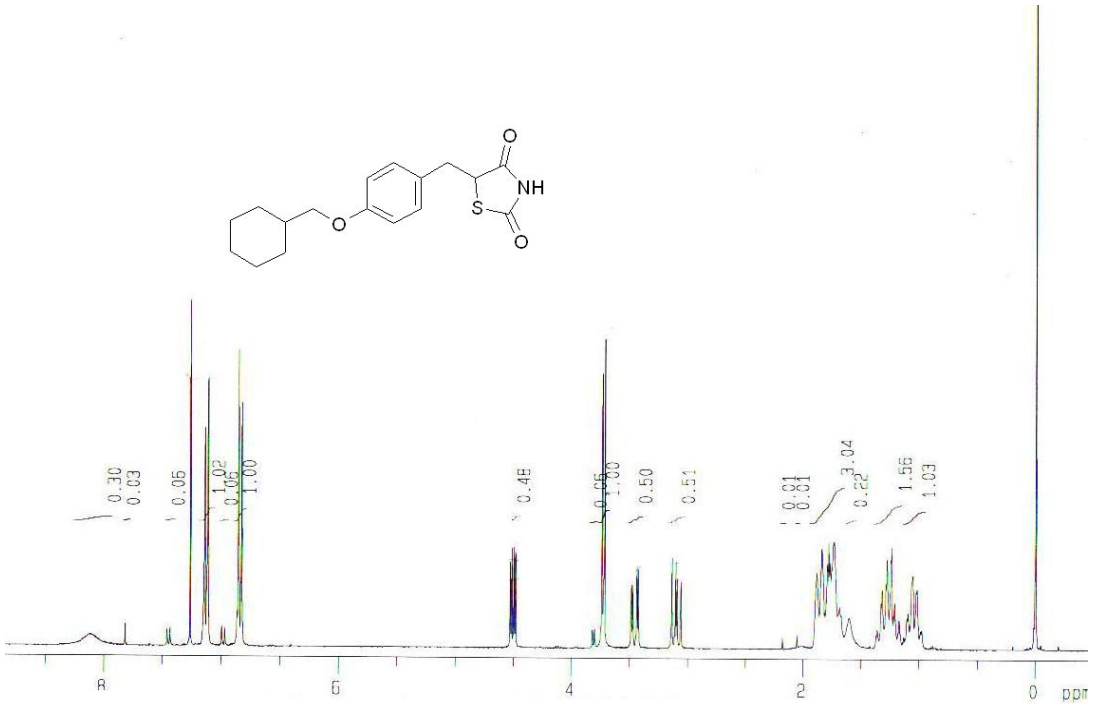
5-[4-(2-cyclohexylethoxy)benzylidene]-3-methyl-1,3-thiazolidine-2,4-dione (97)



