August 2010

MS Thesis

Synthesis and SAR of thiazolidinedione as a novel class of algicides against harmful algal species

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유해조류 제어를 위한 thiazolidinedione 유도체 합성 및 구조 활성 분석

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2010 년 8 월 25 일

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지도교수 조 훈

이 눈문을 공학 석사학위신청 논문으로 제출함

2010 년 4 월

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DUONG THI UYEN 의

석사학위논문을 인준함

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2010 년 5 월

조선대학교 대학원

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LIST OF ABBREVIATIONS

A.sp.: Amphidinium sp.

$CDCl_3$: Choloroform

C. marina: Chattonella marina

C. polykrikoides: Cochlodinium polykrikoides

DEAD: Diethyl azodicarboxylate

DMSO: Dimethylsulfoxide

H. akashiwo: Heterosigma akashiwo

HABs: Harmful algal blooms

Hz: Hertz

IC_{50}: The half maximal inhibitory concentration

NFRDI: National fisheries research & development institute

PPARs: Peroxisome proliferator-activated receptors

P.EPV: Phaeodactylum EPV

Pcs: Phthalocyamines

Ppm: Parts per million

THF: Tetrahydrofuran, anhydrous

TMS: Tetramethylsilane

TD: Thiazolidinedione

TLC: Thin layer chromatography

PPh_3: Triphenylphosphine

초 록

유행조류 제어를 위한 thiazolidinedione 유도체 합성 및 구조 활성 분석

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TD 화합물은 1990 년 말경 제 2 형 당료병 및 관련질환 치료를 위한 보조약물로 사용되기 시작하였다. TD 화합물은 세포내에서 인슐린에 대한 신체반응성을 개선시켜줄 수 있도록 낮은 인슐린저항성을 갖도록 유도하는 것으로 알려져 있다. 따라서 환경적으로 안전하고 선택적인 살조물질을 개발하기위해 본 연구에서는 이미 안전성이 검증된 41 종의 TD 유도체를 합성하였으며, 유해조류에 대한 활성을 측정하였다. 대부분의 TD 유도체들은 무해조류에 대해서는 낮은 살조효과를 보인반면 유해조류인 *Heterosigma akashiwo, Chattonella marina* 그리고 *Cochlodinium polykrikoides* 에 대하여 높은 살조효과를 보였다. 특히, 화합물 **2c, 9c, 13c, 21c, 26c, 35c, 37c** 는 *Cochlodinium polykrikoides* 에 대하여 0.5 μM 보다 낮은 IC_{50} 값에서 살조능을 보였다. 특히, 화합물 **3c, 9c, 22c, 41c** 는 *Heterosigma akashiwo* 및 *Chattonella marina* 에 대해서는 30 - 130 μM 의 높은 IC_{50} 값을 보인 반면 *Cochlodinium polykrikoides* 에 대하여 0.1 - 2 μM 범위의 낮은 IC_{50} 값에서 살조능을 보임으로써 *Cochlodinium polykrikoides* 에 대해 높은 선택성을 보였다. 이러한 결과들은 TD 유도체가 유해조류 제어를 위한 살조제로 사용이 가능할 것으로 보인다.

ABSTRACT

Synthesis and SAR of thiazolidinedione as a novel class of algicides against harmful algal species

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Thiazolidinedione (TD) was introduced in the late 1990s as an adjunctive therapy for diabetes mellitus (type 2) and related diseases. TD have been known to lower an insulin resistance in cells, improving the way that the body responds to insulin. In addition to a healthy diet and exercise, they are another way to control blood sugar levels. Therefore, a design of environmentally safe and selective algicides has been an ongoing research topic to manage a growth of harmful algal species. In this thesis, I describe the synthesis of 41 TD derivatives and tested their algicidal activity against microalgae causing a harmful algal blooming. Among the 41 compounds tested, most of them showed effective for algicidal activity against *Heterosigma akashiwo, Chattonella marina* and C*ochlodinium polykrikoides*, while non-harmful algae were relatively tolerant to these TD derivatives. In particular, compounds **2c, 9c, 13c, 21c, 26c, 35c** and **37c** were the most potent against C. polykrikoides with low IC_{50} values than 0.5 μM. Among the TD derivatives tested, compounds **3c, 9c, 22c** and **41c** were extremely competent and selective to C*ochlodinium polykrikoides* with IC_{50} values ranging from 0.1 to 2 μM, while *Chattonella marina* and *Heterosigma akashiwo* showed an IC_{50} value ranging from 30 to 130 μM. These results show that some TD derivatives can potentially used as algicides against harmful algal blooms.

I. INTRODUCTION

Algae are microscopic plants that are usually aquatic, unicellular, and lack true stems, roots, and leaves. When environmental conditions such as high nutrient or light levels are favorable for their development, these algae can developed rapidly and form high numbers of cells; this is called an algal bloom. Some of these blooms are harmless, but when the blooming organisms contain toxins, other noxious chemicals, or pathogens, it is known as a harmful algal blooms (HABs). From time some time, a bloom often results in a color change in the water. Algal blooms can be any color, but the red or brown colored blooms are most common, referred to red or brown tides.

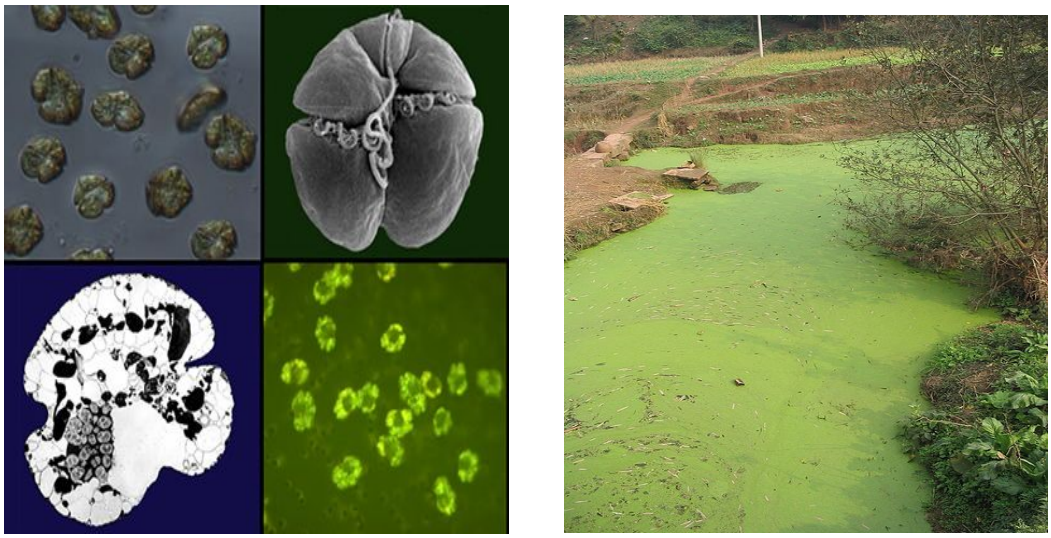


Fig. 1. Algal blooms can present problems for ecosystems and human society

Algal blooms occur in both saltwater and freshwater environments during spring, winter, and summer [1,2], and thus cause harmful through two primary mechanisms. The first category of impacts is the production of toxins: Toxins may kill fish or shellfish directly, or may cause one of several human illnesses following ingestion of contaminated seafood. The second category of impacts is high biomass accumulation, which, in turn, leads to environmental damage or degradation. These effects can include light attenuation, clogging of fish gills, and

depletion of dissolved oxygen upon decay of the algal cells [1,3,4]. Some HABs can even kill fish because of their physical shape, lodging in gill tissues and causing a physiological response leading to death. Moreover, the effect can also be extended to human illness and mortality following consumption of or indirect exposure to HABs toxins, substantial economic losses to coastal communities and commercial fisheries, hindering boat traffic, blocking approaches, obstructing wash processes and catching cavities, creating unattractive foul-smelling loads [1,3,5]. The impact of HABs on aquatic ecosystems, water resources and human health are a major problem throughout the world.

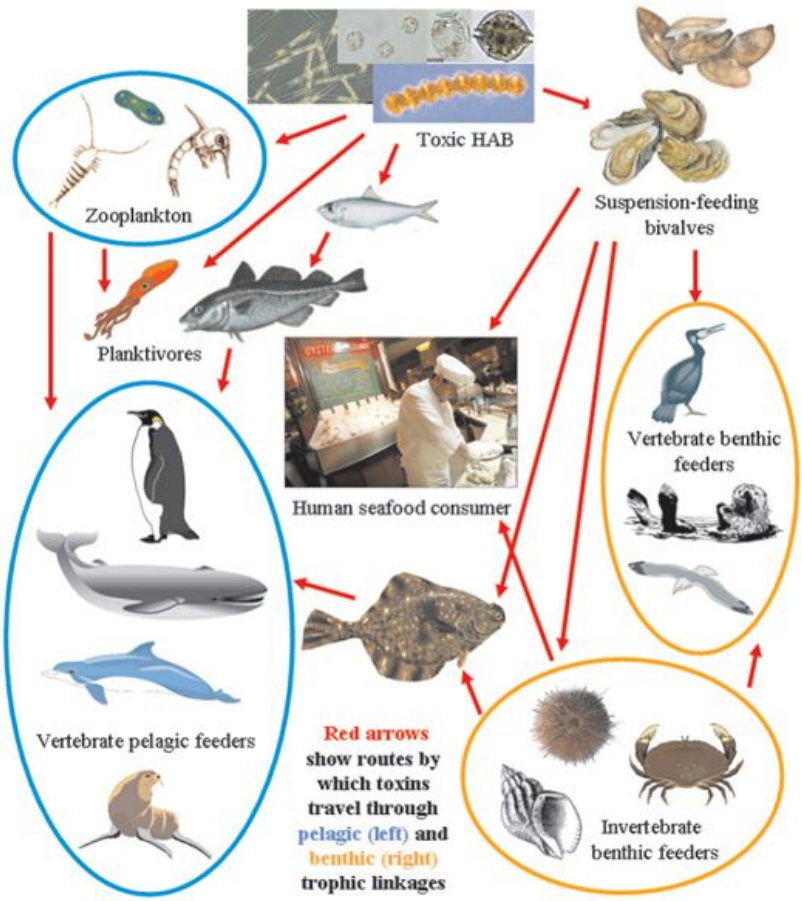


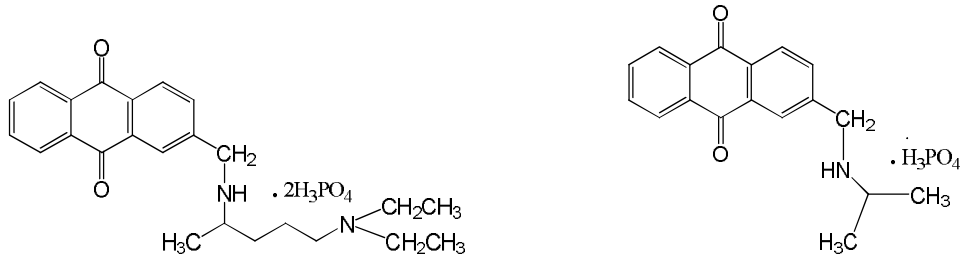
Fig. 2. Trophic linkages between HABs and their ecosystems

Until now, a number of scientists have carried out physiological and ecological studies in the hope of reducing the extent of damage to fisheries caused by HABs [6]. The application of

clay can treat the environmental problems but the toxins released from flocculated cells and the adverse effects on other organisms need to be considered [7]. Clay flocculants are effective in the treatment of Cochlodinium which causes fish deaths in a finfish cage culture in coastal Japan [8] and in Chinese mariculture ponds [9]. Yellow loess is effective in edimenting dinoflagellates [10]. However, ruptured or damaged cells may release intracellular toxins into the urrounding water, which require the use of expensive removal processes, such as activated carbon and/or oxidative ozone and chlorine [11]. Mechanical and physico-chemical methods have been devised in an attempt to manage HABs with a limited success [12].

The application of chemicals is one of the most common methods of controlling the development of noxious phytoplankton, but their use has limitations, such as toxicity towards non-target species [13]. Moreover, some algicides introduce heavy metals to the environment, which, in the long run, can accumulate in sediments. Therefore, considerable effort has been made to identify new compounds that are selectively effective against red tide algae.

Poovey and Getsinger, 2005 evaluated a number of processes of developing selective control techniques for aquatic herbicides. Some chemicals have been used to mitigate HABs, but a search for safer and selective algicidal agents are needed to better control of harmful algal blooms. Copper sulfate, chelated copper compounds, and diuron (3-[3,4-dichlorophenyl]-1,1-dimethylurea), etc. are currently approved by the U.S. Environmental Protection Agency [14]. However, in practice the herbicides diuron and copper sulfate have several drawbacks including broad-spectrum toxicity towards the entire phytoplankton community that can lead to water quality deterioration and subsequent fish death. By use of microtiter plate bioassays, a novel group of compounds (Fig. 3.) derived from the natural 9,10-Anthraquinone have been found to be much more selective toxicity towards cyanobacteria than other phytoplankton.



[A] [B]

Fig. 3. Structures of 2-[methylamino-N-(1'–methyl-4'-N,N-dimethylaminobutyl)] anthraquinone diphosphate [A] and 2-[methylamino-N-(1'–methylethyl)]-9,10-anthraquinone diphosphate [B]

Also, 2-[methylamino-N-(1'–methylethyl)]-9,10-anthraquinone diphosphate [B] has much lower persistence in pond water (half- life of 19h) than diuron, which can persis for weeks in the water column after application to fish aquaculture ponds (half- life of 2 weeks in pond water. Evironment safety issues also persist on the use of copper sulfate in fish ponds, since the copper accumulates in the pond sediments and long-term applications may adversely affect microbial activity in the pond sediments[15].

Judith F. Blom, 2005 demonstrated that nostocarboline **(4)** and seven derivatives (Fig. 4) display potent cyanobacteriocidal and algicidal activity against photosynthetic aquatic organisms. The benefits of nostocarboline **(4)** were known to include potent and fast reduction of phytoplankton growth, cheap and simple preparation, natural algicide, and structure which is amenable to easy modification, resulting in more potent derivatives [35].

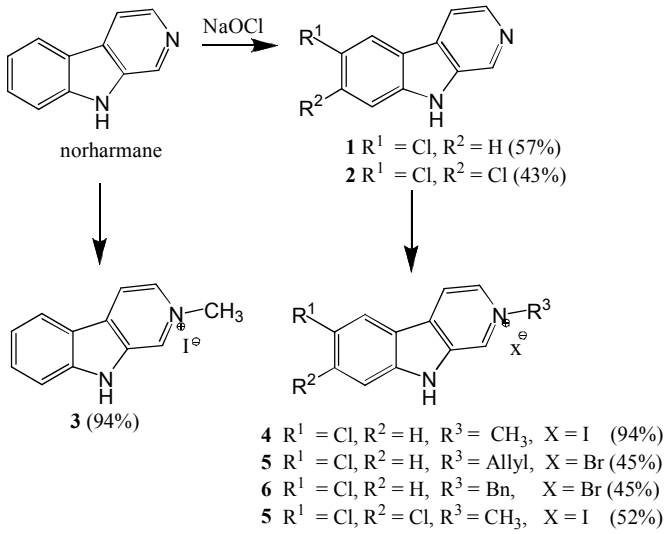


Fig. 4. Preparation of Nostocarboline **(4)** and derivatives

Phthalocyamines (Pcs) belong to the group of photosensitizers. In recent years, the phthalocyamine therapy has also been used against bacterial, yeasts and fungal infections [16,17]. Several studies showed that phthalocyamines appeared to be effective inhibitors of various gram-negative and gram-positive bacteria. Especially, positively charged phthalocyamines were studied regarding their bactericidal effect on gram-negative bacteria [18,19]. It was also favorable when Jancula, D, 2008 synthesized 31 phthalocyamines derivatives that could be new algicidal compounds potentially available for water management,

also investigated toxicity of these compounds to non-target organisms (Daphnia magna) and aimed to find possible negative effect of these compounds.

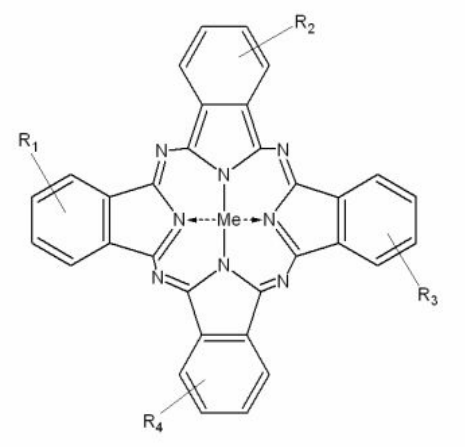


Fig. 5. Common chemical structure of phthalocyamines

The most direct control method involves the use of chemical treatments, such as algicides, including copper, reglone a (diquat, 1,1-ethylene-2,2-dipyridilium dibromide), potassium permanganate, chlorine and simazine (2-chloro-4,6-bis(ethylamino)-s-triazine, clotrimazole [20,21]. Unfortunately, these compounds have undesirable characteristics, including broad-spectrum toxicity towards phytoplankton that can result in the death of the entire phytoplankton community, subsequent water quality deterioration that can result in the death of the entire phytoplankton community, and lengthy persistence that creates environmental safety concerns [14,22]. Natural antialgal compounds extracted from a range of bioresources have also been reported. These include furano-diterpenes [23] at low biosurfactant concentrations [24], alleo-chemical [25], and barley straw. Other studies [25,26, 27] have also attempted to manage red tide growth using controlling agents.

Thiazolidinedione (TD) was introduced in the late 1990s as an adjunctive therapy for diabetes mellitus (type 2) and related diseases. TD act by binding to PPARs (peroxisome proliferator-activated receptors), a group of receptor molecules inside the cell nucleus [28]. The design of environmentally safe, selective algicides to manage the growth of harmful algal species has also been an ongoing research topic. In this preliminary SAR study, various substituents were introduced to the hydroxyl group of 5-(4-hydroxybenzylidene)thiazolidine-2,4-dione and the effects of these derivatives on the growth of a number of harmful algal species were tested. This thesis describes the results of laboratory tests on the efficacy of the

synthetic TD derivatives to control harmful algal species. The TD derivatives were very competent and selective against the HABs studied and exhibited IC_{50} in the nanomolar range.

II. MATERIALS AND METHODS

1. Materials

The chemicals and reagents used in this work were commercially avaible from Sigma-Aldrich or Merck. All the moisture- sensitive reations were performed in an inert atmosphere with either N_2 using distilled dry solvents.

^{1}H NMR spectra in each compound were acquired with spectrometer at 296 K, in 300 MHz. Each sample was dissolved in $CDCl_3$ or DMSO using TMS (tetramethylsilane) as internal standard. Chemical shifts (δ scale) are quoted in parts per million (ppm) and the following abbreviations are used: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) some combinations of these were made by DEPT editing of the spetra. J coupling constants were measured in Hz (Hertz) unit.

Column chromatography was performed by using silica gel after preparing a slurry with the eluent mixtureand packing it into the chromatography column. A fraction of the collected samples were analyzed by thin layer chromatography (TLC).

2. Algal cultures, mediums and culture conditions

Heterosigma akashiwo (CCMP 452) (*H. akashiwo*) was obtained from the Provasoli-guillard center for the culture of marine phytoplankton (CCMP). The microalga, *Chattonella marina* (*C. marina*) and *Amphidinium* sp. Were kindly provided by Professor. M-S. Han at Life Science Department of Hanyang University in Korea.

The red tide causing marine strain *Cocholodium polykrikoides* (*C. polykrikoides*) was obtained from the algal culture collection of National Fisheries Research & Development Institute (NFRDI). *Nannochlopsis* sp. and *Phaeodactylum* EPV were kindly provided by Professor M.-K. Kim from Young Nam University in Korea.

Cultures of *H. akashiwo*, *C. marina* and *C. polykrikoides*, and non-harmful algae were grown in a culture flask (Becton Dickinson Labware, Franklin Lakes, New Jersey, USA) at 20°C under constant light in Guillard's f/2 medium with filtered seawater as reported previously. The f/2 medium was prepared by a sterile-filtering sea water with 0.22 μm filtration units (Nalgene, Rochester, New York, USA) and enriched aseptically by using nutrients and vitamins purchased from Sigma (St. Louis, MO, USA).

3. Screening of algicidal activities of TD compounds

The algicidal activity of the different TD compounds against *H. akashiwo*, *M. aeruginosa* and *C. polykrikoides* were examined at various concentrations. Each experiment was carried out in 24 well tissue culture test plates (SPL) with approximately one ml total volume per well. Various concentrations of the test compounds were introduced to the cultures during the exponential growth phase. All the microalgae were exposed to the compounds at final concentrations of 100, 50, 20, 10, 5, 2, 1 μM, 0.1 μM and 0.05 μM. As the non-harmful algal control, the TD were applied at concentrations > 500 μM. The control cultures were performed without the TD compounds. The algal cell density was counted 3 days after inoculation them with the compounds. The algal cells were counted using a Burker Turk hemacytometer with Sedgwick–Rafter counting chamber under an Olympus light microscope with x40 and x100 magnification (Olympus Co., Tokyo, Japan). Algicidal activity profiling of the TD compounds growth rates were then calculated and are expressed as the reduction ratio (%) from the number of cell divisions per day. The reduction ratio (%) was determined using the following equation: % Algicidal activity = $[(1-Tt)/Ct] \times 100$, where T (treatment) and C (control) are the cell densities with and without each TD compound at different concentrations and t is the inoculation time (day).

