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Novel 1,3-dicarbonyl compounds having 2(3*H*)-benzazolonic heterocycles as PPARγ agonists

Elodie Blanc-Delmas,[a] Nicolas Lebegue,[a,*] Valérie Wallez,[a] Véronique Leclerc,[a] Saïd Yous,[a] Pascal Carato,[a] Amaury Farce,[a] Caroline Bennejean,[b] Pierre Renard,[c] Daniel-Henri Caignard,[d] Valérie Audinot-Bouchez,[e] Pascale Chomarat,[e] Jean Boutin,[e] Nathalie Hennuyer,[f] Katie Louche,[g] Maria Carmen Carmona,[g] Bart Staels,[f] Luc Pénicaud,[g] Louis Casteilla,[g] Michel Lonchampt,[h] Catherine Dacquet,[h] Philippe Chavatte,[a] Pascal Berthelot[a] and Daniel Lesieur[a]

[a]*Laboratoire de Chimie Thérapeutique EA1043, Faculté des Sciences Pharmaceutiques et Biologiques de Lille, 3 rue du ProfesseurLaguesse, B.P. 83 59006 LILLE Cedex, France*
[b]*Planning ressources Institut de Recherche Internationale Servier, 6 place des Pléïades 92 415 Courbevoie Cedex, France*
[c]*Prospectives et Valorisation Scientifiques, Institut de Recherches Servier, 11 rue des Moulineaux, 92 150 Suresnes, France*
[d]*Etudes et Alliances Stratégiques, Institut de Recherches Servier, 125 Chemin de Ronde, 78 190 Croissy sur seine, France*
[e]*Division de Pharmacologie moléculaire et cellulaire, Institut de Recherches Servier 125 Chemin de Ronde, 78 000 Croissy sur seine, France*
[f]*Département d'Athérosclérose Institut Pasteur de Lille, INSERM U545, 1 Rue du Professeur Calmette, 59 019 Lille, France*
[g]*Laboratoire de Neurobiologie, Plasticité tissulaire et Métabolisme UMR5018, Université Paul Sabatier, CHU Rangueil, 1 Avenue Poulhes, 31 054 Toulouse Cedex, France*
[h]*Division de Recherche Maladies Métaboliques, Institut de Recherches Servier, 11 rue des Moulineaux, 92 150 Suresnes, France*

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Abstract—A series of 1,3-dicarbonyl compounds having 2(3*H*)-benzazolonic heterocycles has been synthesized and tested for PPARγ agonist activity. SAR were developed and revealed that 6-acyl-2(3*H*)-benzothiazolone derivatives with 1,3-dicarbonyl group were the most potent. IP administration of compound **22** exhibited comparable levels of glucose and triglyceride correction to PO administration of rosiglitazone in the *ob*/*ob* mouse studies.

1. Introduction

Non-insulin-dependent diabetes mellitus (NIDDM), otherwise known as type 2 diabetes, is a metabolic disorder characterized by insulin resistance, hyperglycemia, and hyperinsulinemia, leading to chronic complications such as neuropathy, nephropathy, retinopathy, and premature atherosclerosis.[1,2] Hyperglycemia in NIDDM is caused not only by impaired insulin secretion from the pancreas but also by the increased insulin resistance of peripheral tissues.[3,4] The treatment generally prescribed for NIDDM is a combination of diet, exercises, and oral hypoglycemic agents, commonly sulfonylurea and biguanides.[5] However, sulfonylurea therapy leads to many problems associated with primary and secondary failure of efficacy, incidence of hypoglycemia,[6] and obesity.[7] Thus, drugs that reverse the onset of insulin resistance fulfill a major unmet medical need for the treatment of NIDDM.[8]

PPARγ is a member of the peroxisome proliferator-activated receptor family. Its mechanistic role in glucose and lipid homeostasis has been the subject of extensive research.[9] As a result, PPARγ agonism is a current treatment for type 2 diabetes. Activation of PPARγ in the cell

Keywords: Diabetes; PPARγ; Benzothiazolone; Benzoxazolone; 1,3-Dicarbonyl derivative; Molecular modeling.
* Corresponding author. Tel.: +33 03 20 96 40 17; fax: +33 03 20 96 49 13; e-mail: nicolas.lebegue@univ-lille2.fr