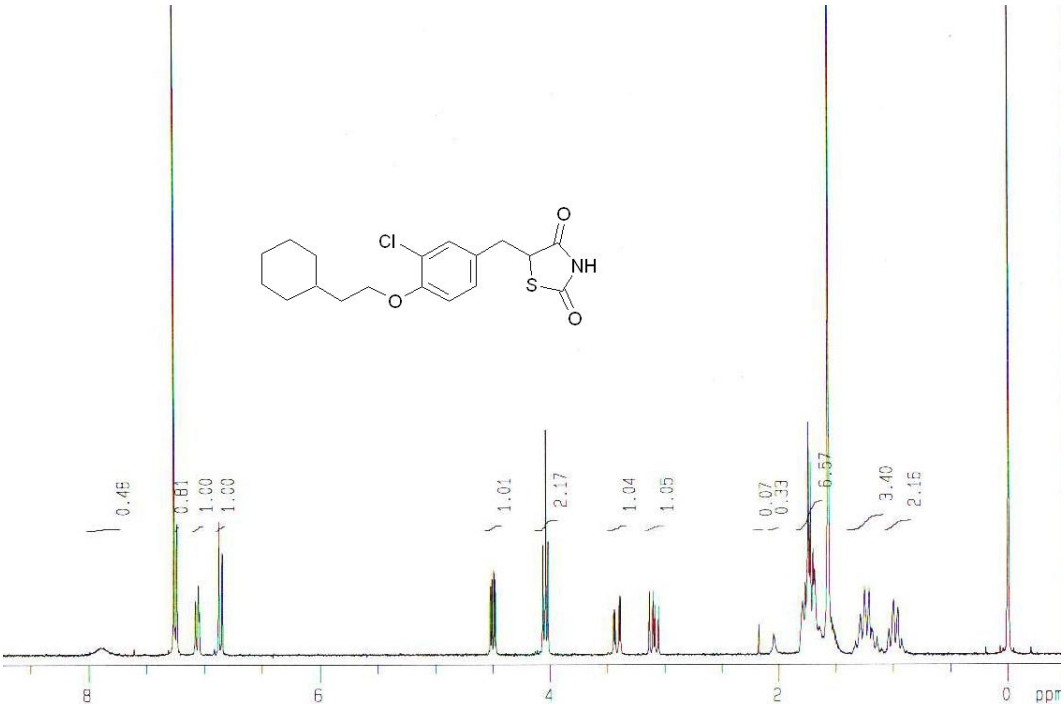
5-[4-(2-cyclohexylethoxy)benzylidene]-3-(hydroxyethyl)-1,3-thiazolidine-2,4-dione (98)



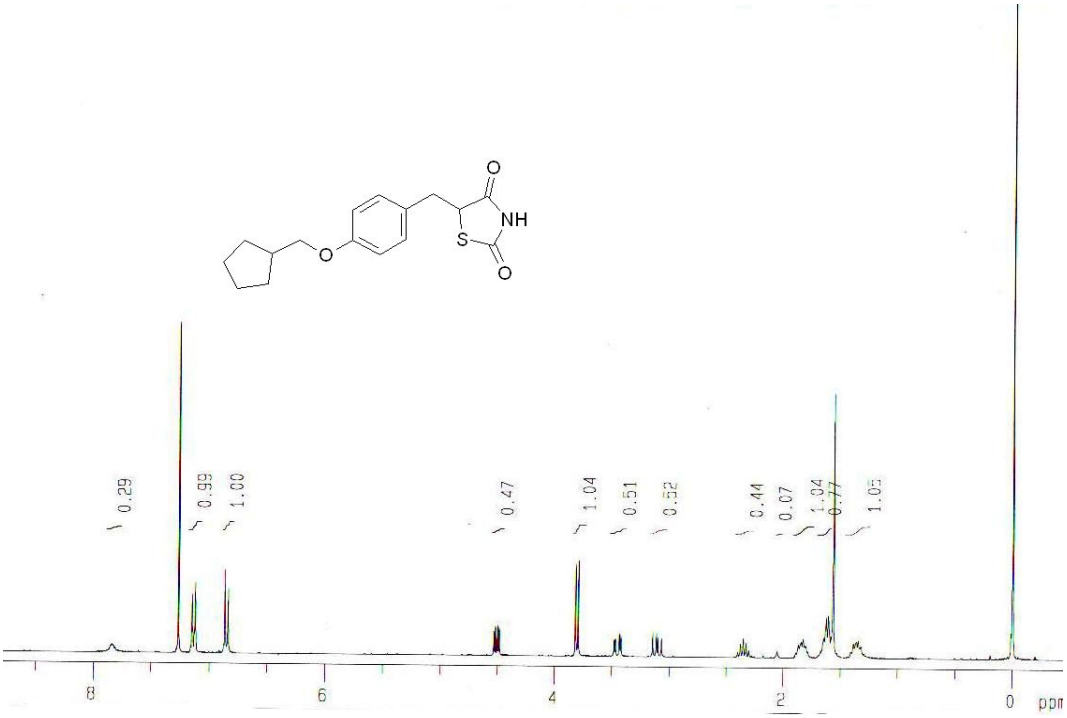
5-(4-(2-cyclohexylethoxy)benzyl) thiazolidine-2,4-dione (99)