4. Statistical data analysis

The experiments were carried out at least three times. The data is reported as mean value ± standard deviation (SD). All statistical analyses were performed using the SPSS 17.0 software (SPSS, USA). The statistical significance between the differences of the mean values was determined by one-way variance analysis (ANOVA) followed by a Tukey's HSD post hoc test. A p value < 0.05 was considered as a significant range.

5. Methods

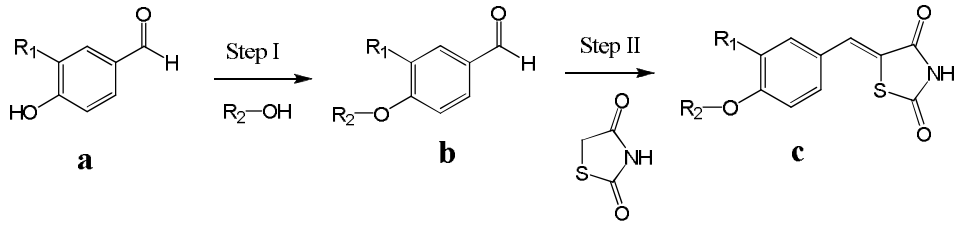
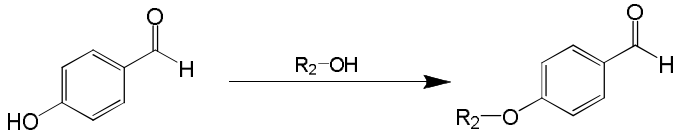


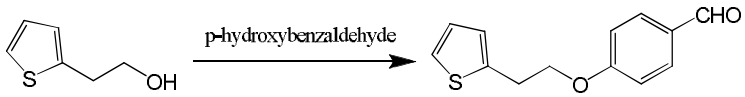
Fig. 6. Summarizes the general synthetic routes for the TD derivatives, R_1= H, CH_3, Cl; R_2 = various substituents to afford substituted benzaldehyde.

5.1. Procedure for the synthesis of compounds b (step I)

5.1.1. General procedure for the synthesis of compound 1b-33b



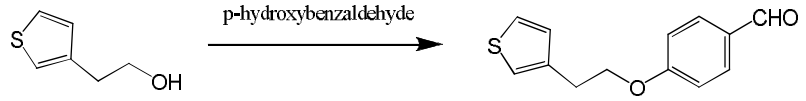
1b: 4-(2-(Thiophen-2-yl)ethoxy)benzaldehyde



1b

To a stirring solution of 2-Thiophene ethanol (1 g, 7.8 mmol), p-hydroxybenzaldehyde (953 mg, 7.8 mmol) and PPh_3 (2.25 g, 8.6 mmol) in THF (20 mL) was added DEAD (40% in toluene, 3.74 g, 8.6 mmol) at 0^oC over 10 min. The mixture was then stirred at room temperature until disappearing the starting materials (TLC analysis). 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 (1.57 g, 86%) of the intermediate products **1b** 4-(2-(Thiophen-2-yl)ethoxy)benzaldehyde as yellow oil; ^1H 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).

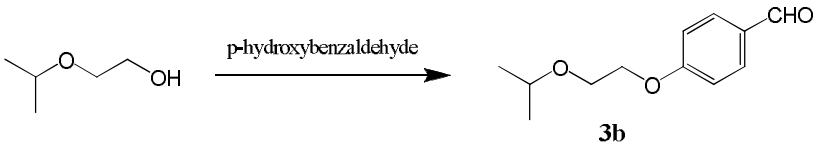
2b: 4-(2-(Thiophen-3-yl)ethoxy)benzaldehyde



2b

To afford intermediate as yellow oil (1.57 g, 86%); ^{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).

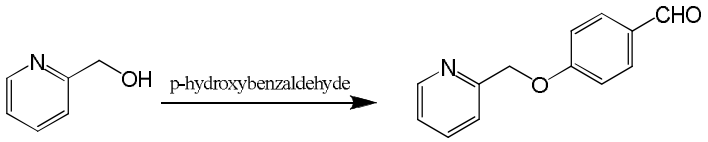
3b: 4-(2-Isopropoxyethoxy)benzaldehyde



3b

To afford intermediate as yellow oil (0.98 g, 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).

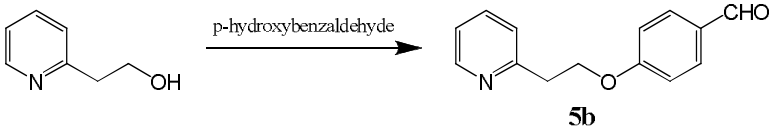
4b: 4-(Piridin-2-ylmethoxy)benzaldehyde



4b

To afford intermediate as yellow oil (1.54 g, 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).

5b: 4-(2-(Piridin-2-yl)ethoxy)benzaldehyde

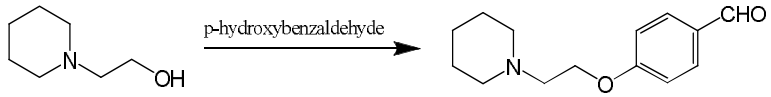


5b

To afford intermediate as yellow oil (1.55 g, 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).

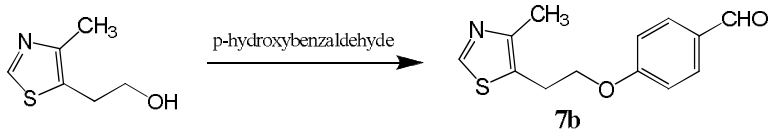
6b: 4-(2-(Piperidin-1-yl)ethoxy)benzaldehyde



6b

To afford intermediate as yellow oil (1.58 g, 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).

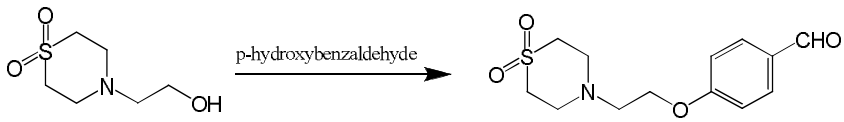
7b: 4-(2-(4-Methylthiazol-5-yl)ethoxy)benzaldehyde



7b

To afford intermediate as yellow oil (1.55 g, 86%); ^{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).

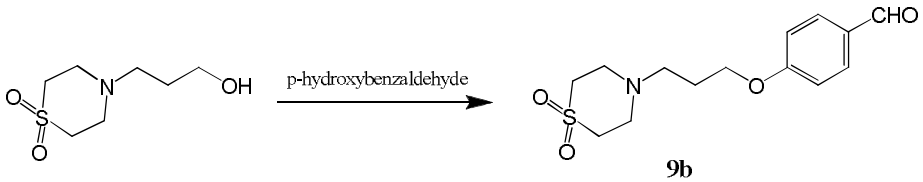
8b: 4-(2-Thiomorpholine 1,1-dioxideethoxy)benzaldehyde



8b

To afford intermediate as yellow oil (1.37 g, 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).

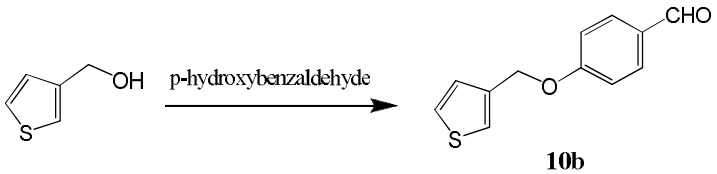
9b: 4-(3-Thiomorpholine 1,1-dioxidepropoxy)benzaldehyde



9b

To afford intermediate as yellow oil (1.38 g, 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).

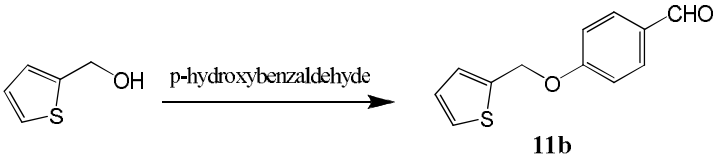
10b: 4-(Thiophen-3-ylmethoxy)benzaldehyde



10b

To afford intermediate as yellow oil (1.55 g, 86%); ^{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).

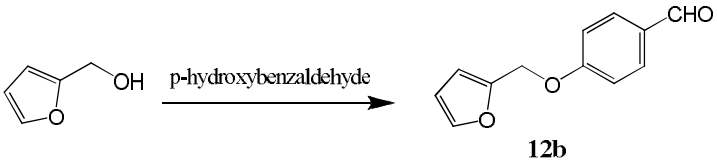
11b: 4-(Thiophen-2-ylmethoxy)benzaldehyde



11b

To afford intermediate as yellow oil (1.56 g, 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).

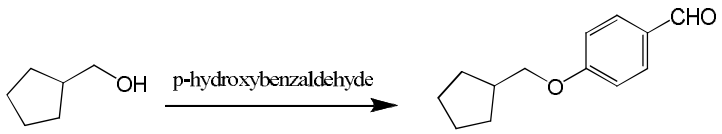
12b: 4-(Furan-2-ylmethoxy)benzaldehyde



12b

To afford intermediate as yellow oil (1.49 g, 86%); ^{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).

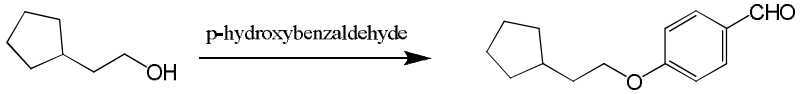
13b: 4-(Cyclopentylmethoxy)benzaldehyde



13b

To afford intermediate as yellow oil (1.54 g, 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)

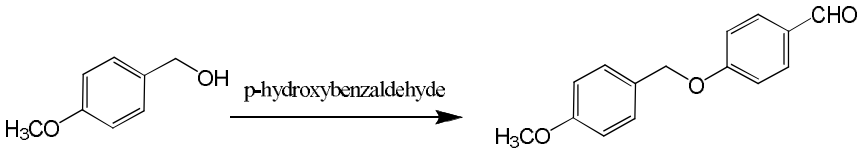
14b: 4-(2-Cyclopentylethoxy)benzaldehyde



14b

To afford intermediate as yellow oil (1.6 g, 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).

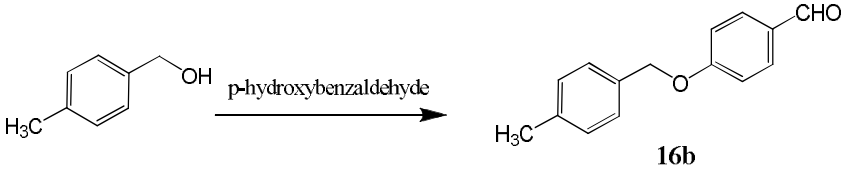
15b: 4-(4-Methoxybenzyloxy)benzaldehyde



15b

To afford intermediate as yellow oil (1.55 g, 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).

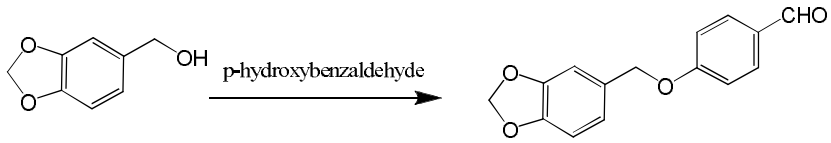
16b: 4-(4-Methylbenzyloxy)benzaldehyde



16b

To afford intermediate as yellow oil (1.54 g, 85%); ^{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).

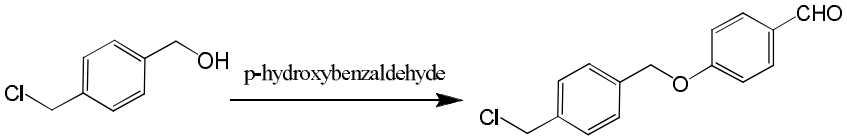
17b: 5-(4-Benzo[d][1,3]dioxol-5-ylmethoxy)benzaldehyde



17b

To afford intermediate as yellow oil (1.57 g, 85%); ^{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).

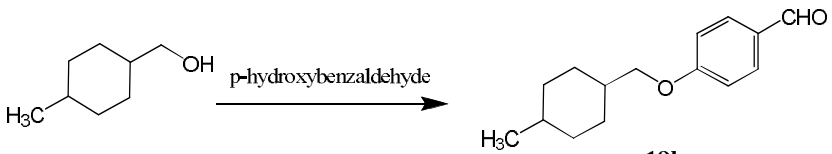
18b: 4-(4-(Chloromethylbenzyloxy)benzaldehyde



18b

To afford intermediate as yellow oil (1.58 g, 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).

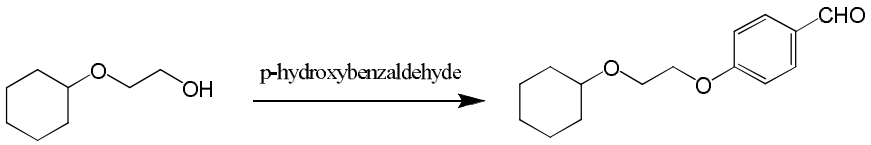
19b: 4-(4-Methylcyclohexylmethoxy)benzaldehyde



19b

To afford intermediate as yellow oil (1.68g, 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).

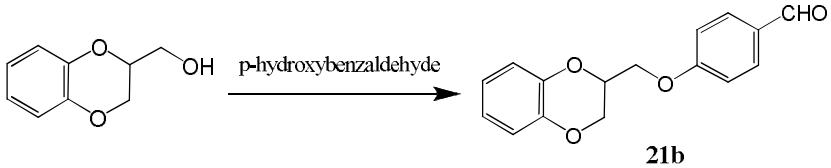
20b: 4-(2-(Cyclohexyloxy)ethoxy)benzaldehyde



20b

To afford intermediate as yellow oil (1.60g, 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).

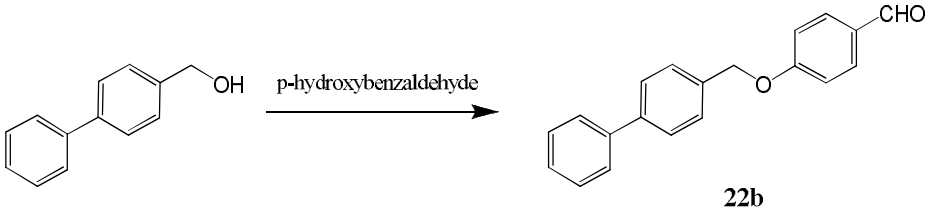
21b: 4-((2,3-Dihydrobenzo[b][1,4]dioxin-2-yl)methoxy)benzaldehyde



21b

To afford intermediate as yellow oil (1.56g, 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).

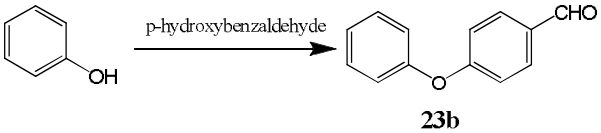
22b: 4-(Biphenyl-4-ylmethoxy)benzaldehyde



22b

To afford intermediate as yellow oil (1.50g, 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).

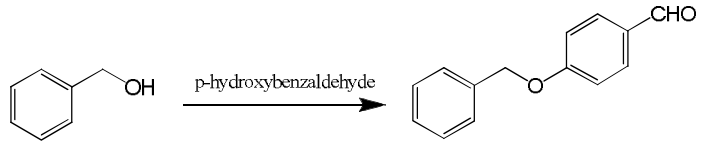
23b: 4-(Phenoxy)benzaldehyde



23b

To afford intermediate as yellow oil (1.50 g,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).

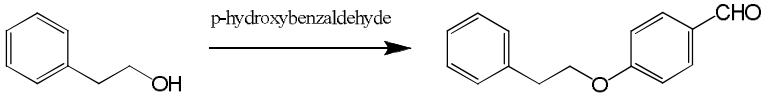
24b: 4-(Penzyloxy)benzaldehyde



24b

To afford intermediate as yellow oil (1.51 g, 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).

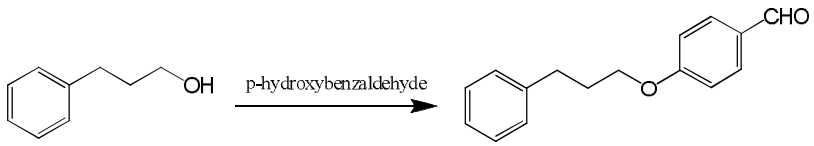
25b: 4-(2-Phenylethoxy)benzaldehyde



25b

To afford intermediate as yellow oil (1.50 g, 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).

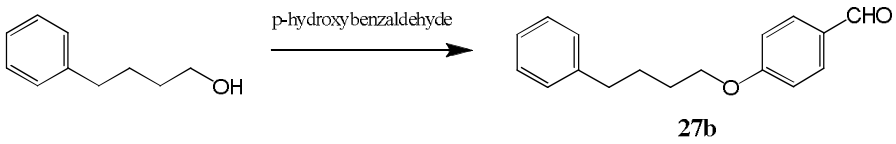
26b: 4-(2-Phenylpropoxy)benzaldehyde



26b

To afford intermediate as yellow oil (1.62 g, 84%);^{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).

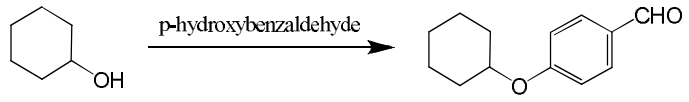
27b: 4-(4-Phenylbutoxy)benzaldehyde



27b

To afford intermediate as yellow oil (1.66 g, 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).

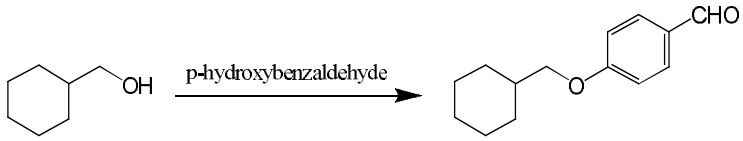
28b: 4-(Cyclohexyloxy)benzaldehyde



28b

To afford intermediate as yellow oil (1.76 g, 89%);^{1}H NMR (300 MHz, $CDCl_3$) δ10.013 (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).

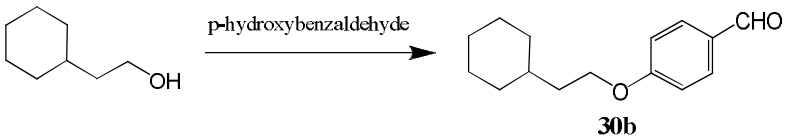
29b: 4-(Cyclohexylmethoxy)benzaldehyde



29b

To afford intermediate as yellow oil (1.29 g,72%); ^{1}H NMR (300 MHz, $CDCl_3$) δ10.00 (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).

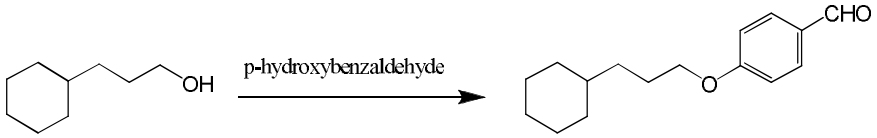
30b: 4-(2-Cyclohexylethoxy)benzaldehyde



30b

To afford intermediate as yellow oil (1.6 g, 89%); ^{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).

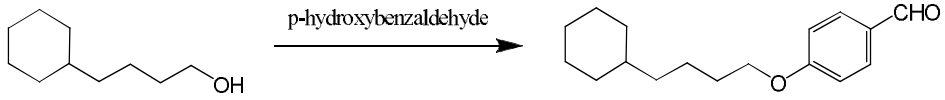
31b: 4-(3-Cyclohexylpropoxy)benzaldehyde



31b

To afford intermediate as yellow oil (1.45 g, 81%); ^{1}H NMR (300 MHz, $CDCl_3$) δ10.001(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).

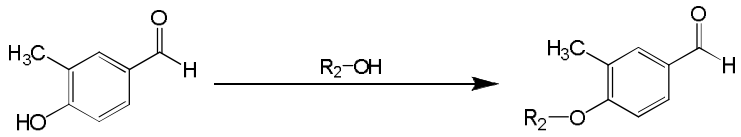
32b: 4-(4-Cyclohexylbutoxy)benzaldehyde



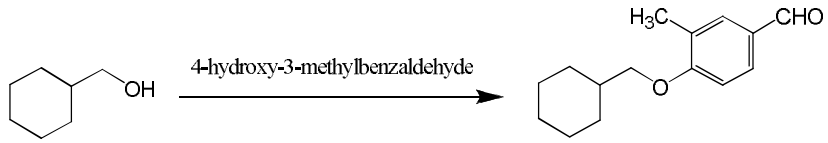
32b

To afford intermediate as yellow oil (1.25 g, 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).