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nucleus initiates heterodimerization with another nuclear receptor, the rexinoid receptor (RXR), with subsequent recruitment of coactivators and induction of genes that are involved in adipogenesis. Studies suggest that adipogenesis provides increased lipid metabolism and free fatty acid uptake in adipose tissue, leading to increased insulin sensitivity and glucose metabolism in muscle and liver.[9a,10,11] Synthetic PPARγ agonists for the treatment of type 2 diabetes[12] have proven successful for glucose control and reduction of HbA_{1c} with the marketed compounds rosiglitazone[13] and pioglitazone[13c,14] (Fig. 1). However, edema and weight gain have been reported in patients after treatment with PPARγ agonists[13b] (it remains to be seen if this is related to individual compounds or activation of PPARγ, and there continues to be interest in new compounds for clinical development).

Replacement of the thiazolidine-2,4-dione ring by an isoxazolidine-3,5-dione (JTT-501)[15,16] and its non-cyclic 1,3-dicarbonyl derivatives (JTP20993),[17] led to compounds which showed very interesting insulin-sensitizing activity in 3T3-L1 cells and hypoglycemic activity in genetically diabetic KKA^y mice (Fig. 1). The framework of JTT-501, like most of PPAR activators, can be divided into three key regions: (A) the acidic head part, (B) the linker part, and (C) the hydrophobic tail part (Fig. 2). Thus, chemical modifications of the acidic head part and the lipophilic part might change their selectivity to PPARα, PPARγ or PPARδ receptors.[18]

Thus, we report on the synthesis and biological results of compounds on which the acidic head part is replaced by malonate derivatives and the lipophilic part modified into benzazolonic heterocycles (2(3*H*)-benzoxazolone **8**, **10**, **12**, 2(3*H*)-benzothiazolone **9a**–**c**, **11a**–**b**, **13**) as well as their derivatives substituted in position 6 (**20**–**27a**–**l**) (Fig. 2). This manuscript provides an account of the synthesis of a novel set of PPARγ agonists which showed in vitro activity in transactivation and binding assays, and which also lowered blood glucose and triglyceride levels in experimental animal models.

2. Chemistry

The general procedure for 1,3-dicarboxylic compounds containing benzazolonic heterocycles (X = O: **8**, **10**, **12**; X = S: **9a**–**c**, **11a**–**b**, **13**) is represented in Scheme 1. Synthesis of aldehydes **4** (X = O) and **5** (X = S) was carried out by condensation of benzoxazolone **2** and benzothiazolone **3** with 4-(2-chloroethoxy)benzaldehyde[19] in the presence of potassium carbonate. Knoevenagel condensation between aldehydes **4**–**5** and malonate diester, which were refluxed in toluene in the presence of piperidine and acetic acid with removal of water via a Dean–Stark trap, afforded the benzylidene diesters **6**, **7a**–**c**. Catalytic hydrogenation with 10% palladium on carbon gave malonate diesters **8** and **9a**–**c**. Partial hydrolysis of these diesters with 1 equiv of potassium hydroxide or sodium hydroxide depending on benzazolonic heterocycles furnished the mono esters **10** and **11a**–**b**. Malonic diacids **12** and **13** were obtained by saponification of the diesters with more than 2 equiv of sodium hydroxide.

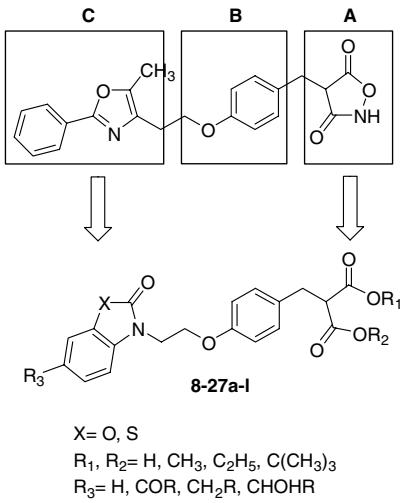


Figure 2. Drug design.