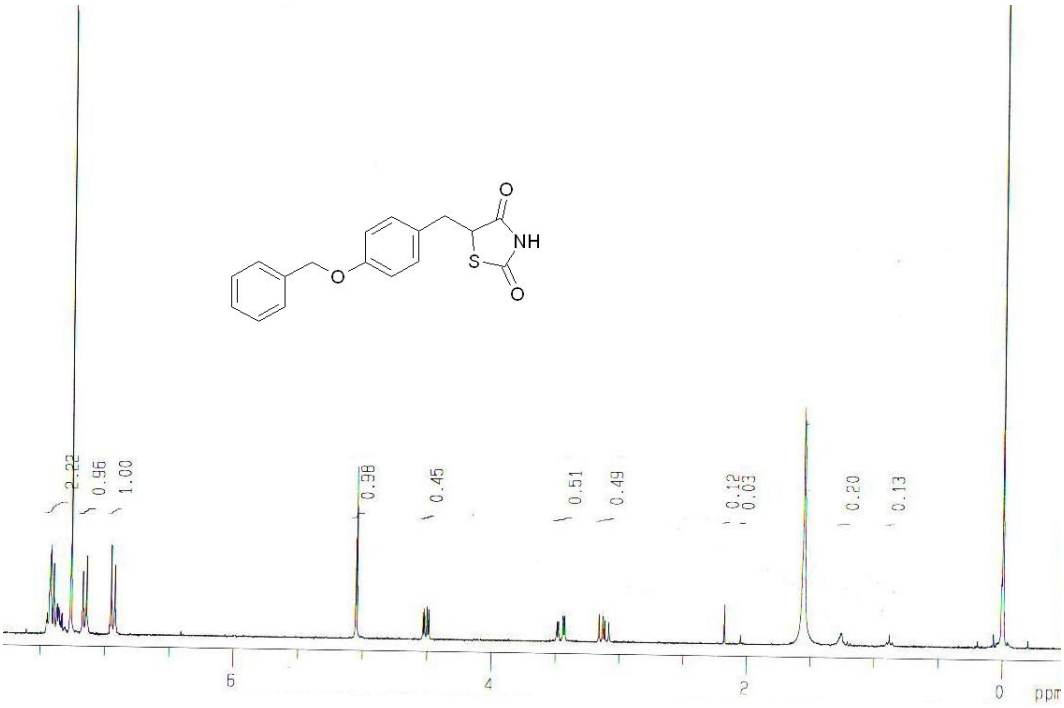
5-(4-(cyclohexylmethoxy)benzyl)thiazolidine-2,4-dione (100)