5.1.2. General procedure for the synthesis of compound 33b-36b



33b: 4-(Cyclohexylmethoxy)-3-methylbenzaldehyde

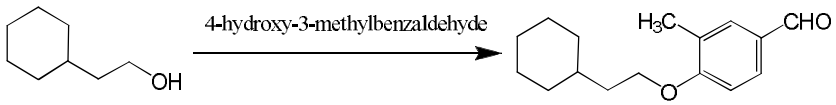


33b

To a stirring solution of Cyclohexylmethanol (1 g, 8.8 mmol), 4-hydroxy-3-methylbenzaldehyde (1.19 g, 8.8 mmol) and PPh_3 (2.79 g, 9.68 mmol) in THF (20 mL) was added DEAD (40% in toluene, 4.21 g, 9.68 mmol) at 0^{o}C over 10 min. The mixture was then stirred at room temperature until the starting materials had disappeared (TLC analysis). 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 (1.62 g, 87%) of the intermediate products **33b** 4-(cyclohexylmethoxy)-3-methylbenzaldehyde as yellow oil; ^{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)

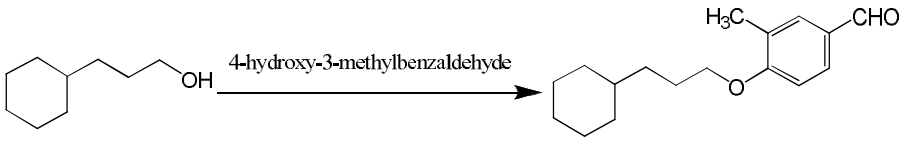
34b: 4-(2-Cyclohexyleyhoxy-3-methyl)benzaldehyde



34b

To afford intermediate as yellow oil (1.6 g, 89%); ^{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),

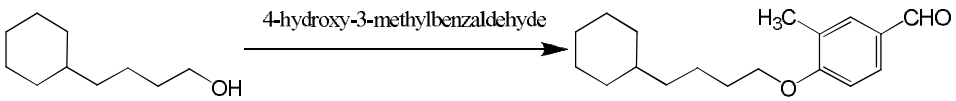
35b: 5-(4-(2-Cyclohexylpropoxy)-3-methylbenzylidene)thiazolidine-2,4-dione



35b

To afford intermediate as yellow oil (1.23 g, 89.1% yield); ^{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).

36b: 5-(4-(2-Cyclohexylbutoxy)-3-methylbenzylidene)thiazolidine-2,4-dione

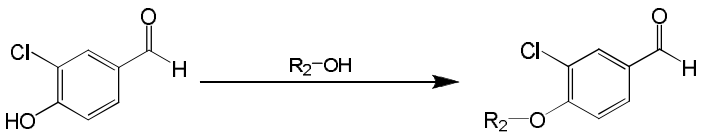


36b

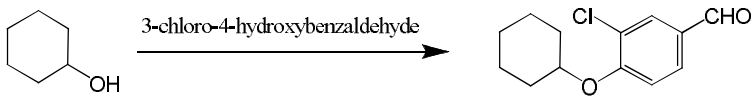
To afford intermediate as yellow oil (1.19 g, 87.5% yield); ^{1}H NMR (300 MHz, DMSO-d_6) δ7.787 (s, 1H), 7.349 (d, J = 8.7 Hz, 2H), 7.291 (s, 1H), 6.903(d, J = 8.7Hz, 2H), 4.045 (t, J

= 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).

5.1.3. General procedure for the synthesis of compound 37b-41b



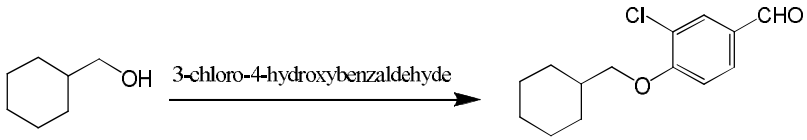
37b: 3-Chloro-4-(cyclohexyloxy)benzaldehyde



37b

To a stirring solution of cyclohexanol (1 g, 10 mmol), 3-chloro-4-hydroxybenzaldehyde (1.22 g, 10 mmol), and PPh_3 (2.89 g, 11 mmol) in THF (20 mL) was added DEAD (40% in toluene, 4.79 g, 11 mmol) at 0^oC over 10 min. The mixture was then stirred at room temperature until the starting materials had disappeared (TLC analysis). 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 intermediate as yellow oil (1.74 g, 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).

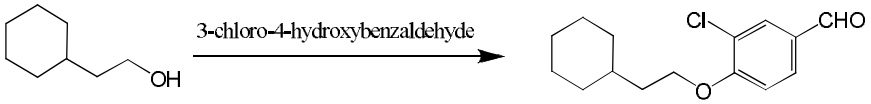
38b: 3-Chloro-4-(cyclohexylmethoxy)benzaldehyde



38b

To afford intermediate as yellow oil (1.67 g, 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).

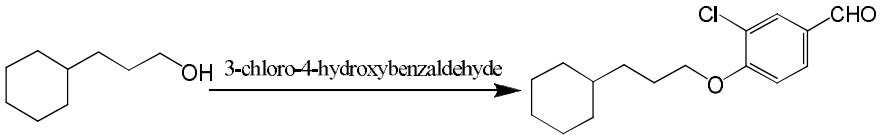
39b: 3-Chloro-4-(2-cyclohexylethoxy)benzaldehyde



39b

To afford intermediate as yellow oil (1.6 g, 89%); ^{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).

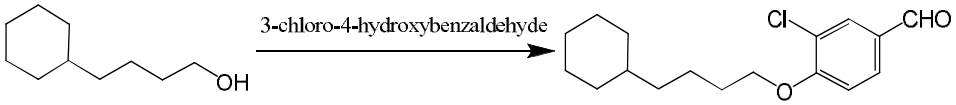
40b: 3-Chloro-4-(3-cyclohexylpropoxy)benzaldehyde



40b

To afford intermediate as yellow oil (1.6 g, 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).

41b: 3-Chloro-4-(4-cyclohexylbutoxy)benzaldehyde

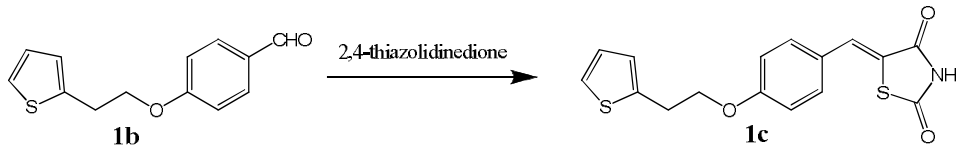


41b

To afford intermediate as yellow oil (1.41 g, 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).

5.2. General procedure for the synthesis of compounds c (step II)

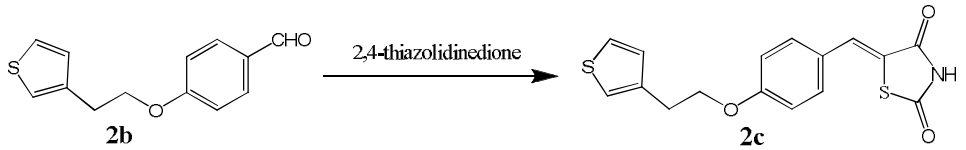
1c: 5-(4-(2-Thiophen-2-yl)ethoxy)benzylidene)thiazolidine-2,4-dione



1b **1c**

A mixture of product **(1b) 4-(2-(thiophen-2-yl)ethoxy)benzaldehyde** (1 g, 4.3 mmol) and 2,4-thiazolidinedione (504 mg, 4.3 mmol), piperidine (0.21 ml, 2.15 mmol), acetic acid (0.12 ml, 2.15 mmol) in toluene (20 mL) was then placed into a round bottom flask fitted with a Dean-Stark water trap and stirred overnight under reflux. After cooling to room temperature, the precipitate was washed with hexane and dried to afford compound **(1c).** Obtained by recrystallization as a yellow solid (1.25 g, 87%); ^{1}H NMR (300 MHz, DMSO-d_6) δ8.12 (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).

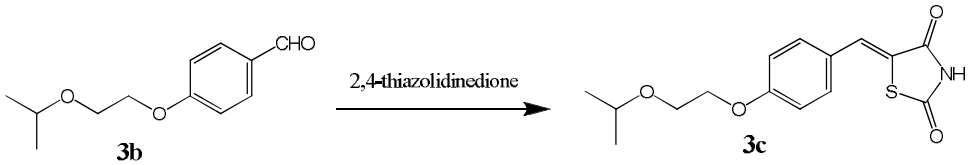
2c: 5-(4-(2-(Thiophen-3-yl)ethoxy)benzylidene)thiazolidine-2,4-dione



2b **2c**

Obtained by recrystallization as a yellow solid (1.24 g, 86% yield); ^{1}H NMR (300 MHz, DMSO-d_6) δ 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).

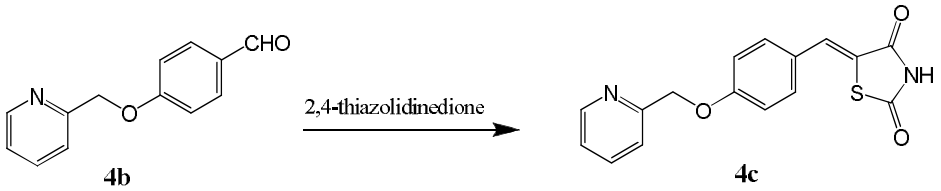
3c: 5-(4-(2-Isopropoxyethoxy)benzylidene)thiazolidine-2,4-dione



3b **3c**

Obtained by recrystallization as a yellow solid (1.26 g, 85.7% yield); ^{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).

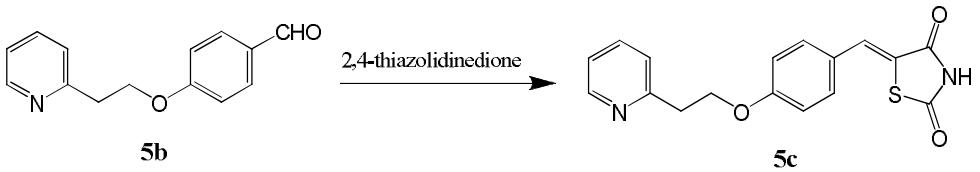
4c: 5-(4-(Piridin-2-ylmethoxy)benzylidene)thiazolidine-2,4-dione



4b **4c**

Obtained by recrystallization as a yellow solid (1.24 g, 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).

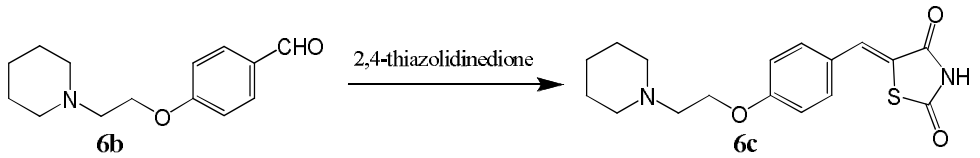
5c: 5-(4-(2-(Piperidin-1-yl)ethoxy)benzylidene)thiazolidine-2,4-dione



5b **5c**

Obtained by recrystallization as a yellow solid (1.13 g, 79.6% yield); ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.522 (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).

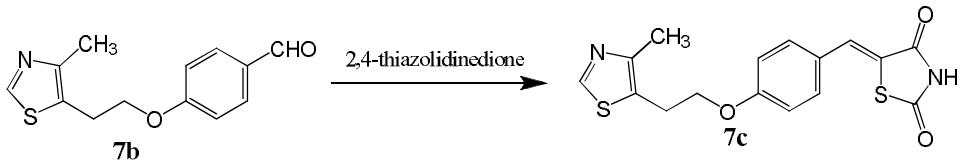
6c: 5-[4-(2-(Piperidin-1-yl)ethoxy)benzylidene]thiazolidine-2,4-dione



6b **6c**

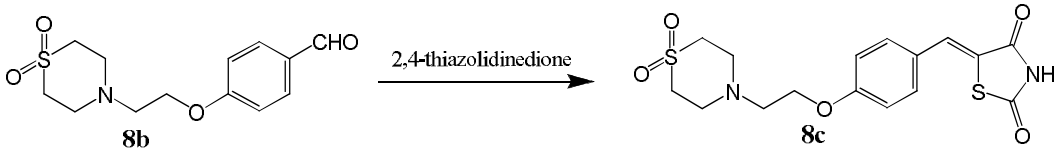
Obtained by recrystallization as a yellow solid (1.26 g, 87%); ^{1}H NMR (300 MHz, DMSO-d_6) δ7.522 (s, 1H), 7.411 (d, J = 10.2 Hz, 2H), 6.967 (d, J = 10.2 Hz, 2H), 4.096 (t, J = 11.1 Hz, 2H), 2.814 (t, J = 11.1 Hz, 2H), 2.379 (m, 4H), 1.410-1.513 (m, 4H), 1.291-1.307 (m, 2H).

7c: 5-(4-(2-(4-Methylthiazol-5-yl)ethoxy)benzylidene)thiazolidine-2,4-dion



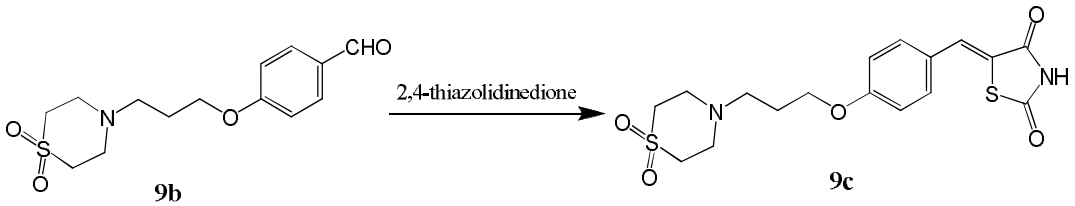
Obtained by recrystallization as a yellow solid (1.27 g, 88% yield); ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.487 (s, 1H), 8.824 (s, 1H), 7.721 (s, 1H), 7.556 (d, J = 8.7 Hz, 2H), 7.102 (d, J = 8.7 Hz, 1H), 4.238 (t, J = 12.3 Hz, 2H), 3.250 (t, J = 12.3 Hz, 2H), 2.284 (s, 3H).

8c: 5-(4-(2-Thiomorpholine 1,1-Dioxideethoxy)benzylidene)-2,4-thiazolidinedione



Obtained by recrystallization as a yellow solid(1.21 g, 88%) ; ^{1}H NMR (300 MHz, DMSO-d_6) δ8.19 (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).

9c: 5-[4-(3-Thiomorpholine-1,1-dioxidepropoxy)benzylidene]-thiazolidine-2,4-dione



Obtained by recrystallization as a yellow solid (1.07 g, 81.1%yield); ^{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 = 14.1 Hz, 2H), 3.06-3.89 (m, 8H), 2.616 (t, J = 14.1 Hz, 2H), 1.819-1.911 (m, 2H).

10c: 5-(4-(Thiophen-3-ylmethoxy)benzylidene)thiazolidine-2,4-dione

10b **10c**

Obtained by recrystallization as a yellow solid (1.24 g, 85.5% yield); ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.504 (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).

11c: 5-(4-(Thiophen-2-ylmethoxy)benzylidene)thiazolidine-2,4-dione

11b **11c**

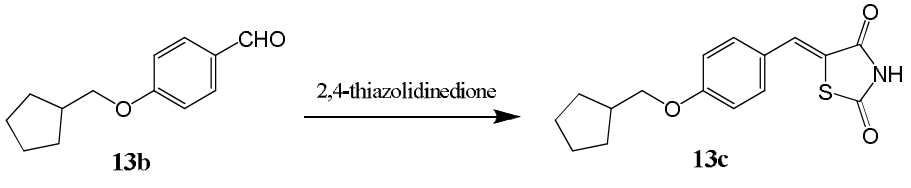
Obtained by recrystallization as a yellow solid (1.17 g, 80.7% yield); ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.513 (s, 1H), 7.745 (s, 1H), 7.569 (d, J = 8.4 Hz, 2H), 7.559 (t, J = 3.3 Hz, 1H), 7.248 (t, J = 3.3 Hz, 1H), 7.194 (d, J = 8.4 Hz, 2H), 7.052 (m, 1H), 5.37 (s, 2H).

12c: 5-(4-(Furan-2-ylmethoxy)benzylidene)thiazolidine-2,4-dione

12b **12c**

Obtained by recrystallization as a yellow solid (1.26 g, 84.6% yield); ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.518 (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).

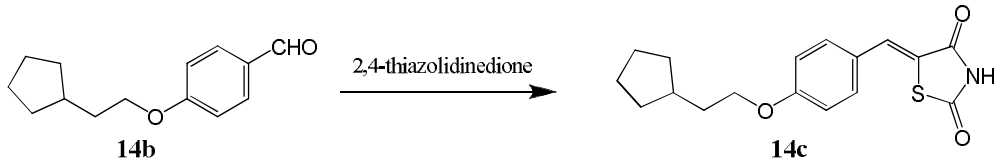
13c: 5-(4-(Cyclopentylmethoxy)benzylidene)thiazolidine-2,4-dione



13b **13c**

Obtained by recrystallization as a yellow solid (1.16 g, 78.0% yield); ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.503 (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).

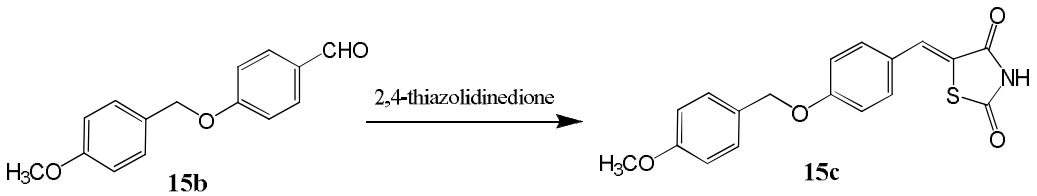
14c: 5-(4-(2-Cyclopentylethoxy)benzylidene)thiazolidine-2,4-dione



14b **14c**

Obtained by recrystallization as a yellow solid (1.16 g, 81% yield); ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.502 (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).

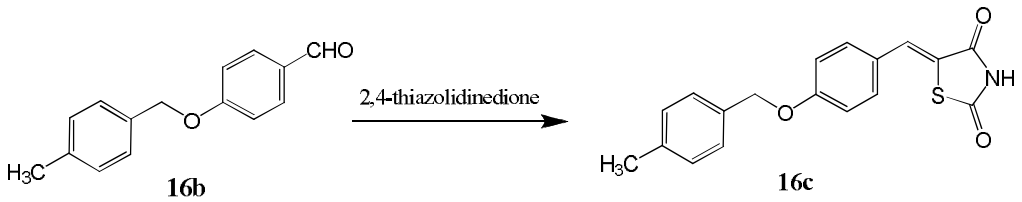
15c: 5-(4-(4-Methoxybenzyloxy)benzylidene)thiazolidine-2,4-dione



15b **15c**

Obtained by recrystallization as a yellow solid (1.19 g, 85.9% yield); ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.523 (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).

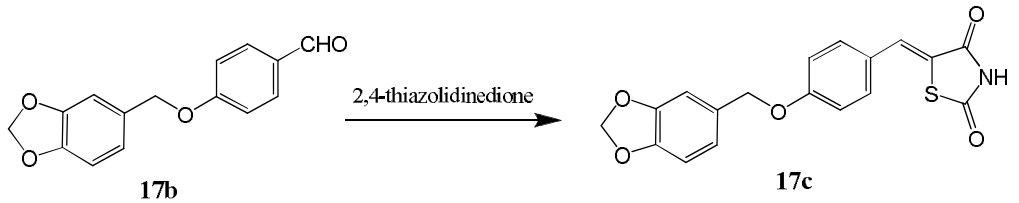
16c: 5-(4-(4-Methylbenzyloxy)benzylidene)thiazolidine-2,4-dione



16b **16c**

Obtained by recrystallization as a yellow solid (1.15 g, 80.4% yield); ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.514 (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).

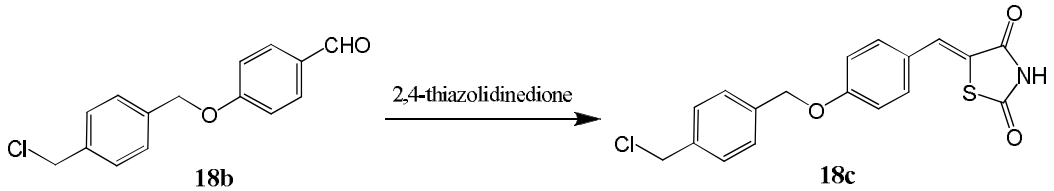
17c: 5-(4-(Benzo[*d*][1,3]dioxol-5-ylmethoxy)benzylidene)thiazolidine-2,4-dione



17b **17c**

Obtained by recrystallization as a yellow solid (1.22 g, 88.4% yield); ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.498 (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).

18c: 5-(4-(4-(Chloromethyl)benzyloxy)benzylidene)thiazolidine-2,4-dione



18b **18c**

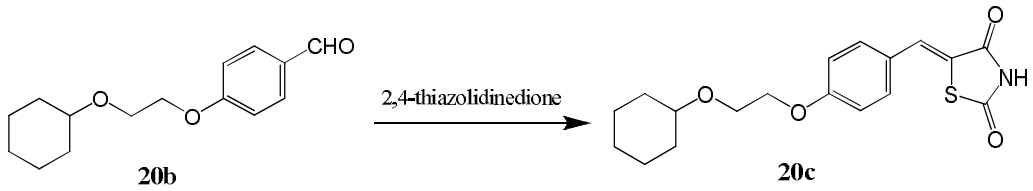
Obtained by recrystallization as a yellow solid (1.12 g, 81.2% yield); ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.549 (s, 1H), 7.748 (s, 1H), 7.58 (d, J = 12.3 Hz, 2H), 7.454 (m, 4H), 7.190 (d, J = 12.3 Hz, 2H), 5.219 (s, 2H), 4.760 (s, 2H).