3. Results and discussion

Our goal was to develop a potent and selective PPARγ agonist that did not contain the 2,4-thiazolidinedione moiety, and displayed both antihyperglycemic and antihyperlipidemic activity in an established animal model of type 2 diabetes. Starting from the SAR and results previously described for JTP20993, we decided to

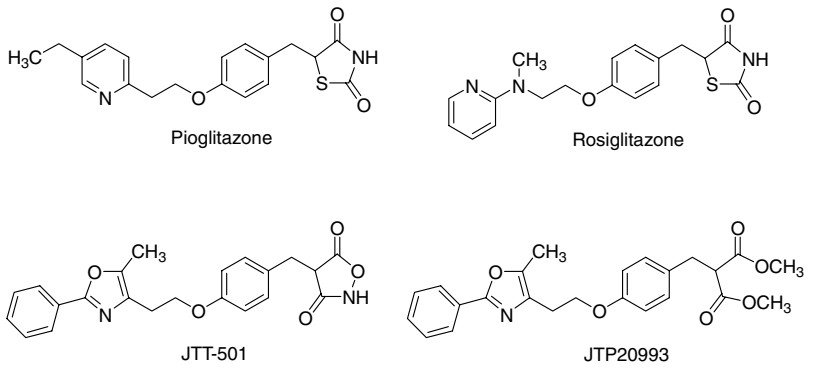
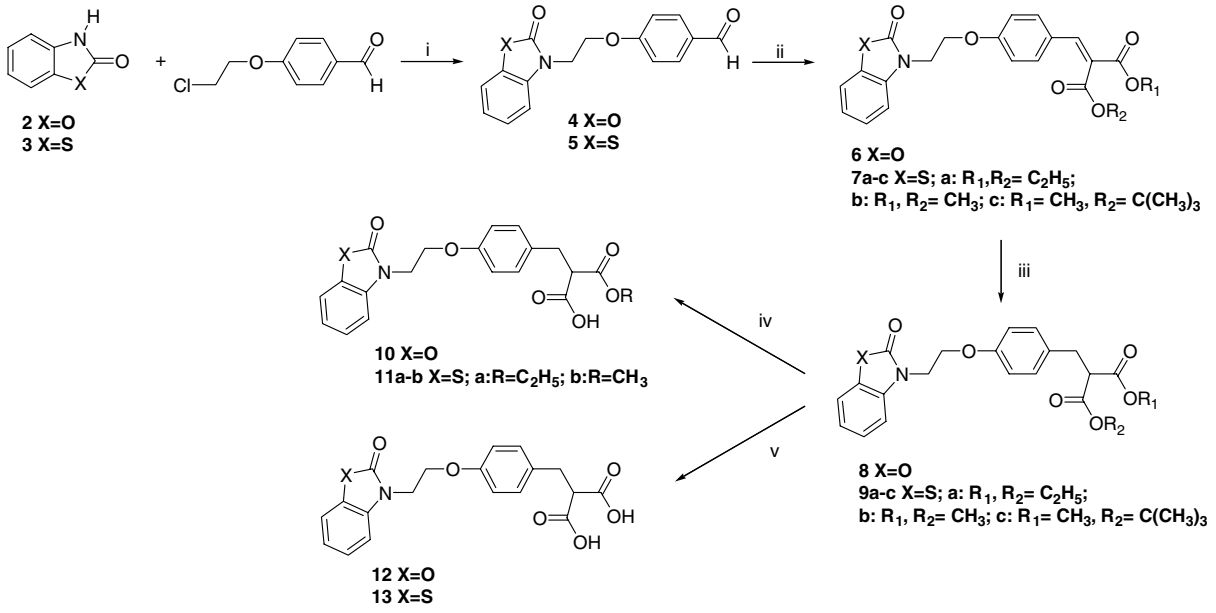


Figure 1. Reference compounds.



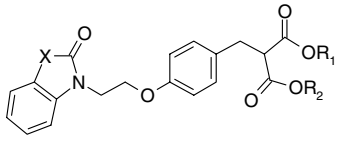
Scheme 1. Reagents and conditions: (i) K_2CO_3, DMF, reflux, 3h; (ii) dialkyl malonate, piperidine, acetic acid, toluene, reflux, 4–6 days; (iii) H_2, 10% Pd/C; (iv) for X = S: KOH 1 equiv, EtOH for X = O: 2 N NaOH 1 equiv, EtOH/THF, rt; (v) NaOH, EtOH/THF, rt.

combine within a common structure the two pharmacophoric patterns: a malonic functionality and a N-substituted heterocycle. The compounds **8**–**13** correspond to these characteristic features and possess 2(3*H*)-benzoxazolone or 2(3*H*)-benzothiazolone heterocycle bearing a 1,3-dicarboxylic group. They were characterized for both binding and functional activity in vitro (Table 1). All the compounds (**8**–**27a**–**l**) were functionally inactive at 10 μM against PPARα and PPARδ (% <50%) (Scheme 2).