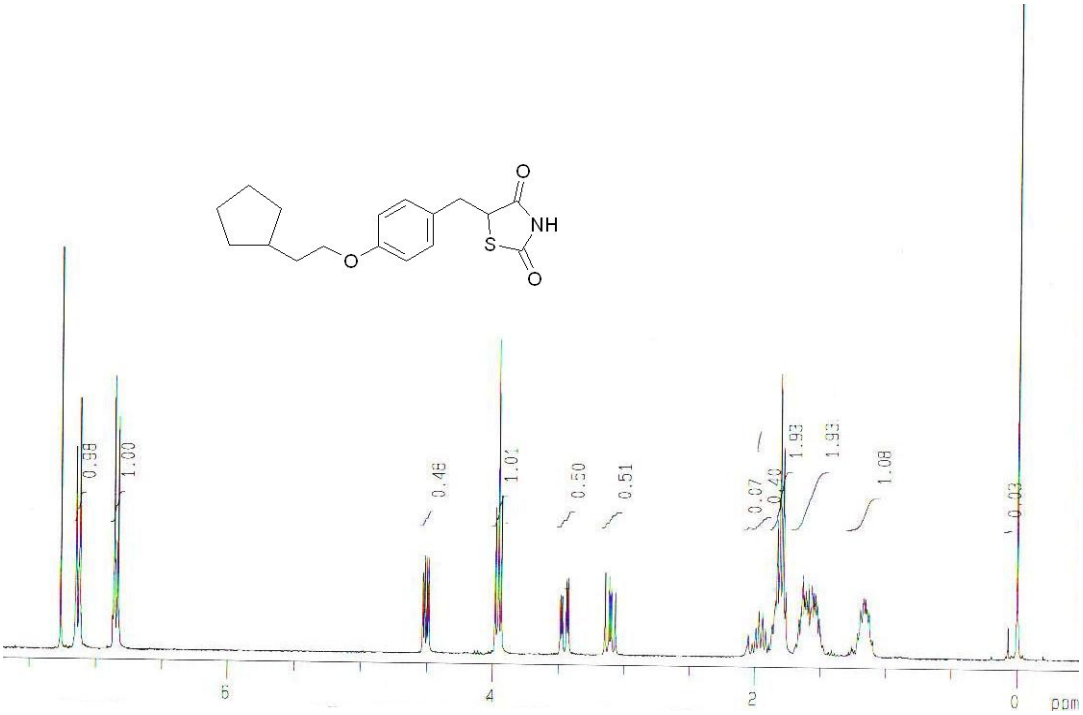
5-(3-chloro-4-(2-cyclohexylethoxy)benzyl)thiazolidine-2,4-dione (101)



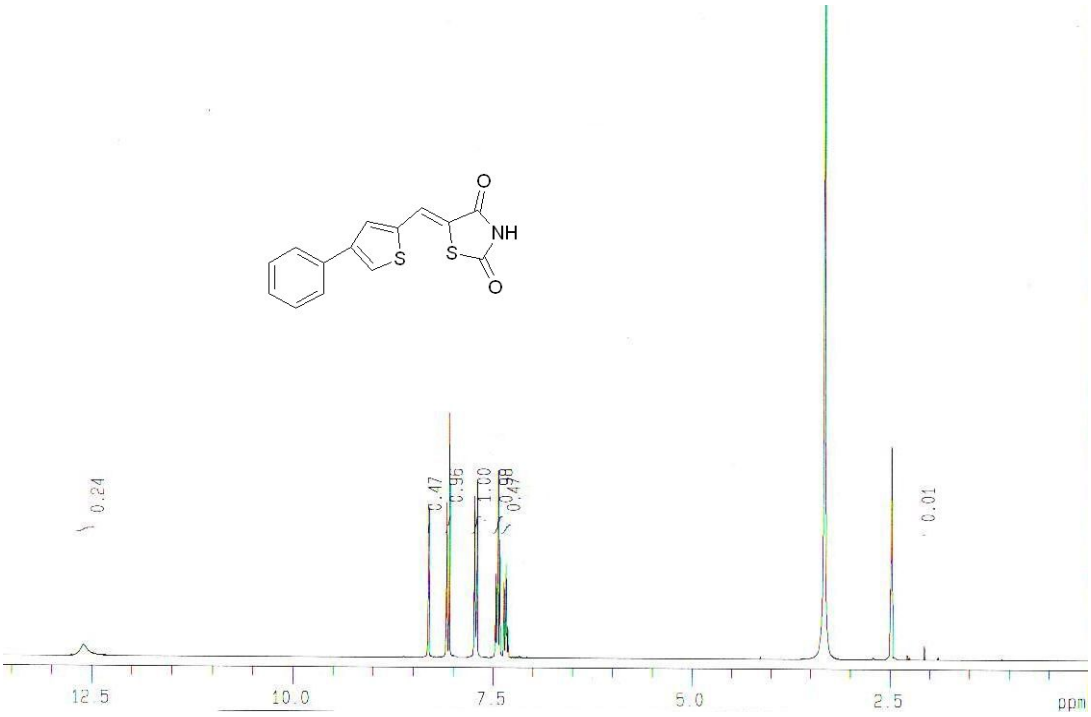
5-(4-(cyclopentylmethoxy)benzyl)thiazolidine-2,4-dione (102)