19c: 5-(4-((4-Methylcyclohexyl)methoxy)benzylidene)thiazolidine-2,4-dione

19b **19c**

Obtained by recrystallization as a yellow solid (1.17 g, 85.6% yield); ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.493 (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 = 6.9 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).

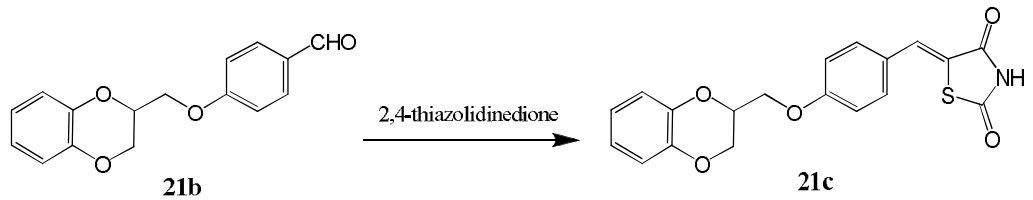
20c: 5-(4-(2-(Cyclohexyloxy)ethoxy)benzylidene)thiazolidine-2,4-dione



20b **20c**

Obtained by recrystallization as a yellow solid (1.14 g, 82.0% yield); ^{1}H NMR (300 MHz, DMSO-d_6) 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).

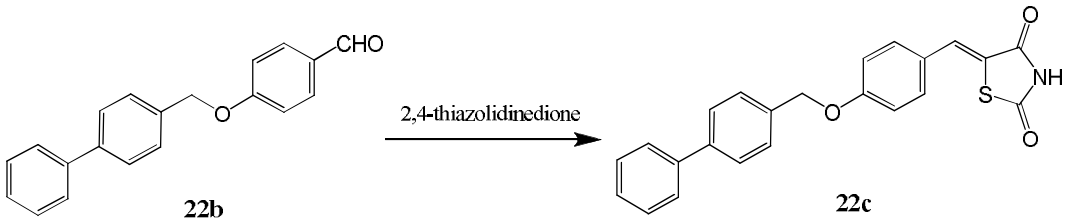
21c: 5-(4-((2,3-Dihydrobenzo[b][1,4]dioxin-2-yl)methoxy)benzylidene)thiazolidine-2,4-dione



21b **21c**

. Obtained by recrystallization as a yellow solid (1.12 g, 82.4% yield); ^{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).

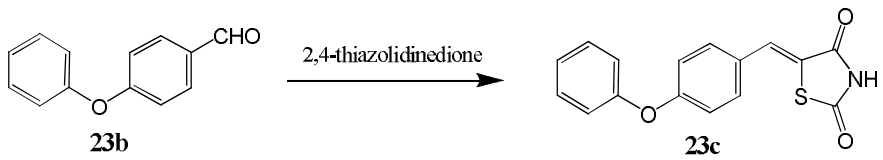
22c: 5-(4-(Biphenyl-4-ylmethoxy)benzylidene)thiazolidine-2,4-dione



22b **22c**

Obtained by recrystallization as a yellow solid (1.12 g, 83.6% yield); ^{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).

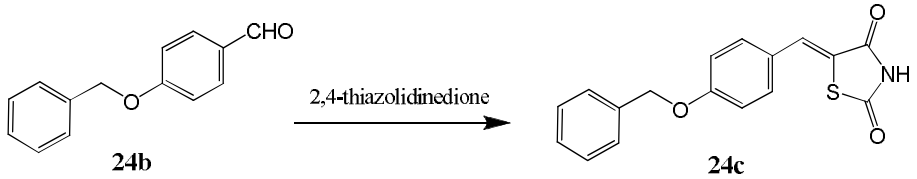
23c: 5-(4-Phenoxybenzylidene)-1, 3-thiazolidine-2, 4-dione



23b **23c**

Obtained by recrystallization as a yellow solid (1.02 g, 72.0% yield); ^{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).

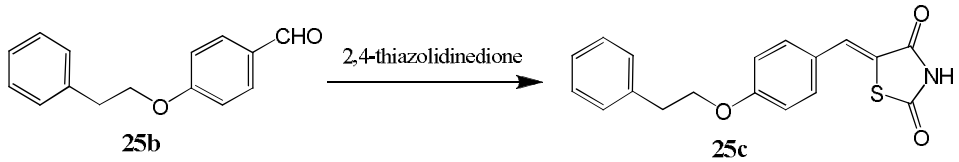
24c: 5-(4-(Benzyloxy)benzylidene)thiazolidine-2,4-dione



24b **24c**

Obtained by recrystallization as a yellow solid (1.2 g, 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).

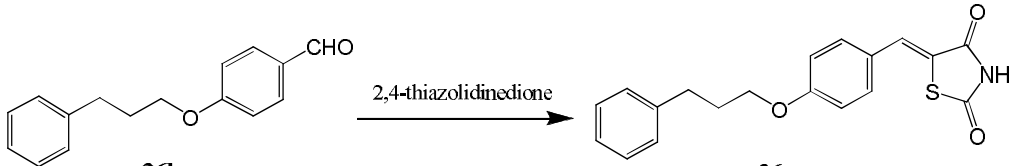
25c: 5-[4-(2-Phenylethoxy)benzylidene]-1,3-thiazolidine-2,4-dione



25b **25c**

Obtained by recrystallization as a yellow solid (0.94 g, 62.7% yield); ^{1}H NMR (300 MHz, DMSO-d_6) 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).

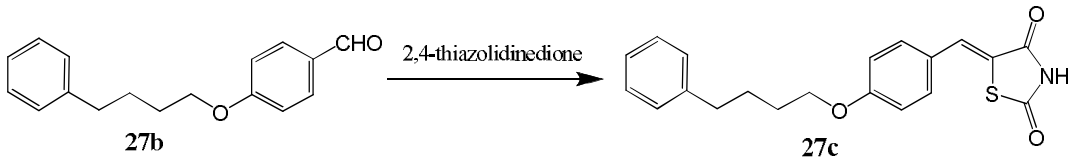
26c: 5-[4-(2-Phenylpropoxy)benzylidene]-1,3-thiazolidine-2,4-dione



26b **26c**

Obtained by recrystallization as a yellow solid (1.12 g, 80.1% yield); ^{1}H NMR (300 MHz, DMSO-d_6) 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).

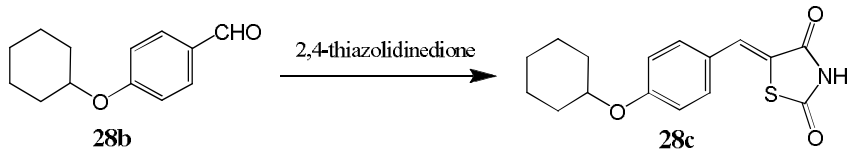
27c: 5-[4-(2-Phenylbutoxy)benzylidene]-1,3-thiazolidine-2,4-dione



27b **27c**

Obtained by recrystallization as a yellow solid (1.15 g, 85.0% yield); ^{1}H NMR (300 MHz, DMSO-d_6) 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).

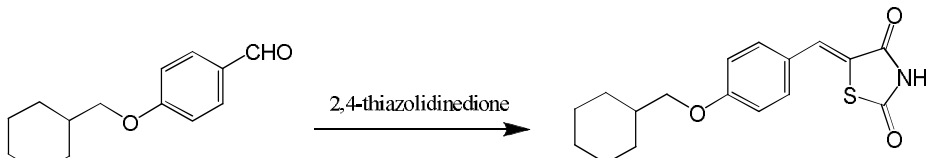
28c: 5-(4-(Cyclohexyloxy)benzylidene)thiazolidine-2,4-dione



28b **28c**

Obtained by recrystallization as a yellow solid(1.3 g, 88%); ^{1}H NMR (300 MHz, DMSO-d_6) 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).

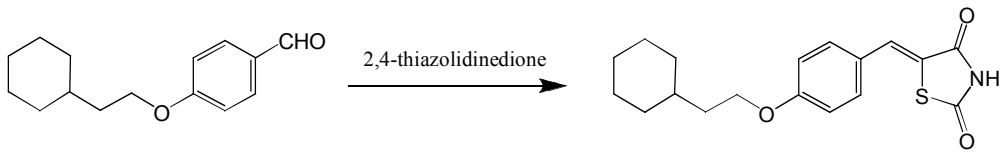
29c: 5-(4-(Cyclohexylmethoxy)benzylidene)thiazolidine-2,4-dione



29b **29c**

Obtained by recrystallization as a yellow solid (1.2 g, 83%); ^{1}H NMR (300 MHz, DMSO-d_6) 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).

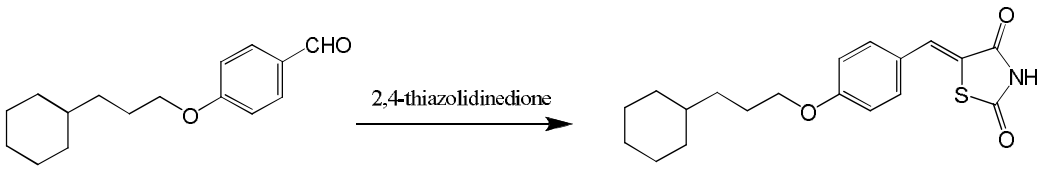
30c: 5-(4-(2-Cyclohexylethoxy)benzylidene)thiazolidine-2,4-dione



30b **30c**

Obtained by recrystallization as a yellow solid (1.28 g, 90.01% yield); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.195 (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).

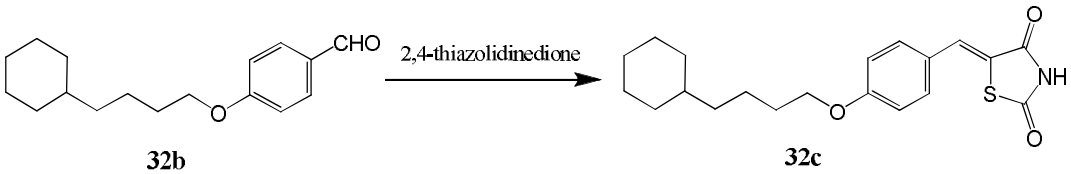
31c: 5-(4-(3-Cyclohexylpropoxy)benzylidene)thiazolidine-2,4-dione



31b **31c**

Obtained by recrystallization as a yellow solid (1.2 g, 86%); ^{1}H NMR (300 MHz, DMSO-d_6) 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).

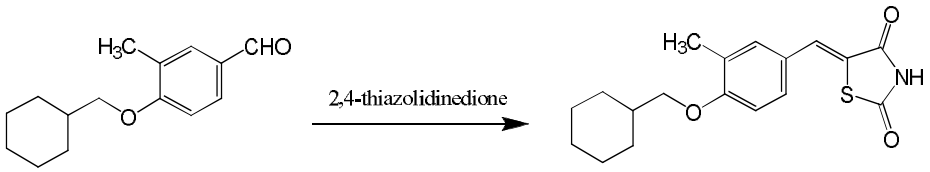
32c: 5-(4-(4-Cyclohexylbutoxy)benzylidene)thiazolidine-2,4-dione



32b **32c**

Obtained by recrystallization as a yellow solid (1.13 g, 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).

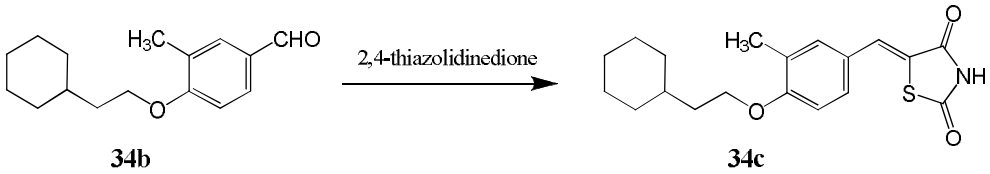
33c: 5-(4-(2-Cyclohexylmethoxy)-3-methylbenzylidene)thiazolidine-2,4-dione



33b **33c**

Obtained by recrystallization as a yellow solid (1.10 g, 77.5% yield); ^{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).

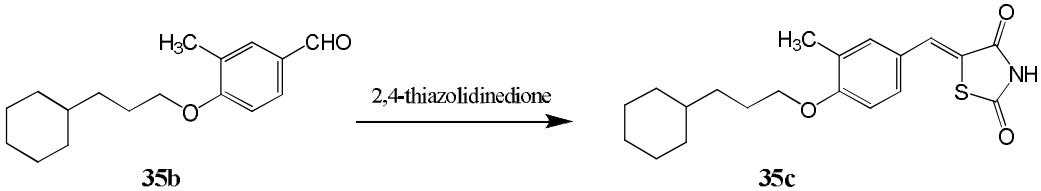
34c: 5-(4-(2-Cyclohexylethoxy)-3-methylbenzylidene)thiazolidine-2,4-dione



34b **34c**

Obtained by recrystallization as a yellow solid (1.25 g, 86%); ^{1}H NMR (300 MHz, DMSO-d_6) 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).

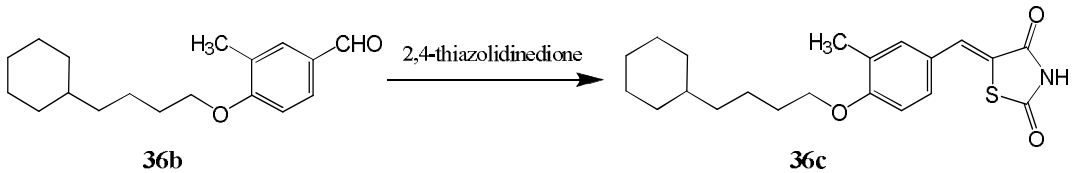
35c: 5-(4-(2-Cyclohexylpropoxy)-3-methylbenzylidene)thiazolidine-2,4-dione



35b **35c**

Obtained by recrystallization as a yellow solid (1.23 g, 89.1% yield); ^{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).

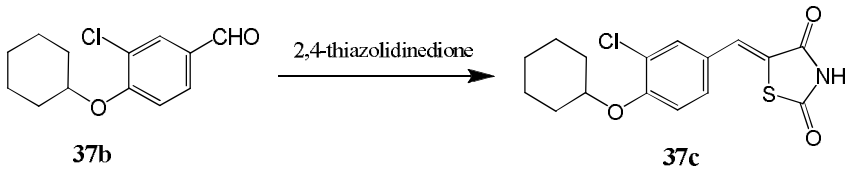
36c: 5-(4-(2-Cyclohexylbutoxy)-3-methylbenzylidene)thiazolidine-2,4-dione



36b **36c**

Obtained by recrystallization as a yellow solid (1.19 g, 87.5% yield); ^{1}H NMR (300 MHz, DMSO-d_6) δ7.787 (s, 1H), 7.421(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).

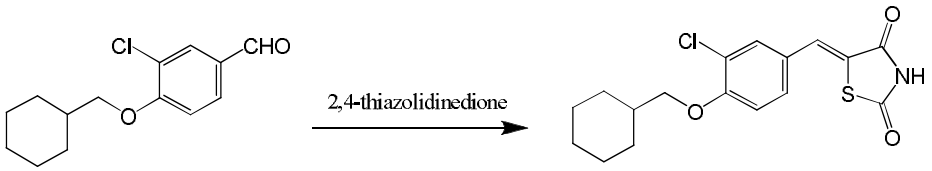
37c: 5-(3-Chloro-4-(cyclohexyloxy)benzylidene)thiazolidine-2,4-dione



37b **37c**

Obtained by recrystallization as a yellow solid (1.3 g, 88%); ^{1}H NMR (300 MHz, DMSO-d6) 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).

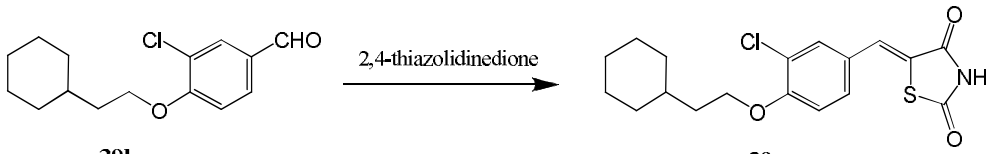
38c: 5-(3-Chloro-4-(cyclohexylmethoxy)benzylidene)thiazolidine-2,4-dione



38b **38c**

Obtained by recrystallization as a yellow solid (1.3 g, 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).

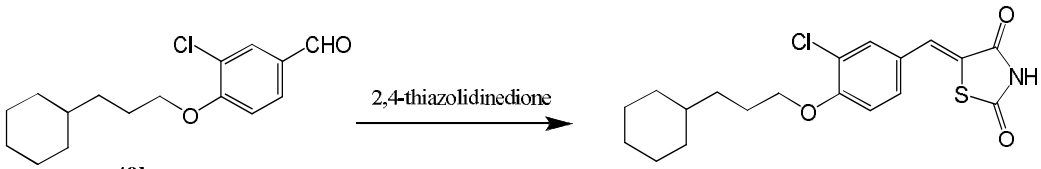
39c: 5-(3-Chloro-4-(2-cyclohexylethoxy)benzylidene)thiazolidine-2,4-dione



39b **39c**

Obtained by recrystallization as a yellow solid (1.22 g, 84%); ^{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).

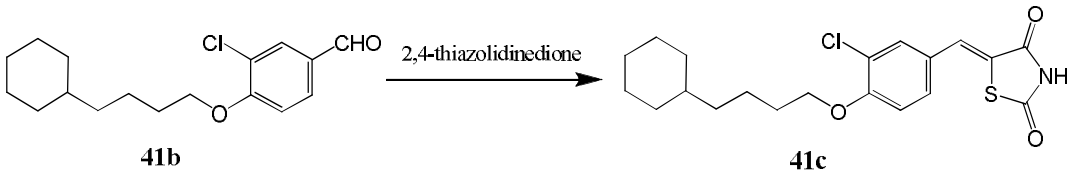
40c: 5-(3-Chloro-4-(cyclohexylpropoxy)benzylidene)thiazolidine-2,4-dione



40b **40c**

Obtained by recrystallization as a yellow solid (1.29 g, 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).

41c: 5-(3-Chloro-4-(cyclohexylbutoxy)benzylidene)thiazolidine-2,4-dione



41b **41c**

Obtained by recrystallization as a yellow solid (1.28 g, 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).

III. RESULTS AND DISCUSSION

Fig. 6. shows the general synthetic routes for the TD derivatives. As a starting material p-hydroxybenzaldehyde, 4-hydroxy-3-methylbenzaldehyde or 3-chloro-4-hydroxybenzaldehyde, were reacted with various substituents to afford the substituted benzaldehyde, an intermediate, in good yield. The intermediate was then used in the coupling reaction with thiazolidine-2,4-dione to afford the appropriated TD derivatives.

The different TD derivatives were screened for their algicidal activity against harmful algae. The specificity and potency of all 41 TD compounds against *Heterosigma akashiwo (H. akashiwo), Chattonella marina (C. marina)* and C*ochlodinium polykrikoides (C. polykrikoides)* were determined. The synthesized compounds were tested under the assay conditions at various micro molar concentrations, and the results and statistical significance were verified. Their inhibitory activity (IC_{50}) values are listed in Table 1. When algicidal activity of the TD to *H. akashiwo, C. marina* and *C. polykrikoides* were compared, some of the TD required high concentrations to inhibit growth, whereas a number of TD showed moderate algicidal activity at the lowest concentrations against the red tide causing alga selected for this study.

TD compounds, such as compounds **1c, 2c, 10c, 11c, 14c, 16c, 17c, 24c, 25c, 27c, 33c, 37c** and **39c** exhibited IC_{50} values < 4 μM for all HABs studied, which makes them possible candidates for algicidal application. In contrast, compounds **8c, 23c** and **32c** exhibited relatively high IC_{50} values ranging from 30 to 120 μM, which suggests that the HABs are tolerant to these TD. These compounds were potent for both HABs and non-harmful dianoflagellates indicating that these compounds are unsuitable as algicidal compounds (Table 1).

The growth inhibition patterns of the HABs, including non-harmful algae, were examined upon exposure to compounds **2c** and **14c** at different concentrations (Fig. 7). The growth patterns showed an exponential decrease with increasing concentration of the selective TD in the medium (Fig. 7). On the other hand, the non-harmful algae were relatively tolerant to these selective TD.