3.1. Binding studies

Compounds were characterized by determining the binding affinity to human PPARγ using a competitive binding assay with [^{3}H]rosiglitazone, appropriate radioligand for PPARγ. The binding profiles of compounds were compared to the profiles of two marketed insulin sensitizers rosiglitazone and pioglitazone. No binding was detected with compounds **8** and **9a** (K_i > 10,000 nM) all substituted by two C_2H_5 functions

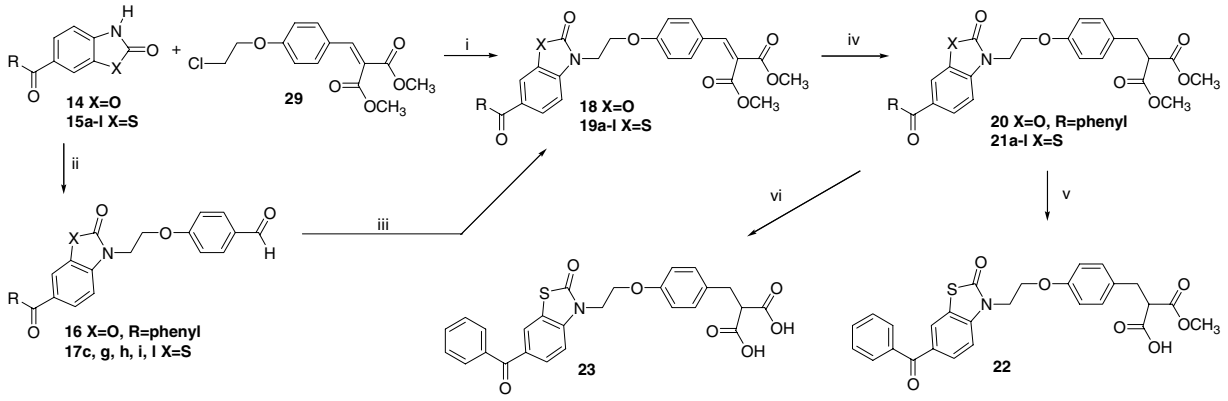
Table 1. In vitro profile of PPARγ agonists: compounds **8**–**13**



Compound	X	R_1	R_2	Binding K_i[a] (nM)	Transactivation: full-length PPRE human PPARγ potency (% of pioglitazone 1 μM)	EC_{50}[b] (nM)
8	O	C_2H_5	C_2H_5	>10,000	81	1200
9a	S	C_2H_5	C_2H_5	>10,000	89	850
9b	S	CH_3	CH_3	4140	89	376
9c	S	CH_3	$C(CH_3)_3$	>10,000	63	1310
10	O	H	C_2H_5	900	56	4800
11a	S	H	C_2H_5	225	92	1760
11b	S	H	CH_3	47	79	843
12	O	H	H	>10,000	2	10,000
13	S	H	H	>10,000	16	10,000
Rosiglitazone				8	75	40
Pioglitazone				364	100	160

[a] K_i values were calculated according to the equation $K_i = IC_{50}/(1 + [L]/K_d)$, where IC_{50} is the concentration of test compound required to inhibit 50% of the specific binding of the radioligand, [L] is the concentration of the radioligand used, and K_d is the dissociation constant for the radioligand at the receptor.

[b] EC_{50} is the concentration of the test compound required to induce 50% of the maximal pioglitazone response. All the compounds were functionally inactive at 10 μM against human PPARα and PPARδ (%<50%). Each experiment was performed twice and points were in triplicate.



	a	b	c	d	e	f
R	n-propyl	n-pentyl	Phenyl	2-tolyl	3-toyly	4-tolyl
	g	h	i	j	k	l
R	2-chlorophenyl	3-chlorophenyl	4-chlorophenyl	3,5-dichlorophenyl	3-methoxyphenyl	4-methoxyphenyl

Scheme 2. Reagents and conditions: (i) K_2CO_3, DMF, 80 °C, 1–4 days; (ii) DMF, 4-(2-chloroethoxy)benzaldehyde, K_2CO_3, reflux, 3 h; (iii) dimethyl malonate, piperidine, acetic acid, toluene, reflux, 2–4 days; (iv) H_2, 10% Pd/C; (v) KOH 1 equiv, MeOH/THF, rt; (vi) NaOH, MeOH/THF, rt.