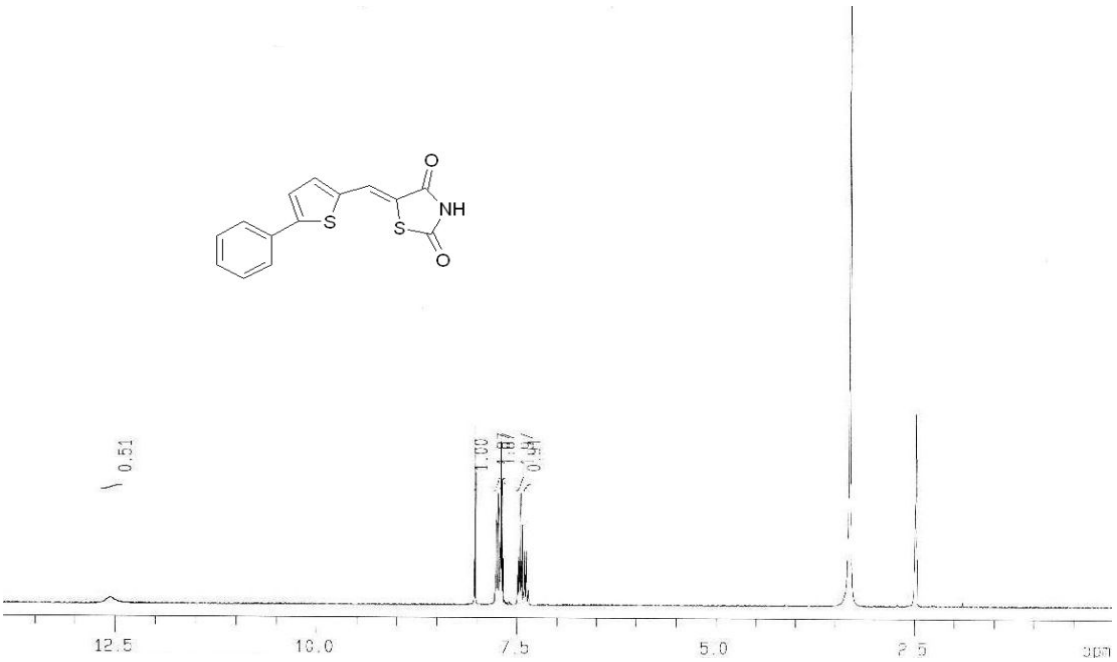
5-(4-(benzyloxy)benzyl)thiazolidine-2,4-dione (103)