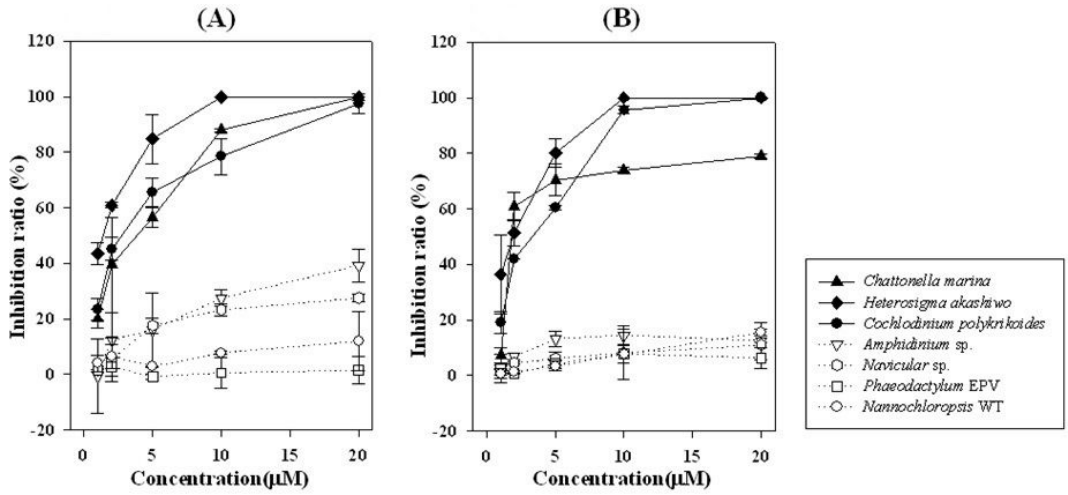


Fig. 7. Growth inhibition ratio against harmful and non-harmful algal species**.** (A) Compound **2c**, (B) Compound **14c** at different concentrations of TD compounds selected, the letters in graphs (A) and (B) represent the means that are significantly different ($P < 0.05$) using a Tukey's post hoc test

C. polykrikoides blooms have caused heavy damage to fish farms in the Republic of Korea, Japan and other countries [29,30,31]. The use of non-specific chemical algicides have been reported to have a number of drawbacks, including broad-spectrum toxicity towards phytoplankton [14,20,21,22].

Of the compounds examined, compounds **1c, 2c, 3c, 4c, 7c, 9c, 10c, 11c, 12c, 13c, 14c, 15c, 16c, 17c, 21c, 24c, 25c, 35c, 37c** and **41c** were most potent against *C. polykrikoides* exhibiting IC_{50} values < 1 μM. In particular, compounds **3c, 9c, 22c** and **41c** were extremely competent and selective against *C. polykrikoides* and exhibited an IC_{50} value ranging from 0.1 to 2 μM, while *C. marina* and *H. akashiwo* showed an IC_{50} value ranging from 30 to 130 μM. Therefore, these compounds may have structural competence to *C. polykrikoides* but the mechanisms of this selectivity need to be examined further.

Red tide inhibitors made with Chinese herbs, such as golden thread and areca seed, had the merits of a low concentration and short reaction time [13]. Some natural materials were found to be selective against blue-green algae [32,33,34]. However, their large scale use in the environment is still problematic. Biological control has many logistical problems and is far from the application stage [1]. The chemical structure of the TD may be the reason for their

selective and wide range of algicidal activity. The effective concentrations, potency, growth inhibition ratio and their selective pattern to their corresponding functional groups of derivatives were studied (Table 1). The high activities of particular compounds, which are specific against only harmful algal species, might take advance of specific functional groups and their position. Their structural relation and importance in algicidal actions are discussed based on these results.

Microscopic observation of *C. marina, H. akashiwo, C. polykrikoides* without treating TD **37c** (a) and after treating 1 μM of TD **37c** with difference time are show in Fig. 8, Fig. 9, Fig. 10.

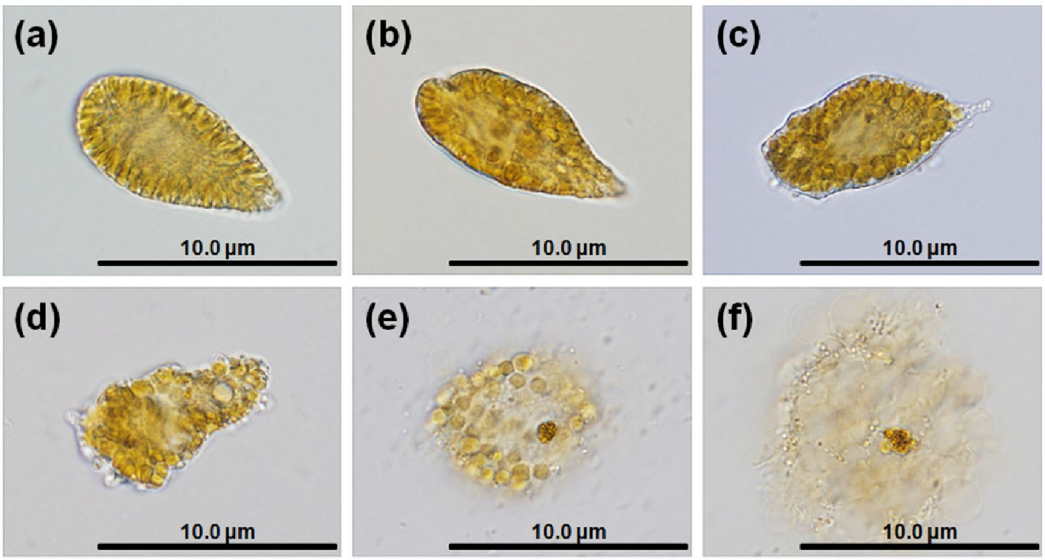


Fig. 8. Microscopic observation of *C. marina* without treating TD **37c** (a); *C. marina* after treating 1 μM of TD **37c** (b)~(f) (b: 6hr; c: 9hr; d: 12hr; e: 15hr; f: more than 15hr).

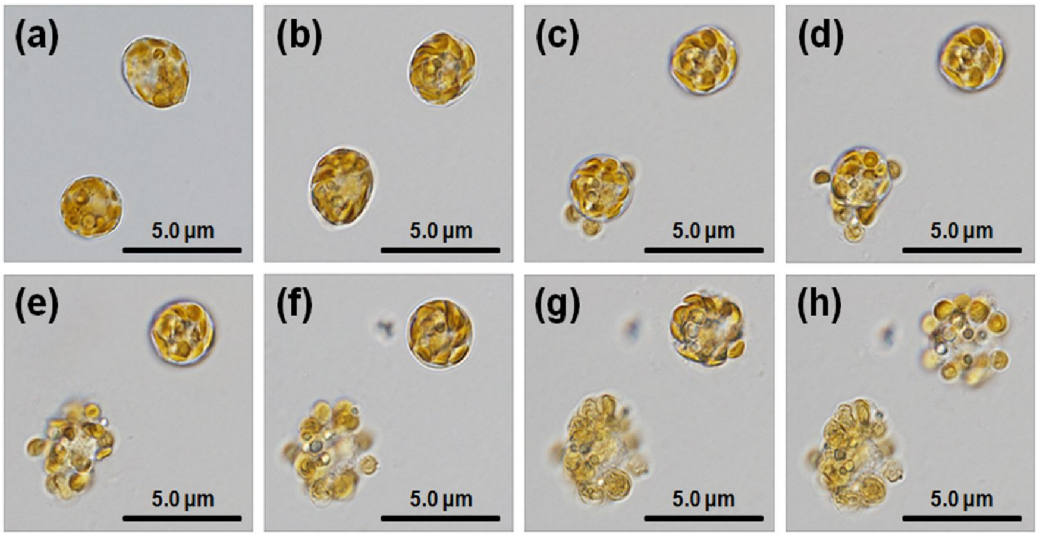


Fig. 9. Microscopic observation of *H. akashiwo* without treating TD **37c** (a); *H. akashiwo* after treating 1μM of TD **37c** (b) ~ (f) (b: 1hr; c: 2hr; d:4hr; e: 6hr; f: 8hr; g:10hr; h: more than 10hr).

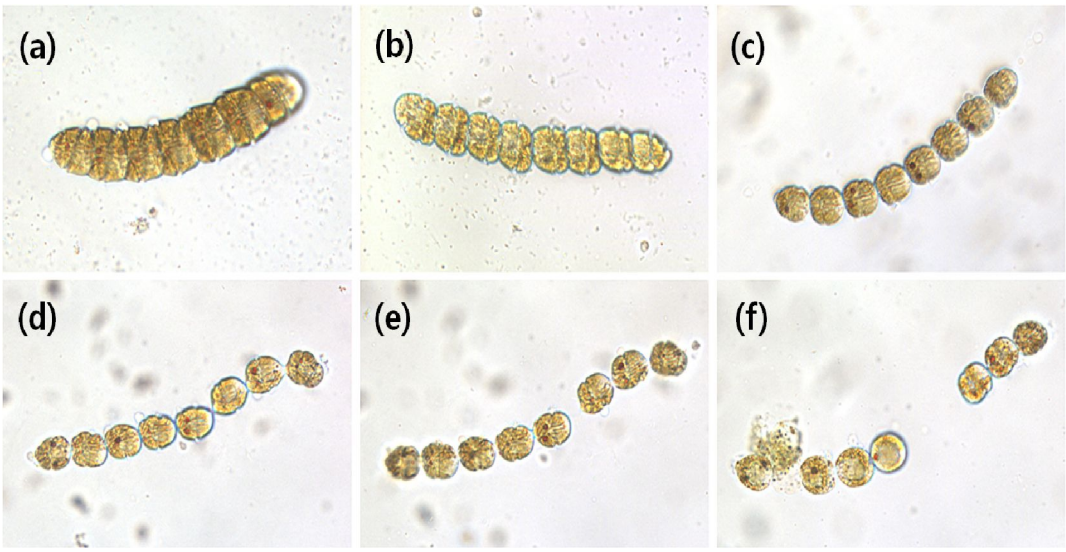
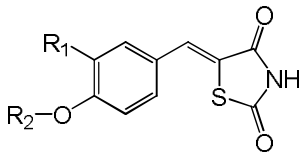


Fig. 10. Microscopic observation of *C. polykrikoides* without treating TD **37c** (a);*C. polykrikoides,* after treating 1μM of TD **37c** (b)~(f) (b: 1hr; c: 2hr; d: 3hr; e: 4hr; f: 5hr), Magnification X400.

For the purpose of preliminary structure activity relationship studies, various substituents were introduced at the hydroxyl group of 5-(4-hydroxybenzylidene)thiazolidine-2,4-dione. The introduction of the 5-member ring at the hydroxyl group of 5-(4-hydroxybenzylidene)thiazolidine-2,4-dione resulted in a significant increase in its inhibitory potency against *C. polykrikoides*, as indicated for compounds **1c, 2c, 7c, 10c, 11c, 12c, 13c** and **14c**. Interestingly, the 3-thiomorpholine-1,1-dioxidepropyl group as a substituent also increased the inhibitory potency against *C. polykrikoides* significantly as indicated for compound **9c**. However, a deletion of the methylene group of the 3-thiomorpholine-1,1-dioxidepropyl derivative (compound **8c)** decreased the inhibitory potency of compound **9c**. In contrast, a deletion of the methylene group of the 2-(pyridine-2-yl)ethyl derivative (compound **5c**) increased the inhibitory potency against *C. polykrikoides* significantly of compound **4c**. Replacement of the cyclohexyl ring (compound **19c**) with a benzene ring (compound **16c**) increased the inhibitory potency. The most potent inhibitors of this series of compounds against *C. marina, H. akashiwo and C. polykrikoides* are compounds 5-(3-chloro-4-(cyclohexyloxy)benzylidene)thiazolidine-2,4-dione (compound **37c**), 5-[4-(2-phenylethoxy)benzylidene]-1,3-thiazolidine-2,4-dione (compound **25c**) and 5-(3-chloro-4-(cyclohexyloxy)benzylidene)thiazolidine-2,4-dione (compound **37c**) with an IC_{50} of 0.160, 0.454 and 0.086, respectively. Table 1 gives a summary of the inhibitory potency of all these compounds.

Table 1. Algicidal effects of the various synthetic thiazolidinediones



S.No	R_1	R_2	IC_{50}[a] (μM)				
			Harmful algal species			Non-harmful algal species	
			C.marina	H.akashiwo	C.polykrikoides	A.sp.	P.EPV
1c	H	2-(Thiophen-2-yl)ethyl	1.650 ± 0.578	2.428 ± 0.928	0.712 ± 8.254	100 >	ND
2c	H	2-(Thiophen-3-yl)ethyl	2.015 ± 0.653	2.838 ± 0.223	0.457 ± 9.280	69.306 ± 6.224	
3c	H	2-Isopropoxyethyl	41.793 ±2.030	39.928±18.410	0.980 ± 8.604	95.723 ± 1.047	
4c	H	Pyridin-2-ylmethyl	6.109 ± 0.605	13.100 ±6.152	0.741 ± 0.000	7.214 ± 7.475	
5c	H	2-(Pyridin-2-yl)ethyl	37.495 ±1.949	17.151 ±1.110	27.195 ±8.011	100 >	
6c	H	2-(Piperidin-1-yl)ethyl	2.886 ± 0.185	6.565 ± 1.025	16.141 ±2.445	82.282 ± 4.078	
7c	H	2-(4-Methylthiazol-5-yl)ethyl	8.503 ± 0.821	10.216 ±0.552	0.562 ± 6.738	86.910 ± 4.142	

8c	H	2-Thiomorpholine-1,1-dioxideethy	122.001±8.647	93.660 ± 9.818	118.373±14.27	98.136 ± 2.731	ND
9c	H	3-Thiomorpholine-1,1-dioxidepropyl	90.497 ±3.386	128.642±6.611	0.133 ± 8.764	100 >	
10c	H	Thiophen-3-ylmethyl	3.658 ± 2.385	2.789 ± 0.016	0.570 ± 8.099	39.148 ± 6.851	
11c	H	Thiophen-2-ylmethyl	1.203 ± 1.601	1.927 ± 0.009	0.616 ± 0.000	5.904 ± 3.265	
12c	H	Furan-2-ylmethyl	5.453 ± 0.130	7.642 ± 0.499	0.779 ± 5.922	5.016 ± 1.253	
13c	H	Cyclopentylmethyl	4.221 ± 3.172	2.717 ± 0.002	0.254 ± 0.000	100 >	
14c	H	2-Cyclopentylethyl	1.515 ± 1.193	3.282 ± 0.426	0.846 ± 1.886	100 >	
15c	H	4-Methoxybenzyl	11.920 ±9.570	15.226 ±4.244	0.793 ± 4.831	100 >	
16c	H	4-Methylbenzyl	2.141 ± 1.391	2.022 ± 0.633	0.560 ± 0.001	52.124 ± 10.460	
17c	H	Benzo[*d*][1,3]dioxol-5-ylmethyl	2.582 ± 0.263	3.057 ± 0.311	0.877 ± 0.000	98.788 ± 1.884	
18c	H	4-(Chloromethyl)benzyl	6.168 ± 0.415	10.178 ±1.357	2.267 ± 0.066	100 >	
19c	H	(4-Methylcyclohexyl)methyl	1.754 ± 1.207	8.026 ± 0.987	2.799 ± 6.123	100 >	
20c	H	2-(Cyclohexyloxy)ethyl	5.349 ± 1.293	3.294 ± 0.072	4.430 ± 0.002	13.618 ± 3.462	

21c	H	(2,3-Dihydrobenzo[*b*][1,4]dioxin-2-yl)methyl	1.242 ± 0.677	8.806 ± 1.667	0.462 ± 0.000	100 >	ND
22c	H	Biphenyl-4-ylmethyl	29.537 ± 0.000	115.097 ± 5.390	2.046 ± 6.144	100 >	
23c	H	Phenyl	62.007 ± 1.836	ND	53.818 ± 1.205	100 >	
24c	H	Benzyl	3.716 ± 0.268	1.798 ± 4.984	0.853 ± 1.326	100 >	
25c	H	Phenylethyl	3.764 ± 1.532	0.454 ± 0.870	0.449 ± 0.000	100 >	
26c	H	Phenylpropyl	5.040 ± 1.331	2.205 ± 0.151	1.192 ± 0.015	100 >	
27c	H	Phenylbutyl	3.395 ± 1.956	2.966 ± 0.201	2.972 ± 0.130	100 >	
28c	H	Cyclohexyl	2.843 ± 1.223	12.950 ± 4.355	5.770 ± 0.234	100>	
29c	H	Cyclohexylmethyl	1.933 ± 0.025	7.348 ± 2.709	3.353 ± 0.071	100 >	
30c	H	Cyclohexylethyl	2.224 ± 0.035	17.668 ±0.113	5.821 ± 1.146	34.308 ± 1.005	
31c	H	Cyclohexylpropyl	11.419 ± 1.314	97.696 ± 1.354	41.709 ± 6.852	18.5 ± 0.676	
32c	H	Cyclohexylbutyl	102.924 ± 2.929	75.910 ± 1.246	101.421 ±3.007	100 >	
33c	CH_3	Cyclohexylmethyl	2.885 ± 0.087	2.050 ± 0.630	1.250 ± 0.000	71.888 ± 4.468	
34c	CH_3	Cyclohexylethyl	5.938 ± 2.952	7.029 ± 0.182	1.244 ± 0.000	100 >	

35c	CH_3	Cyclohexylpropyl	16.321 ± 7.672	17.949 ± 5.642	0.319 ± 0.000	100 >	ND
36c	CH_3	Cyclohexylbutyl	32.644 ± 1.627	5.758 ± 2.052	1.963 ± 3.082	100 >	
37c	Cl	Cyclohexyl	0.160 ± 0.315	1.070 ± 0.009	0.086 ± 0.000	100 >	
38c	Cl	Cyclohexylmethyl	1.672 ± 0.167	19.300 ± 3.180	17.590 ± 0.143	100 >	
39c	Cl	Cyclohexylethyl	2.347 ± 2.505	0.568 ± 1.020	4.035 ± 0.000	43.430 ± 1.011	
40c	Cl	Cyclohexylpropyl	10.366±0.183	85.950 ± 0.045	1.864 ± 0.000	100 >	
41c	Cl	Cyclohexylbutyl	119.100 ±6.087	ND	0.702 ± 0.000	100 >	

[a] Values are the mean ± SD of three experiments. ND, no detectable activity.

IV. CONCLUSION

In summary, examined thiazolidinedione derivatives as potential algicidal agents. The synthesis of TD compounds provide a strong evidence that several TD derivatives can have effective algicidal activity against HABs, but are safe to non harmful algae. A few of the TD exhibited remarkable algicidal activity against *H. akashiwo, C. marina, and C. polykrikoides* with low IC_{50} values (0.1 to 2 μM). The most potent inhibitors of this series of compounds against *C. marina, H. akashiwo, and C. polykrikoides* are compounds **37c, 25c** and **37c** with IC_{50} lower than 0.5 μM. Insights regarding the use of TD compounds may not be limited or restrict by the growth of other organisms due to their selectivity. A precise insight into the inhibitory action against the red tide algal remains to be determined. In addition, there are many aspects of potent or competent algal inhibitors in the treatment of harmful algal blooms that need to be clarified including safety, lifetime, water solubility, and stability.