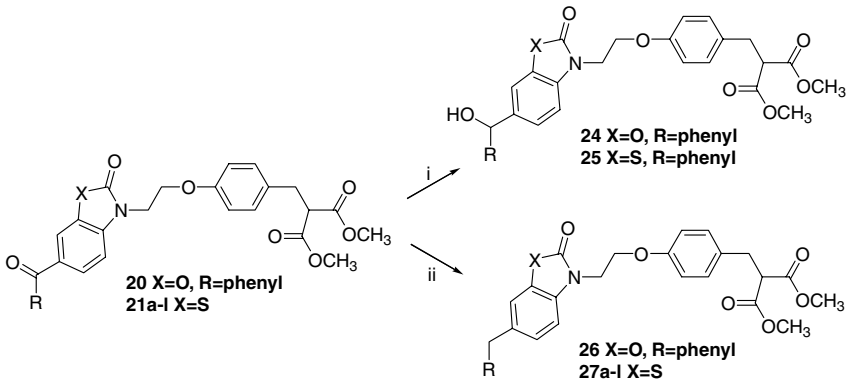
whatever benzazolonic heterocycle. Diacids 12 and 13 were also without binding affinity to human PPARγ. Better results were obtained with compounds which were substituted by methyl diester function like **9b** with $K_i = 4140$ nM, and particular with monoester and monoacid compounds: **10** and **11a**, with $K_i < 1000$ nM and **11b** which had the best binding affinity on PPARγ (**11b**: 47 nM, see Table 1). These observations show us that monoester malonates present stronger affinities than the corresponding diester or diacid malonates (Scheme 3).

3.2. Transactivation assays

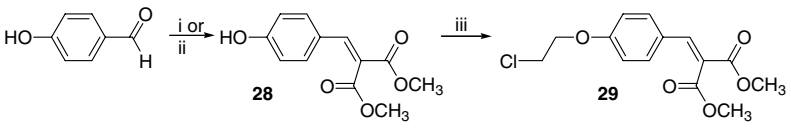
Functional activity was measured in a transient transfection assay using pGal4hPPARα, pGal4hPPARδ, pGal4hPPARγ, and PPARγ full-length PPRE systems. All the compounds were functionally inactive at 10 μM against human PPARα and PPARδ (% <50%). Compounds that elicited at least 75 % activation versus pioglitazone were considered full agonists. The best compounds were **9a**, **9b**, and **11b** which displayed more than 75% activation and $EC_{50} < 1000$ nM, suggesting that with a cellular system, the ester function allowed to reach the intracellular compartment. This was confirmed with the inactive diacid compounds **12** and **13** having very weak activities with EC_{50} in the range of 10 μM, because of lower lipophilicity. Compound **9b** behaves as full agonist like pioglitazone with an EC_{50} 376 nM versus 160 nM but the binding affinity was different certainly because of weaker interactions than pioglitazone in the PPARγ LBD. In order to well understand the binding affinity and functional potency, we decided to realize molecular modeling studies with compound **9b** bearing a 2(3*H*)-benzothiazolone which seems to be most tolerant of the benzazolone heterocycle in comparison with 2(3*H*)-benzoxazolone in the PPARγ LBD (Scheme 4).

3.3. Molecular modeling studies

Docking simulations were carried out in order to predict the binding mode of compound **9b** into the active site of PPARγ formerly occupied by rosiglitazone. The most stable docking model shows a binding mode very similar to the crystal orientation of rosiglitazone. Compound **9b** interacts via hydrogen bonding with His323 (between the imidazole NH and one sp2 oxygen from **9b**),



Scheme 3. Reagents and conditions: (i) $NaBH_4$, MeOH, room temperature, 18 h; (ii) Et_3SiH, THF, room temperature, 1–3 days.



Scheme 4. Reagents: (i) dimethyl malonate, $TiCl_4$, CCl_4, THF, pyridine; (ii) dimethyl malonate, MeOH, piperidine; (iii) 1-bromo-2-chloroethane, K_2CO_3, DMF.