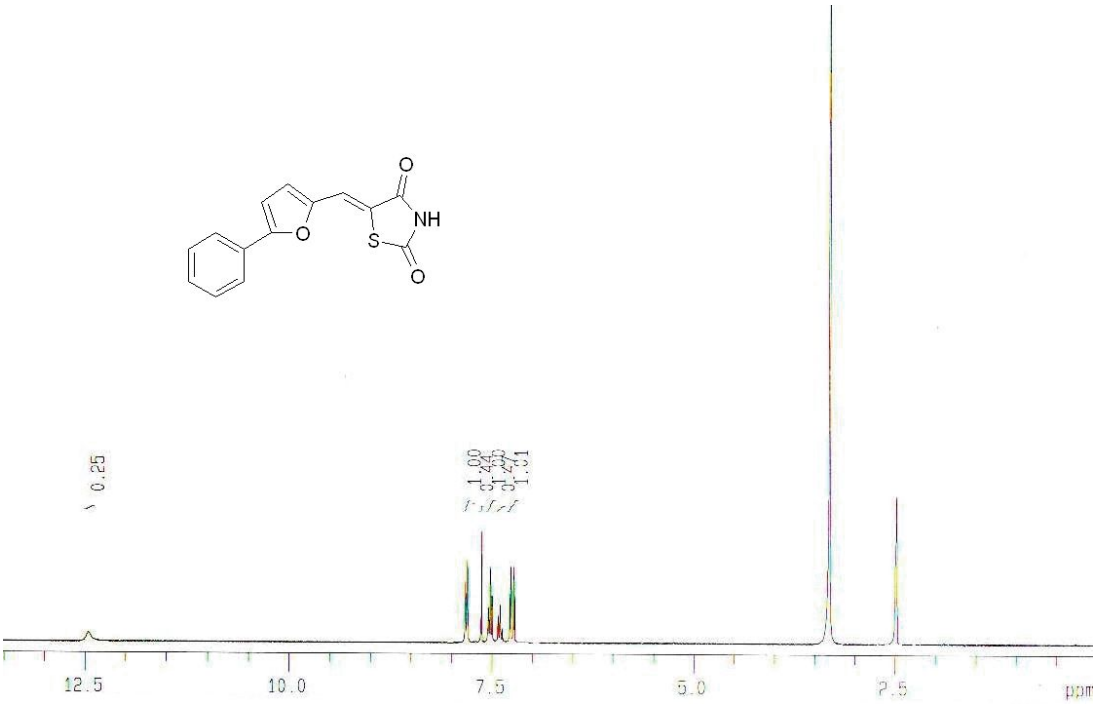
5-(4-(2-cyclopentylethoxy)benzyl)thiazolidine-2,4-dione (106)



5-((4-phenylthiophen-2-yl)methylene)thiazolidine-2,4-dione (107)



5-[(5-phenylthiophen-2-yl)methylidene]-1,3-thiazolidine-2,4-dione (108)



5-[(5-phenylfuran-2-yl)methylidene]-1,3-thiazolidine-2,4-dione (109)

Acknowledgements

I would like to express sincere gratitude to principal supervisor, Prof. Hoon Cho, for providing this especial opportunity and support. By this constant guidance, I have been able to complete it successfully. I would like to thank Prof. Jae-Kon Choi, Prof. Ji-Kang Yoo, Prof. Joon-Seop Kim, Prof. Jin-Who Hong and Prof. Cheol-Hee Choi for their valuable suggestion. I am also grateful to all other members of our lab for their help during my study period.

Last but not least, I would like to express heartfelt to my family members for their constant support and encouragement to me in my pursuit.

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논문제목	한글: 약물설계를 위한 thiazolidinedione계 15-PGDH 억제제 합성 및 구조 활성 분석 영문: Synthesis and structure activity relationship of thiazolidinedione derivatives as 15-PGDH inhibitors				

본인이 저작한 위의 저작물에 대하여 다음과 같은 조건아래 조선대학교가 저작물을 이용할 수 있도록 허락하고 동의합니다.

- 다 음 -

1. 저작물의 DB구축 및 인터넷을 포함한 정보통신망에의 공개를 위한 저작물의 복제, 기억장치에의 저장, 전송 등을 허락함
2. 위의 목적을 위하여 필요한 범위 내에서의 편집과 형식상의 변경을 허락함. 다만, 저작물의 내용변경은 금지함.
3. 배포・전송된 저작물의 영리적 목적을 위한 복제, 저장, 전송 등은 금지함.
4. 저작물에 대한 이용기간은 5년으로 하고, 기간종료 3개월 이내에 별도의 의사표시가 없을 경우에는 저작물의 이용기간을 계속 연장함.
5. 해당 저작물의 저작권을 타인에게 양도하거나 또는 출판을 허락을 하였을 경우에는 1개월 이내에 대학에 이를 통보함.
6. 조선대학교는 저작물의 이용허락 이후 해당 저작물로 인하여 발생하는 타인에 의한 권리 침해에 대하여 일체의 법적 책임을 지지 않음
7. 소속대학의 협정기관에 저작물의 제공 및 인터넷 등 정보통신망을 이용한 저작물의 전송・출력을 허락함.

동의여부 : 동의(O) 반대( )

2010 년 6 월

저작자: 무영 (인)

조선대학교 총장 귀하