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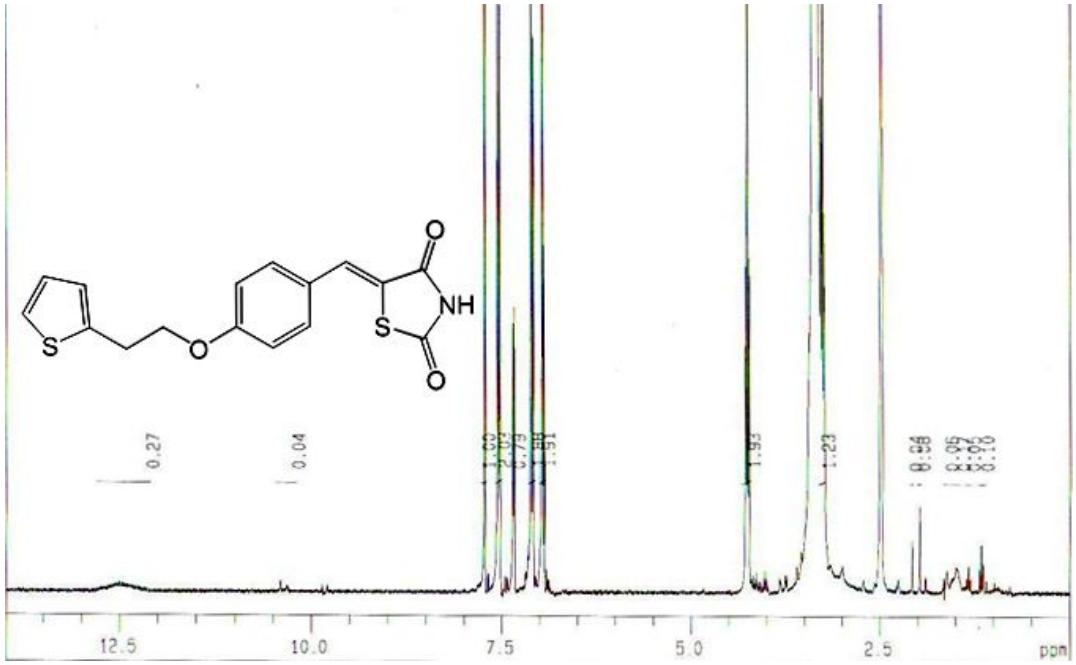
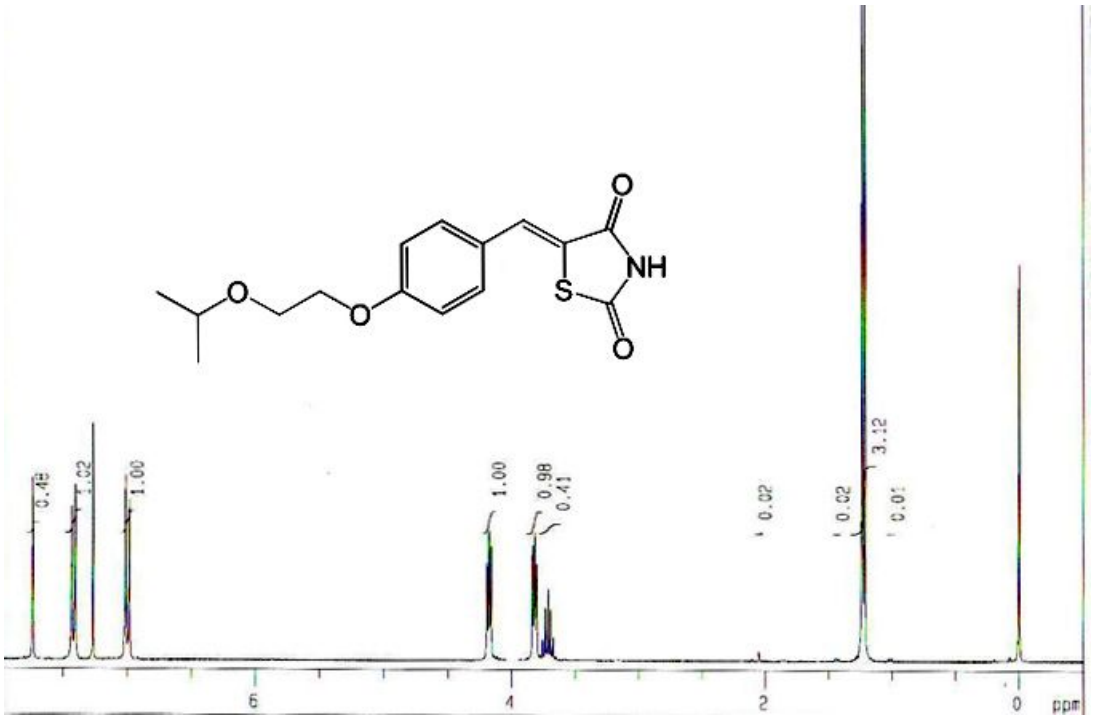
^{1}H NMR Spectra



1c: 5-(4-(2-Thiophen-2-yl)ethoxy) benzylidene)thiazolidine-2,4-dione



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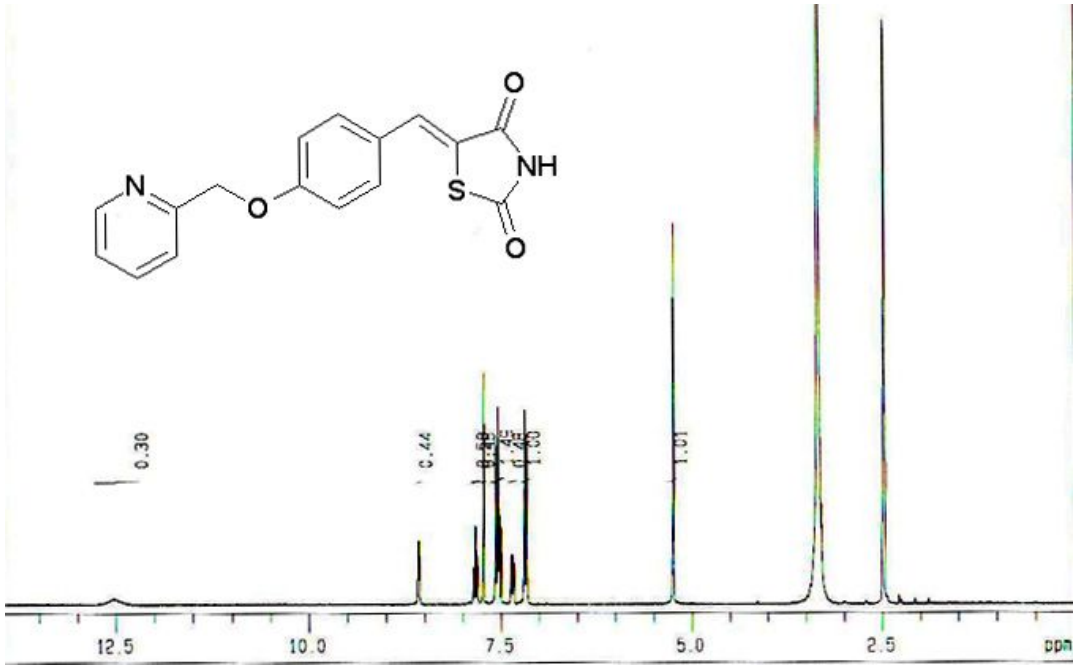

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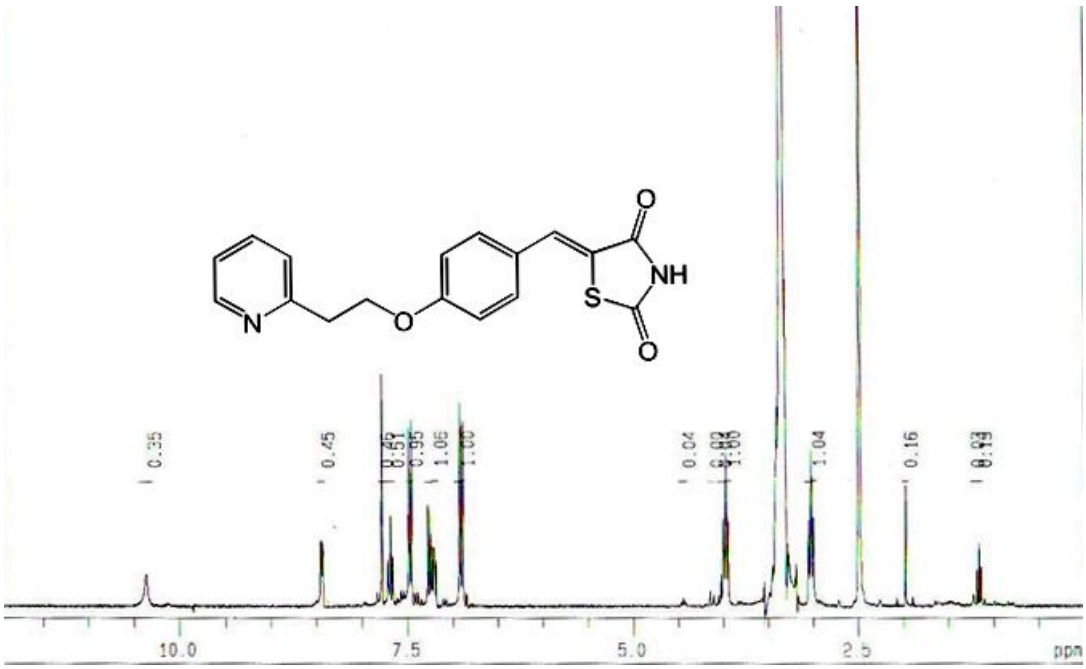

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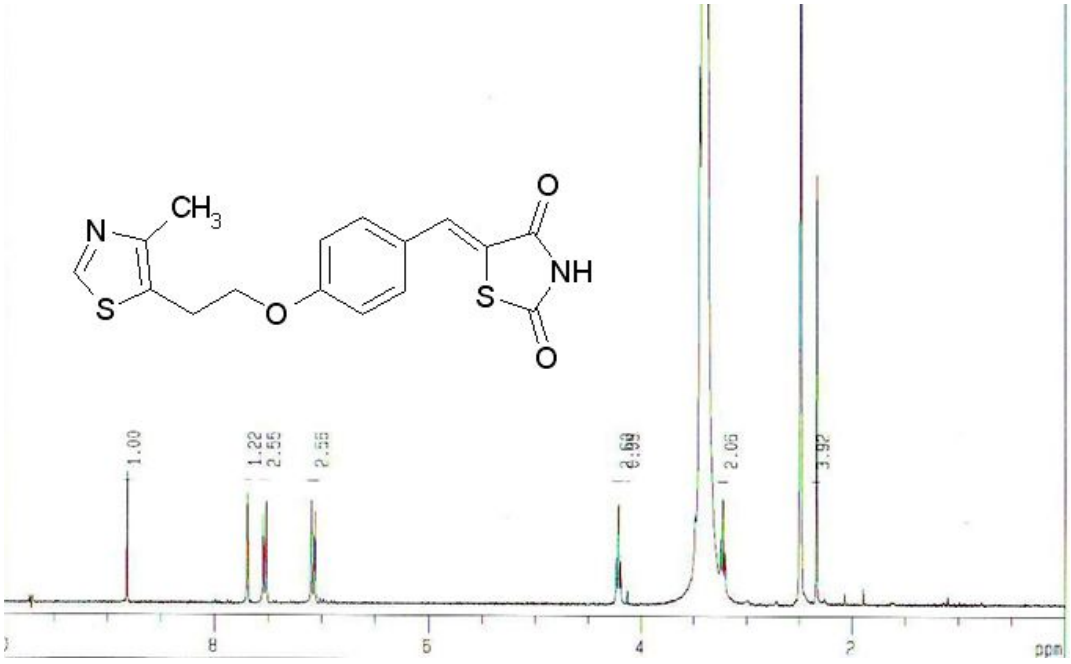

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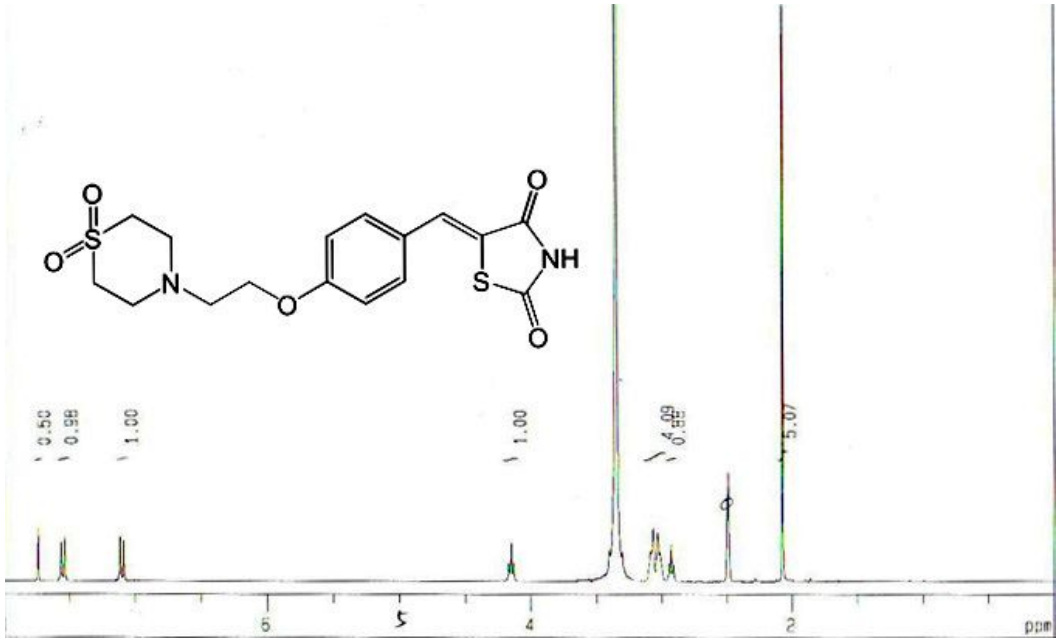
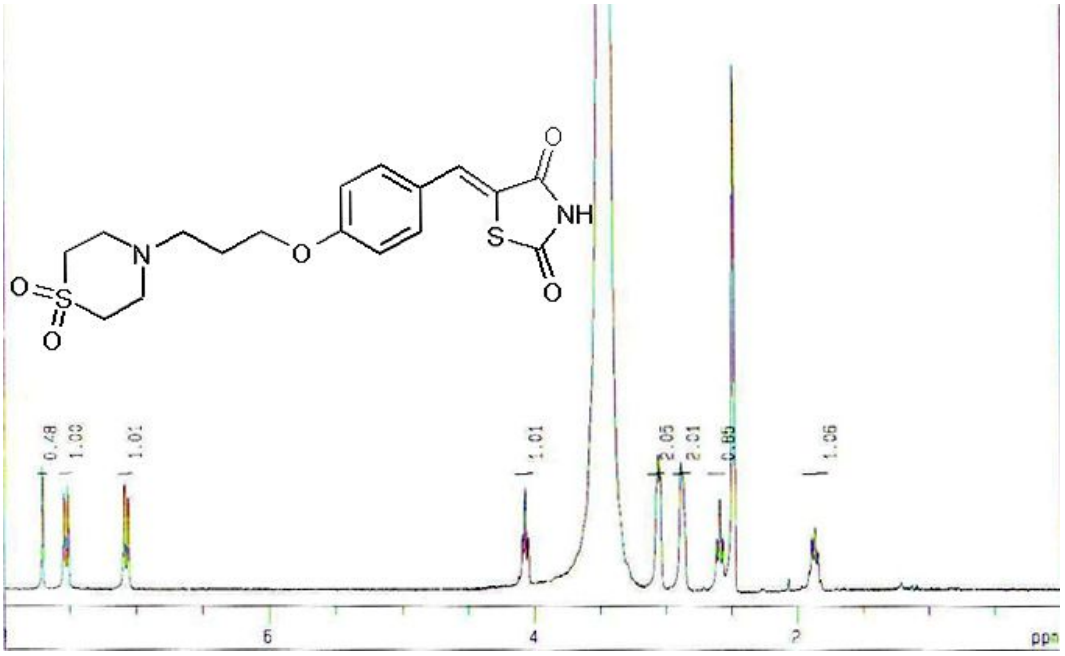


8c: 5-(4-(2-Thiomorpholine 1,1-Dioxideethoxy)benzylidene)-2,4-thiazolidinedione



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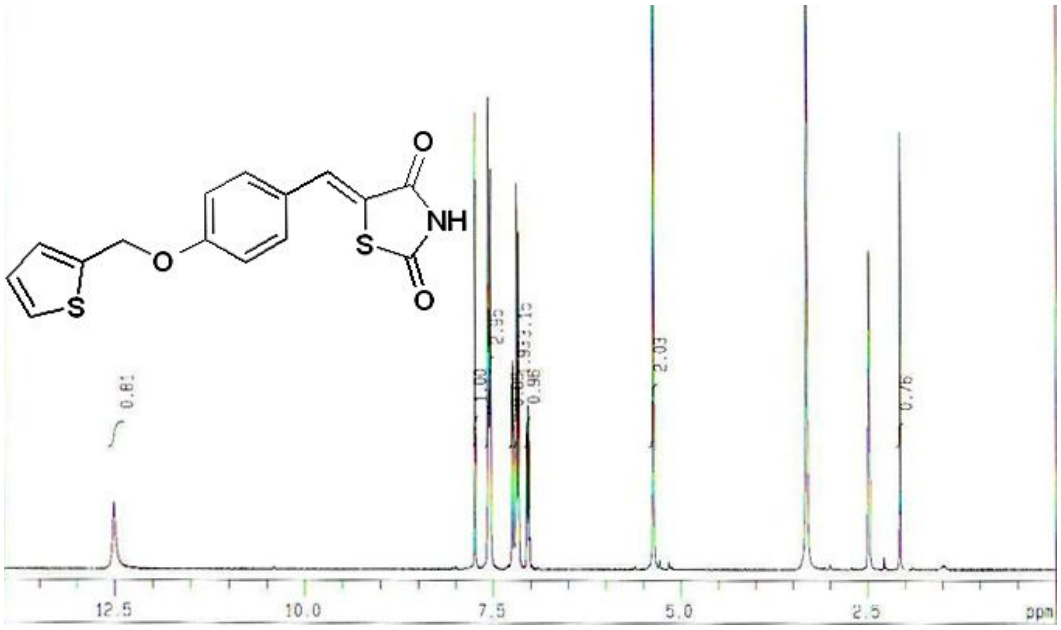

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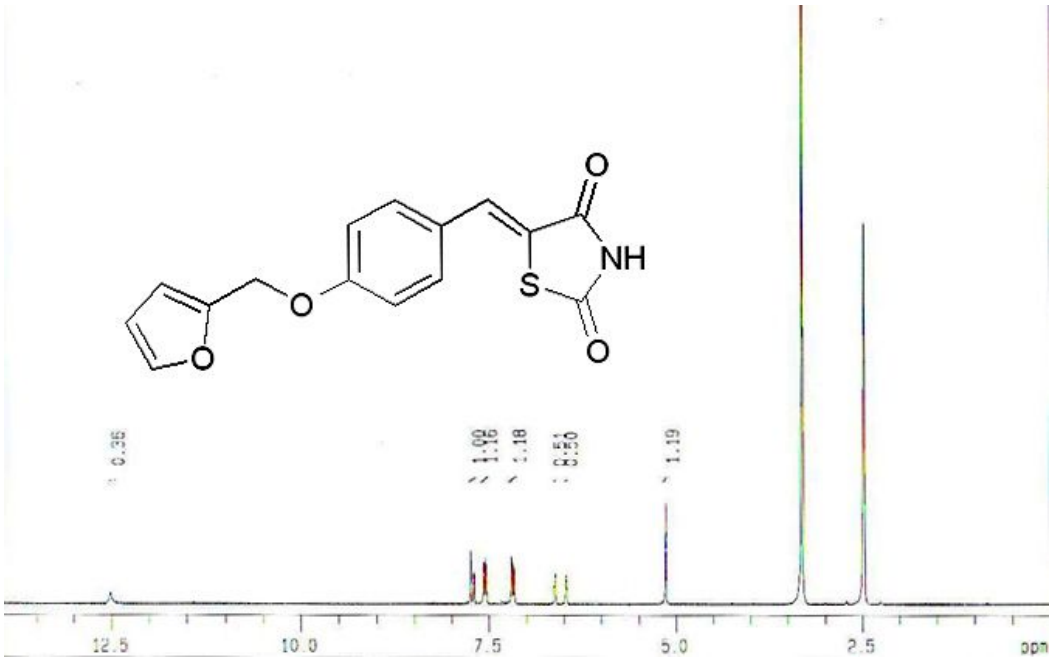

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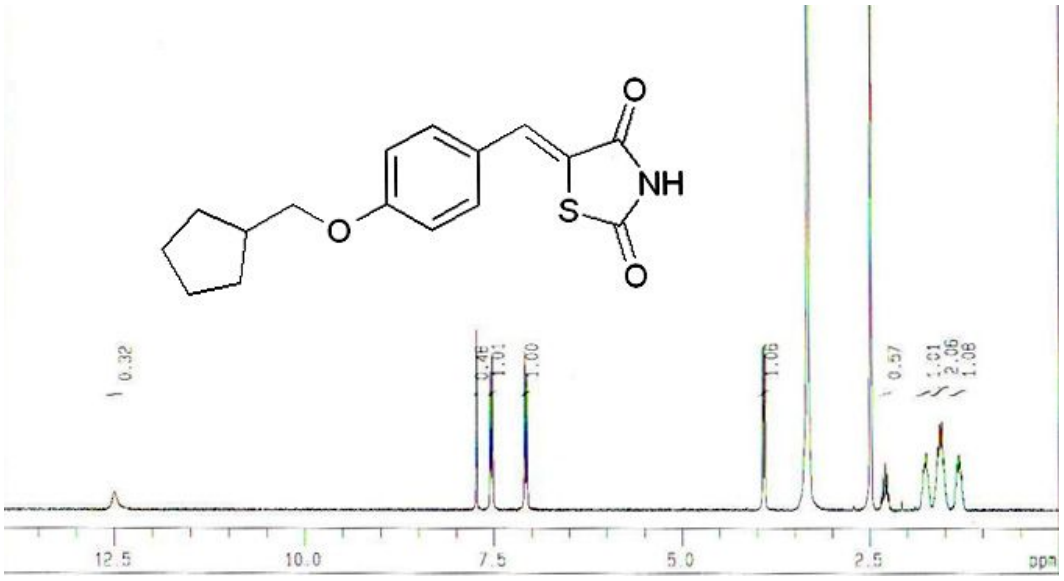

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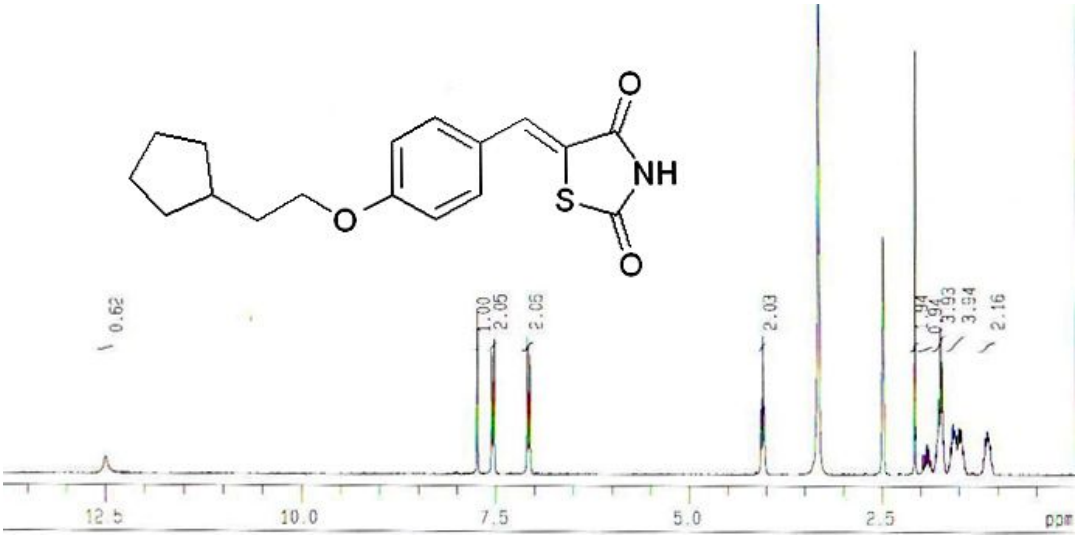