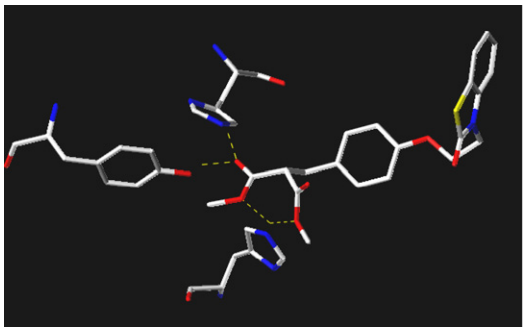


Figure 3. Compound **9b** docked into the PPARγ active site. Interactions with His323, His449 and Tyr473. H-bonds are shown (dashed lines).

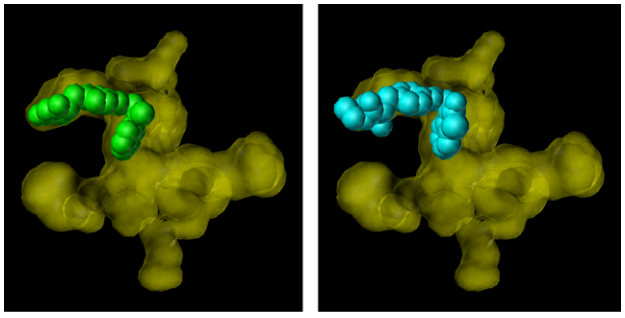


Figure 4. Surface representations of the occupied space in the PPARγ LBD by rosiglitazone (green) and compound **9b** (cyan) conformations.

His449 (between the imidazole NH and the two sp3 oxygens from **9b**), and Tyr 473 (between the OH and one sp2 oxygen from **9b**) (Fig. 3). We also compared the volume occupied by rosiglitazone and **9b** in the active site. Both compounds adopt essentially the same conformation and the same volume (Fig. 4). Nevertheless we noticed that there was a wide unoccupied hydrophobic cavity close to the 2(3*H*)-benzothiazolone ring. This observation led us to introduce different bulky substituents, such as benzyl, hydroxybenzyl or benzoyl, at position 6 on the 2(3*H*)-benzothiazolone heterocycle in order to strengthen the ligand–receptor interactions and by the way probably to increase the affinity.

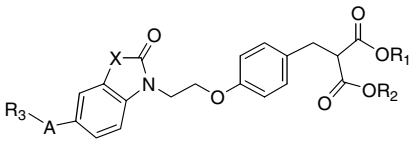
Acylation[20–22] at the 6 position of the 2(3*H*)-benzoxazolonic or 2(3*H*)-benzothiazolonic heterocycles improved both the binding affinity and the functional activity with EC_{50} values in the range of 2–840 nM and 7–120 nM, respectively, as shown in Table 2. As in the first series, 2(3*H*)-benzothiazolone seems to be most tolerant of the benzazolone heterocycle in comparison with 2(3*H*)-benzoxazolone. Compounds **21g**, **22**, and **23** showed difference in the transactivation EC_{50} values (36, 32, and 6200 nM, respectively) for full-length PPRE where the heterodimer PPARγ/RXRα was present and chimeric GAL4 PPARγ system (13, 8, and 650 nM, respectively) in a manner similar to rosiglitazone (EC_{50} = 40 nM for PPRE and 4 nM for GAL4). EC_{50} were better in GAL4 chimeric system suggesting an interaction with the heterodimer less favorable with these three compounds. On the contrary, other compounds like **20**, **24**, and **26** had a better EC_{50} on the full-length PPARγ like pioglitazone. This difference suggested a conformational configuration of the protein more favorable when heterodimer is present and a difference in the profile of coactivator and co-repressor recruitment. This observation was shown with all the oxo compounds tested suggesting an implication of the central cycle in the activation of PPARγ transcription factor. The other tested compounds have the same EC_{50} in the two transactivation assays. Compounds bearing benzyl function (compounds **26**, **27c**, **27g**, and **27h** with values of, respectively, 112%, 202%, 112%, and 130% compared to palmitate control conditions) showed highest adipocyte differentiation. On the contrary, a reduction of adipocyte differentiation was observed with compound **21g** displaying a value of 88%. It seems that in terms of adipocyte differentiation, 2(3*H*)-benzothiazolonic heterocycle must be acylated by a benzoyl moiety which is 2-chloro substituted phenyl ring.