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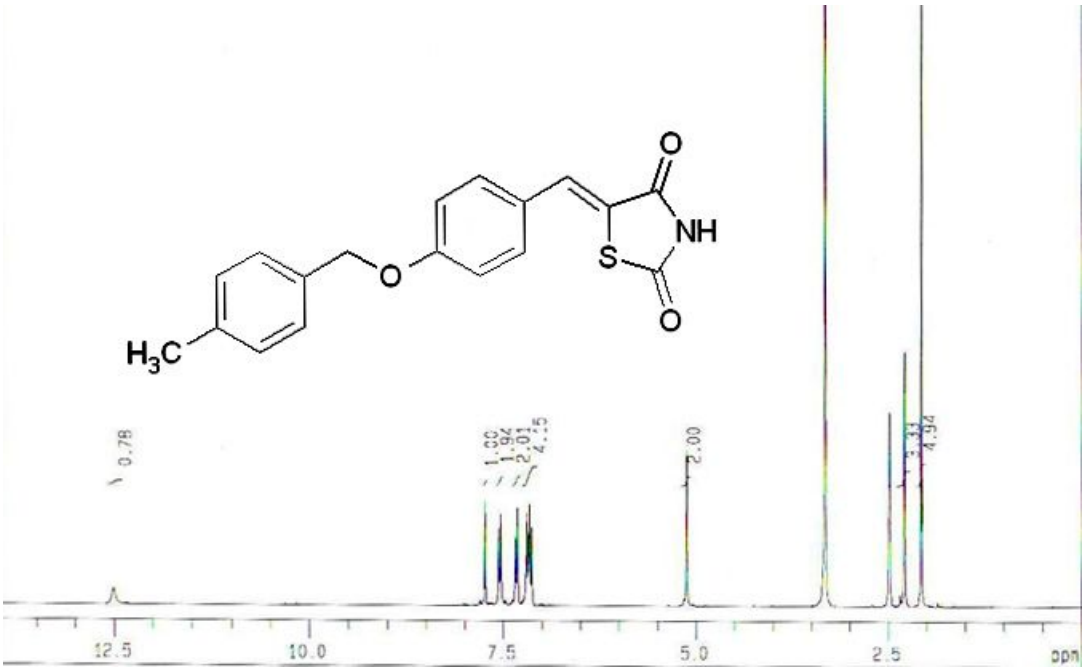

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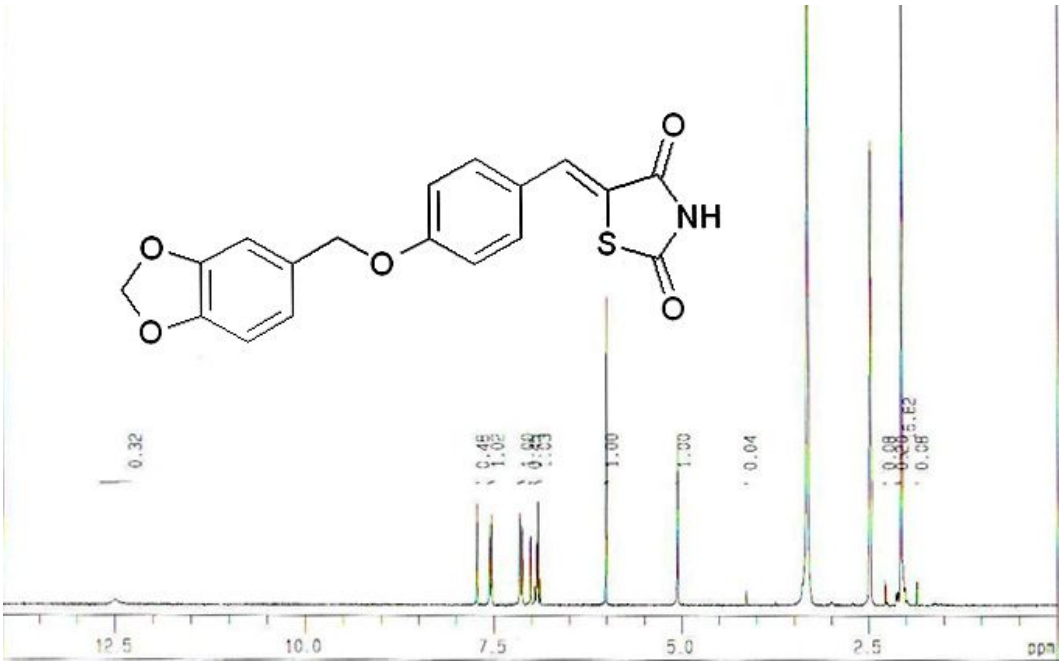

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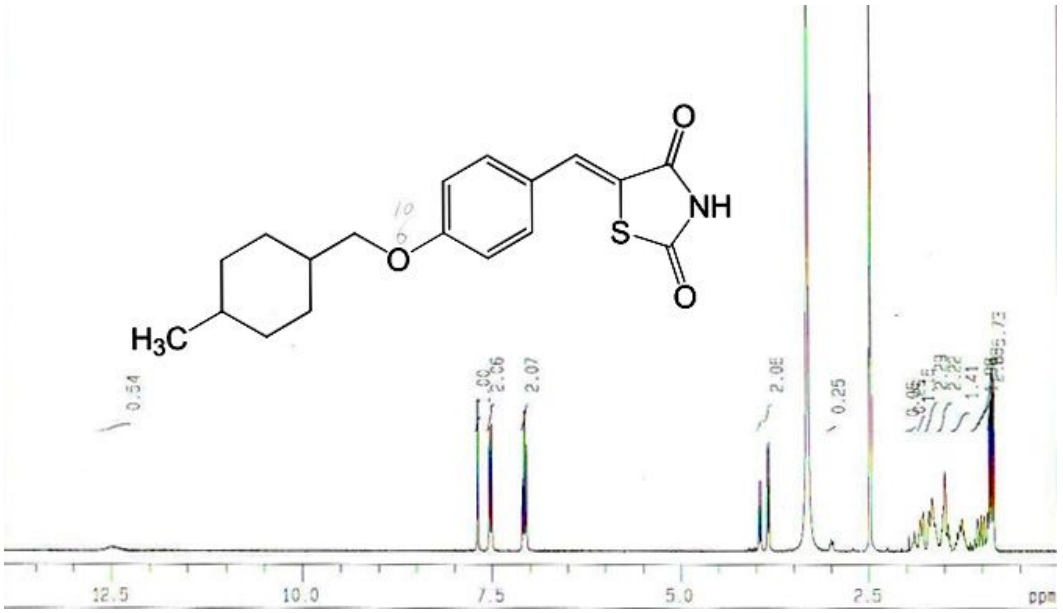

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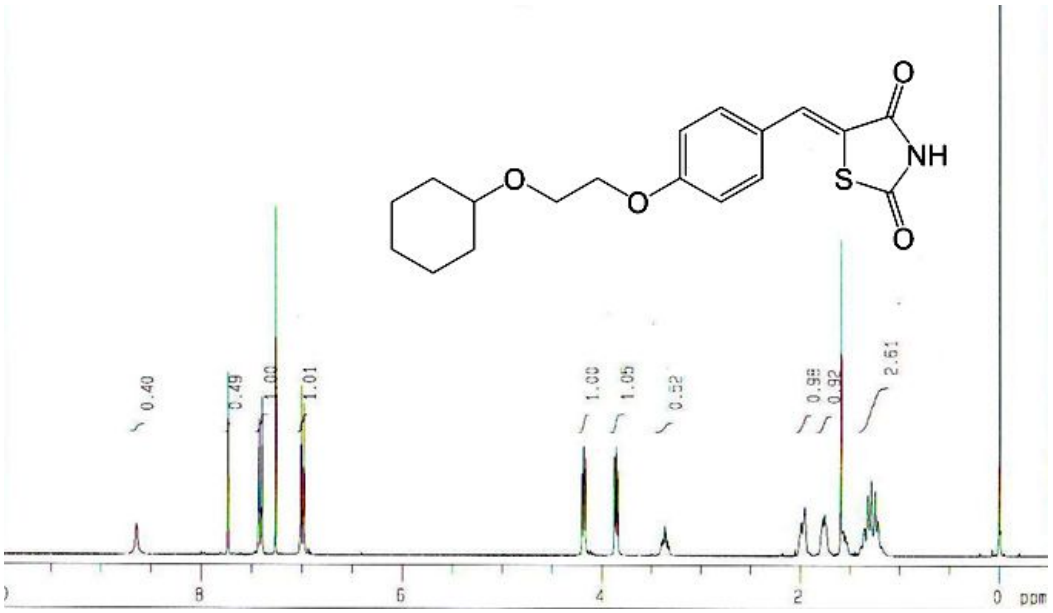

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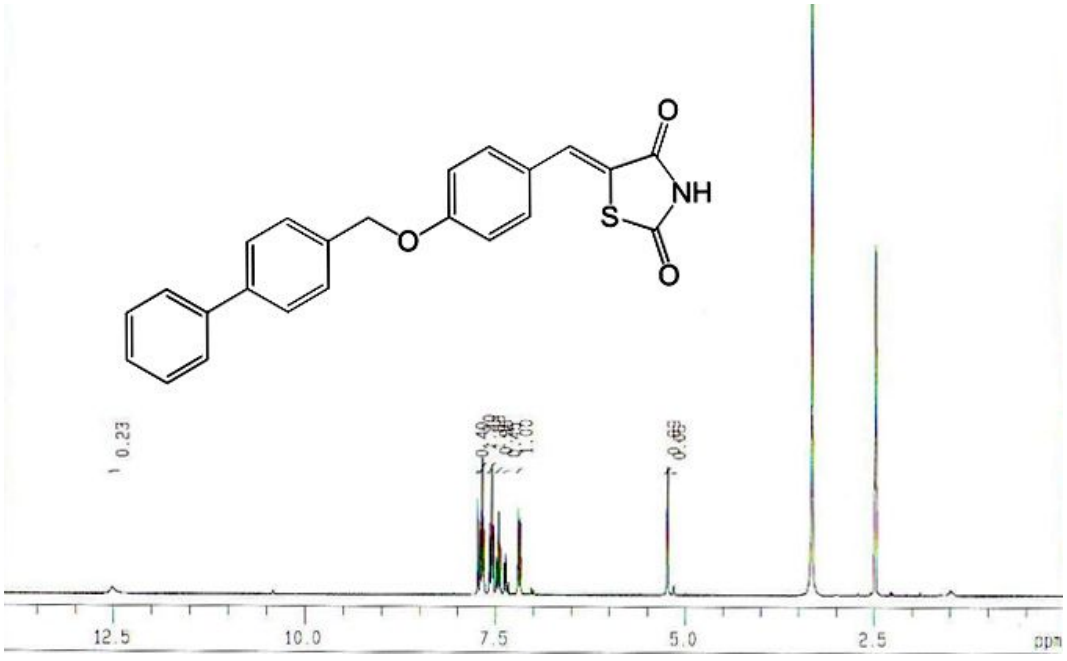

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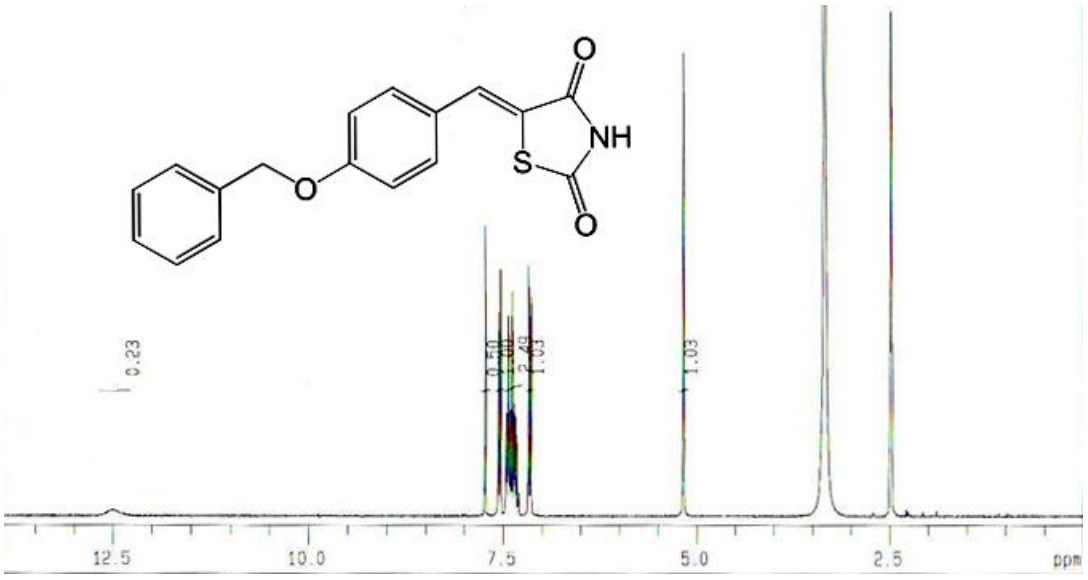
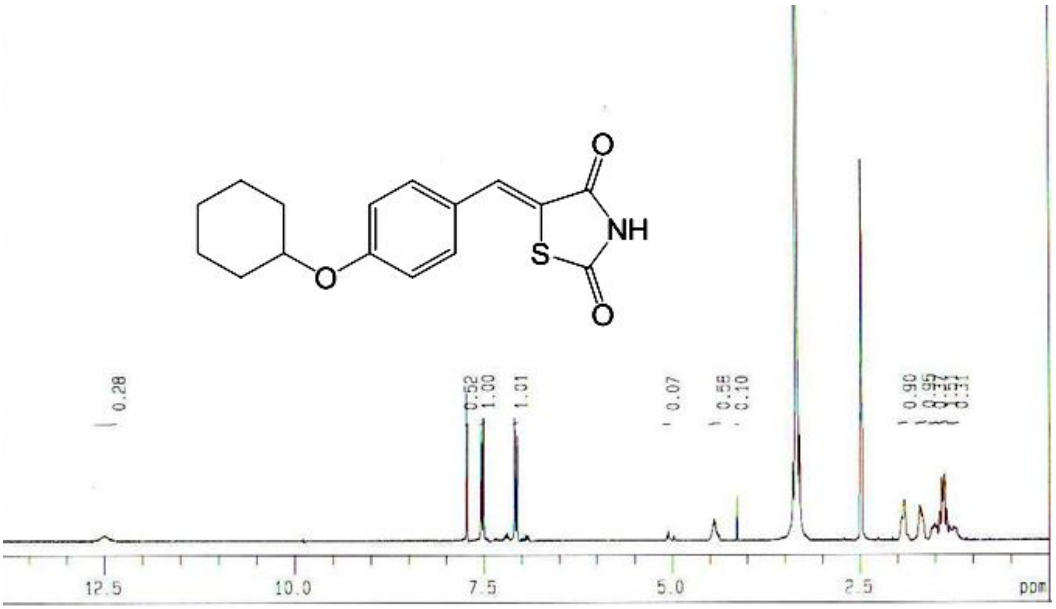


24c: 5-(4-(benzyloxy)benzylidene)thiazolidine-2,4-dione

25c: 5-[4-(2-phenylethoxy)benzylidene]-1,3-thiazolidine-2,4-dione

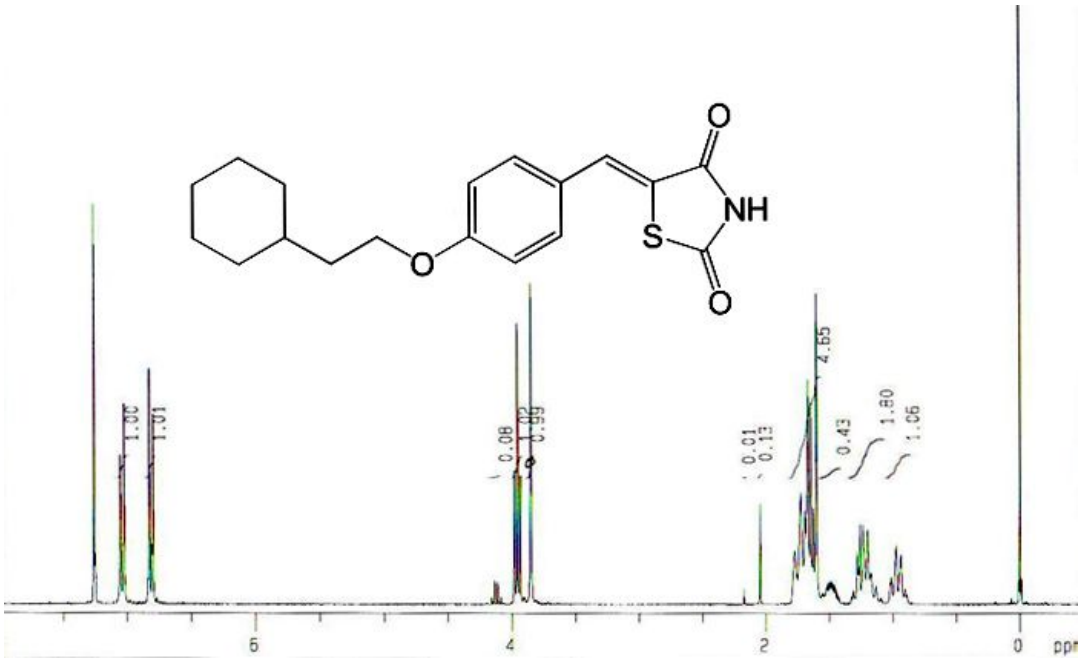
26c: 5-[4-(2-Phenylpropoxy)benzylidene]-1,3-thiazolidine-2,4-dione

27c: 5-[4-(2-phenylbutoxy)benzylidene]-1,3-thiazolidine-2,4-dione



28c: 5-(4-(cyclohexyloxy)benzylidene)thiazolidine-2,4-dione

29c: 5-(4-(cyclohexylmethoxy)benzylidene)thiazolidine-2,4-dione



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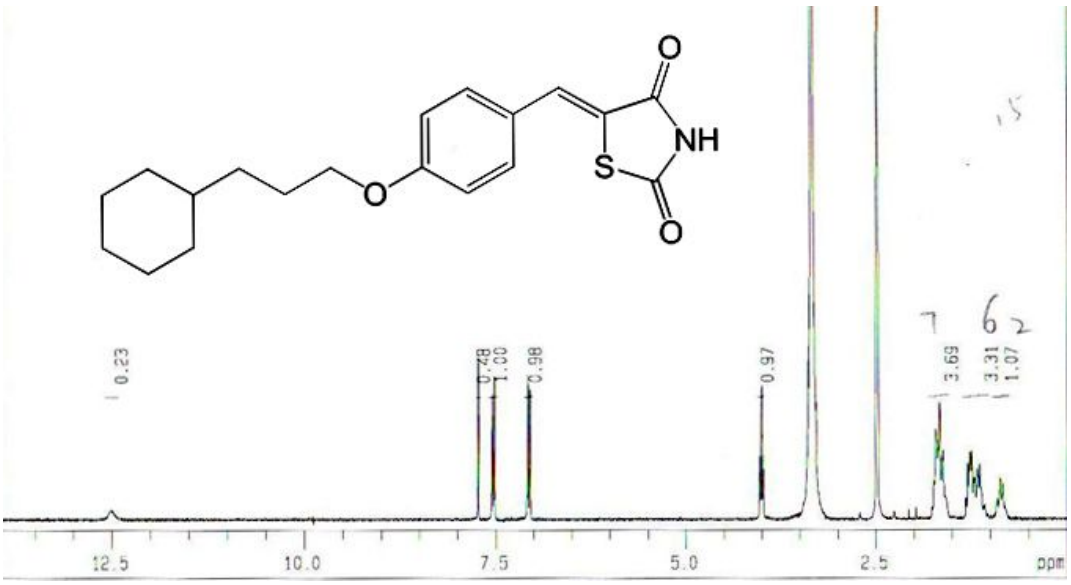

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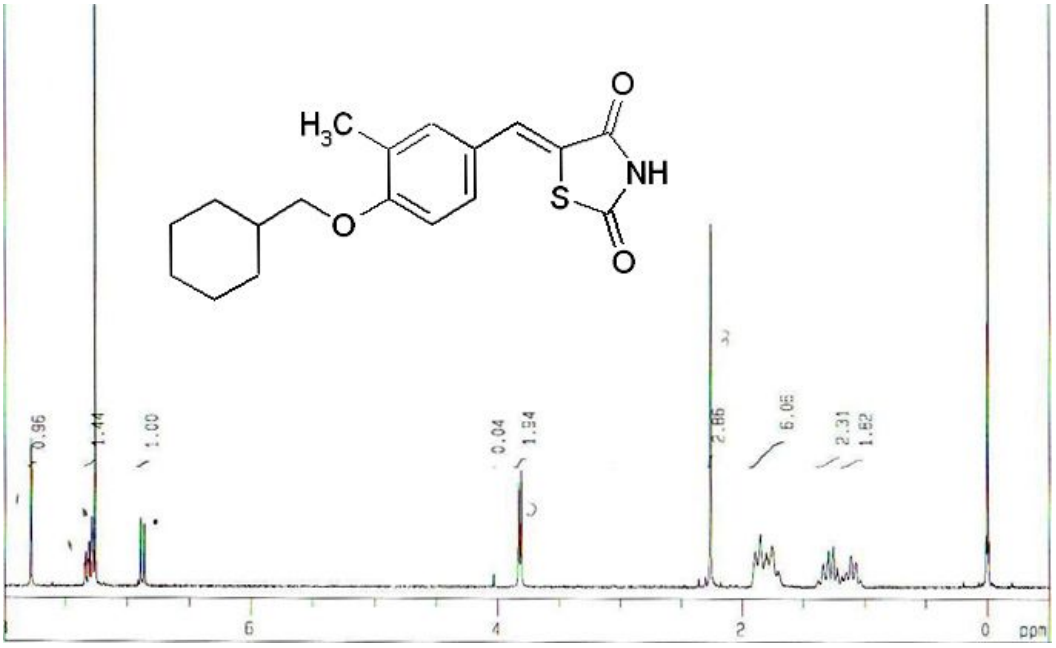

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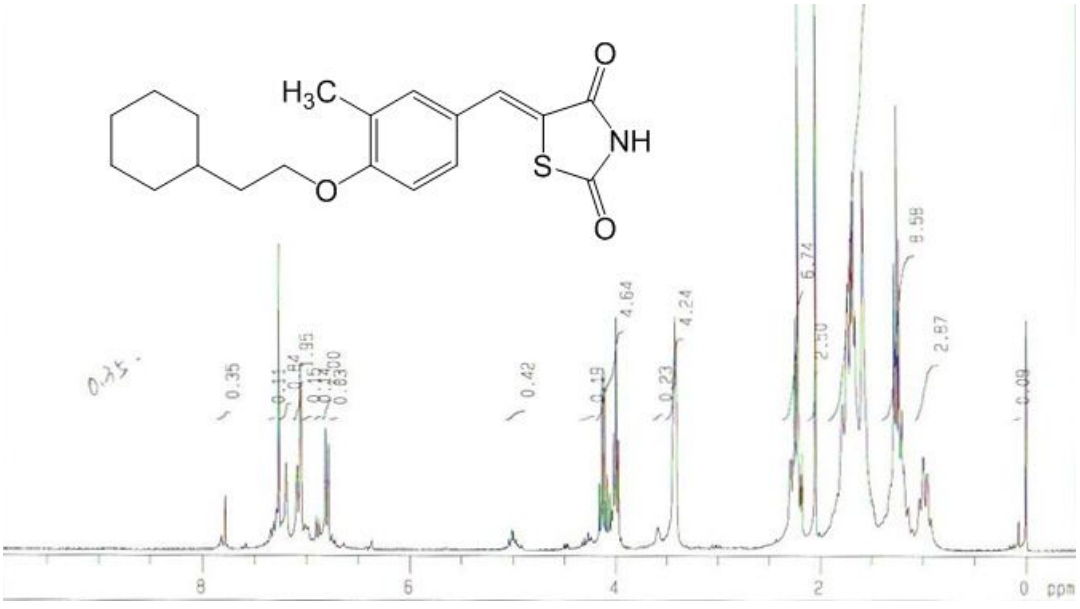

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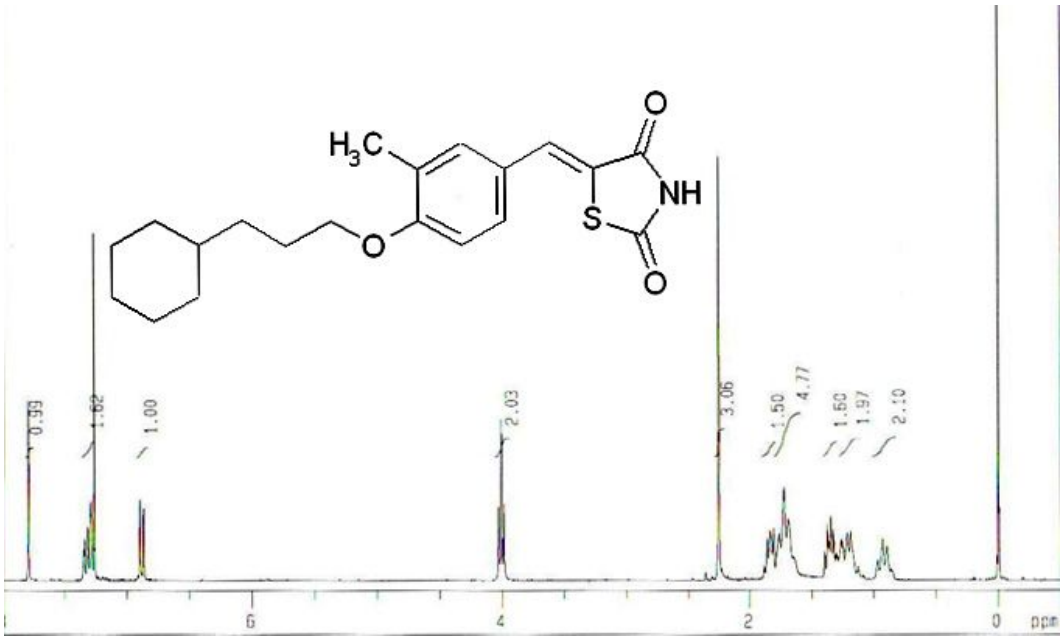

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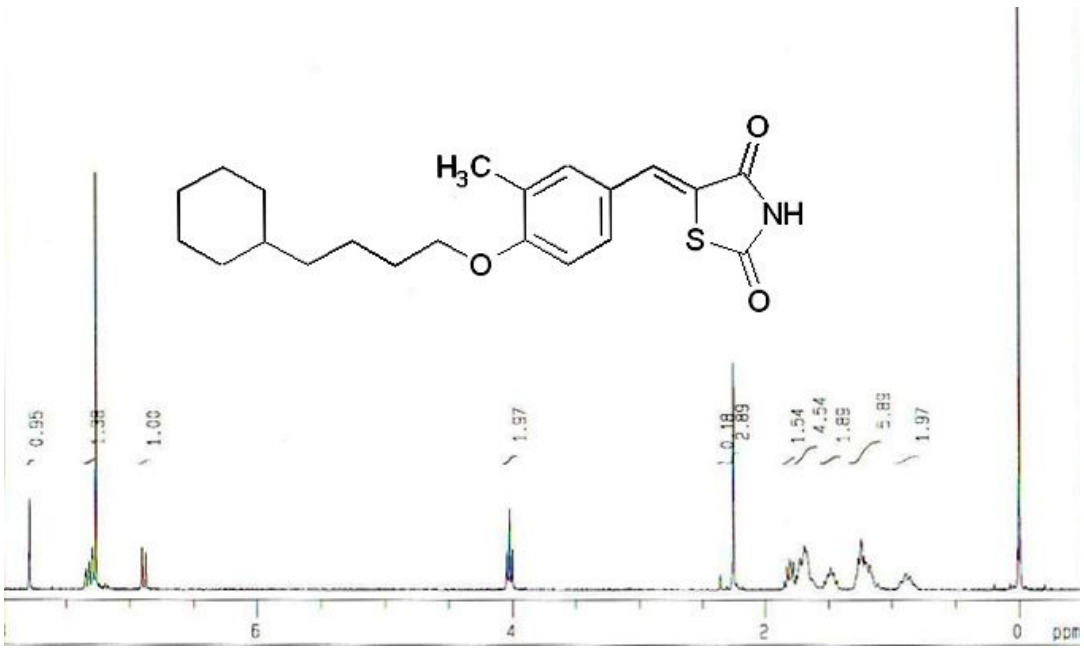
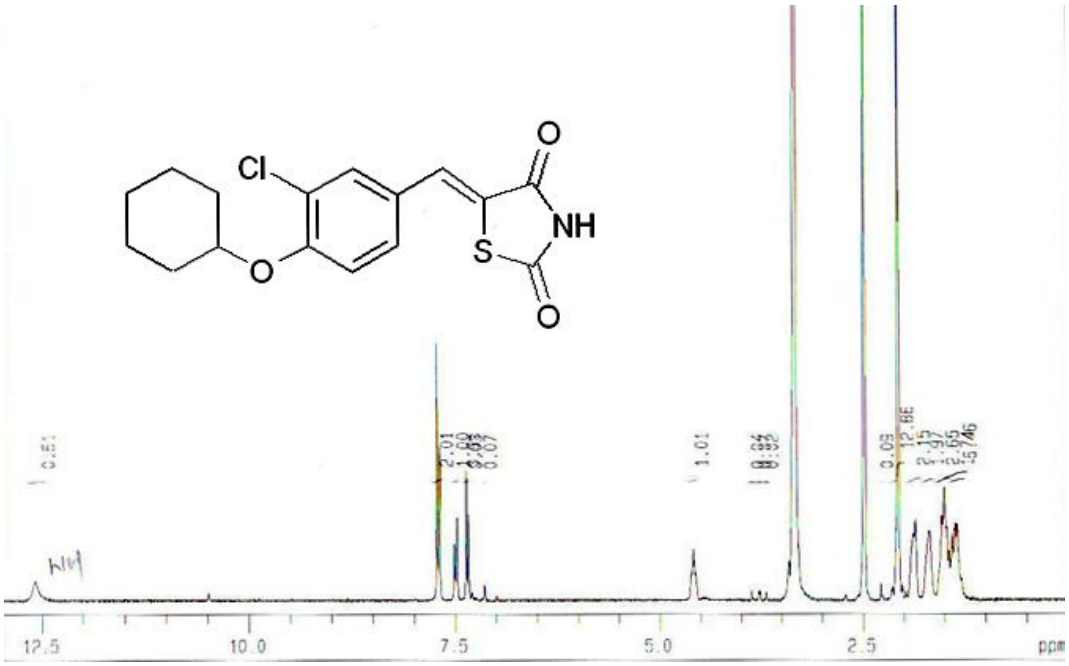
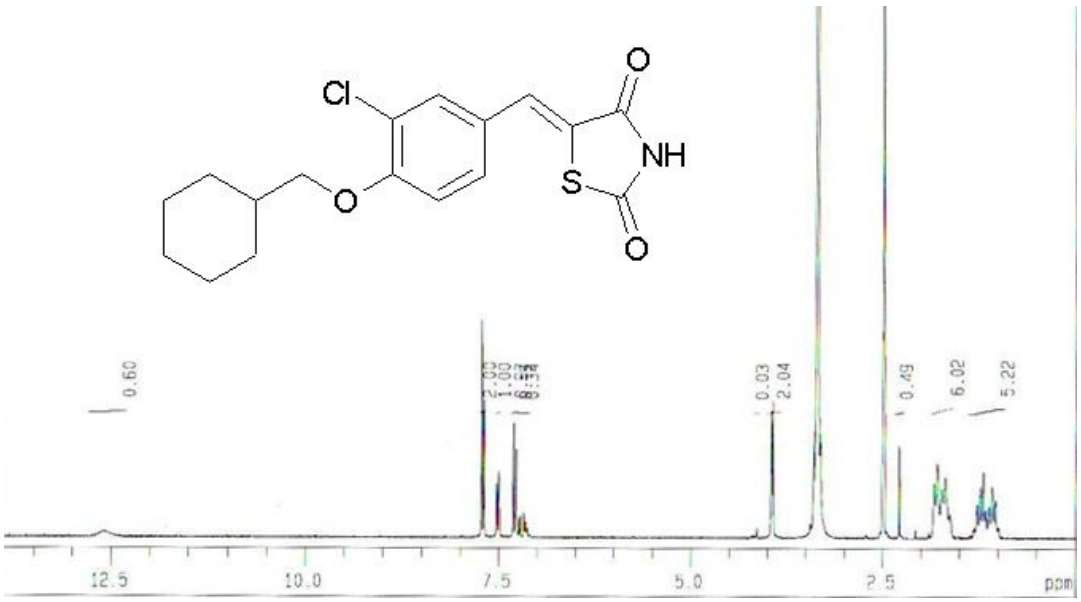


36c: 5-(4-(2-Cyclohexylbutoxy)-3-methylbenzylidene)thiazolidine-2,4-dione



37c: 5-(3-Chloro-4-(cyclohexyloxy)benzylidene)thiazolidine-2,4-dione



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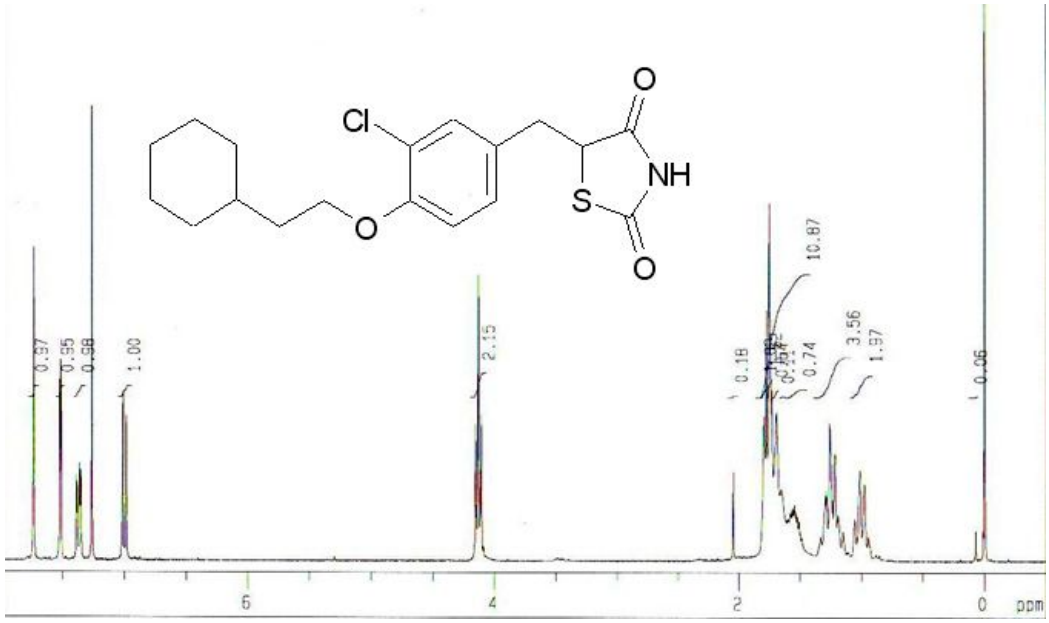

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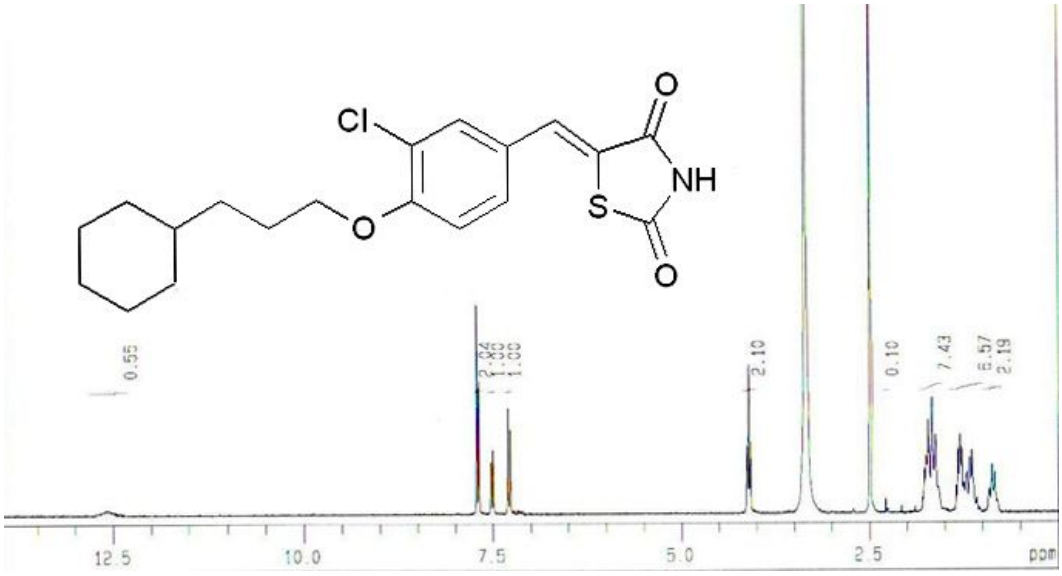

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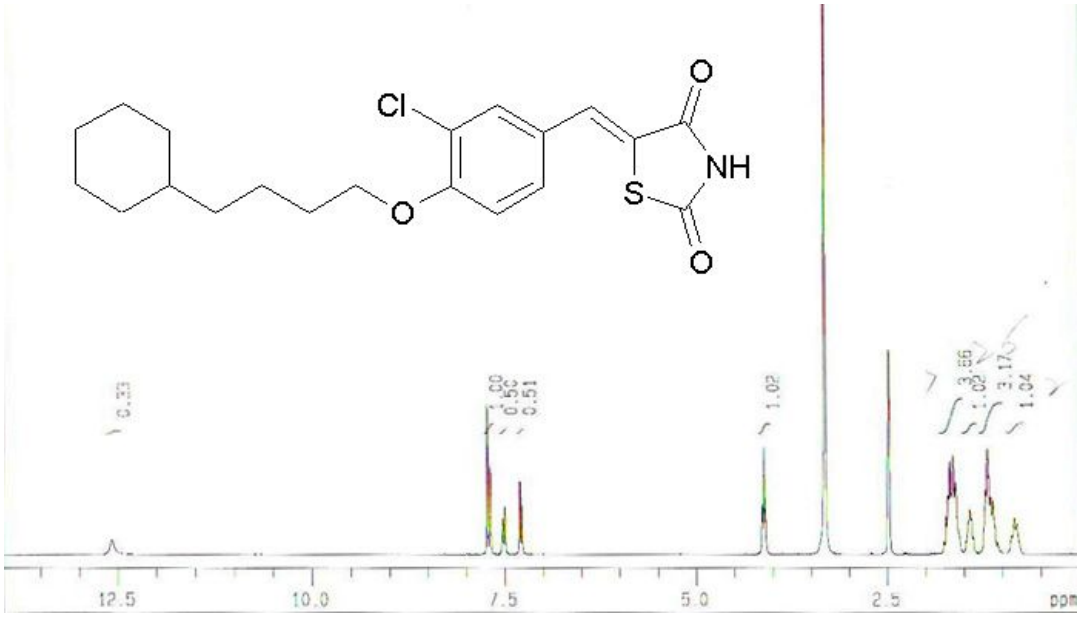

41c: 5-(3-chloro-4-(cyclohexylbutoxy)benzylidene)thiazolidine-2,4-dione

ACKNOWLEDGEMENTS

My greatest gratitude was owed to my thesis advisor, Professor Hoon Cho, for his instruction in this study. His guidance and advice made this thesis more comprehensive and readable. I am also grateful to all of the Professor in the department of Polymer Science and Engineering who have taught me various subjects.

Much respect to my labmates. Thanks to Mu Ying, Sandeep, Le Hang and many others for providing me with advice, and for helping my lab-work as well as my life in Korea. I hope we will keep in touch in the future no matter what we are. I will miss all of you a lot after an unforgettable period at Chosun University.

Finally, I would like to thank my family and my brother Hong Quan who have always been the most important of my life, and have believed in me and supported me througout. You know who you are, and I love you all.

For Quang Tu, I feel fortunate to have met you four years ago. Your endless love, patience and encourgement are never limitted, especically who they are most needed.

저작물 이용 허락서

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논문제목	한글: 유해조류 제어를 위한 thiazolidinedione 유도체 합성및 구조 활성 분석 영문: Synthesis and SAR of thiazolidinedione as a novel class of algicides against harmful algal species				

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

- 다 음 -

1. 저작물의 DB 구축 및 인터넷을 포함한 정보통신망에의 공개를 위한 저작물의 복제, 기억장치에의 저장, 전송 등을 허락함
2. 위의 목적을 위하여 필요한 범위 내에서의 편집・형식상의 변경을 허락함. 다만, 저작물의 내용변경은 금지함.
3. 배포・전송된 저작물의 영리적 목적을 위한 복제, 저장, 전송 등은 금지함.
4. 저작물에 대한 이용기간은 5 년으로 하고, 기간종료 3 개월 이내에 별도의 의사표시가 없을 경우에는 저작물의 이용기간을 계속 연장함.
5. 해당 저작물의 저작권을 타인에게 양도하거나 또는 출판을 허락을 하였을 경우에는 1 개월 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(0) 반대( )

2010 년 6 월 일

작자: 두옹띠우엔(서명 또는 인)

조선대학교 총장 귀하