Among all compounds tested, dimethyl malonate **21c** and monomethyl malonate **22** showed higher potency in vitro than the corresponding dicarboxylic acid **23**. This indicated that a methyl ester combined with another methyl ester or a carboxylic acid was the optimum structure. Since **21c** can be partially hydrolyzed to **22** in vitro, and since both **21c** and **22** are probably hydrolyzed to the less potent dicarboxylic acid **23**, it is difficult to decide which is the best combination: dimethyl malonate or monomethyl malonate. The glucose and triglyceride-lowering activities of the compounds prepared were tested using *ob*/*ob* mice (Table 3). It is interesting to note that all the selected compounds showed a poor pharmacological action on *ob*/*ob* mice when they were administered by oral gavage. Compound **22** showed the best effect on the glycemia and triglyceridemia reductions in comparison with compound **21c**. The ester acid functionality seems to be more bioavailable than diester function.

4. Conclusion

We have identified a series of novel benzazolonic heterocycles, which could replace the 2-phenyloxazole of JTP20993, bearing a 1,3-dicarboxylic functionality as

Table 2. In vitro profile of PPARγ agonists: binding, transactivation, and adipocyte differenciation: compounds **20**–**27a**–**l**



Compound	X	R_1	R_2	A	R_3	Binding	Transactivation				Adipocyte differentiation
							Full-length		Chimeric		
						K_i[a] (nM)	PPARγ PPRE[b] %	EC_{50}[c] (nM)	PPARγ GAL4[b] %	EC_{50} (nM)	% Palmitate control
20	O	CH_3	CH_3	C=O	Phenyl	79	74	53	93	102	ND
21a	S	CH_3	CH_3	C=O	*n*-Propyl	463	60	120	ND	ND	90 ± 6
21b	S	CH_3	CH_3	C=O	*n*-Pentyl	703	67	22	ND	ND	ND
21c	S	CH_3	CH_3	C=O	Phenyl	18	85	39	100	53	97 ± 1
21d	S	CH_3	CH_3	C=O	2-Tolyl	106	75	18	ND	ND	ND
21e	S	CH_3	CH_3	C=O	3-Tolyl	28	78	8	ND	ND	ND
21f	S	CH_3	CH_3	C=O	4-Tolyl	62	83	19	ND	ND	ND
21g	S	CH_3	CH_3	C=O	2-Chlorophenyl	840	77	36	100	13	88 ± 6
21h	S	CH_3	CH_3	C=O	3-Chlorophenyl	24	81	7	105	12	101 ± 2
21i	S	CH_3	CH_3	C=O	4-Chlorophenyl	76	71	21	100	24	106 ± 6
21j	S	CH_3	CH_3	C=O	3,5-Dichlorophenyl	36	71	15	ND	ND	ND
21k	S	CH_3	CH_3	C=O	3-Methoxyphenyl	102	83	34	ND	ND	ND
21l	S	CH_3	CH_3	C=O	4-Methoxyphenyl	147	82	21	ND	ND	ND
22	S	H	CH_3	C=O	Phenyl	2	100	32	100	8	99 ± 6
23	S	H	H	C=O	Phenyl	170	71	6200	84	650	102 ± 5
24	O	CH_3	CH_3	CHOH	Phenyl	722	75	96	77	287	ND
25	S	CH_3	CH_3	CHOH	Phenyl	185	73	92	85	126	ND
26	O	CH_3	CH_3	CH_2	Phenyl	8 900	85	40	93	102	112 ± 9
27a	S	CH_3	CH_3	CH_2	*n*-Propyl	518	65	16	100	9	105 ± 7
27b	S	CH_3	CH_3	CH_2	*n*-Pentyl	157	75	9	ND	ND	ND
27c	S	CH_3	CH_3	CH_2	Phenyl	77	80	13	100	9	202 ± 16
27e	S	CH_3	CH_3	CH_2	3-Tolyl	630	84	13	ND	ND	ND
27g	S	CH_3	CH_3	CH_2	2-Chlorophenyl	83	73	8	ND	ND	112 ± 10
27h	S	CH_3	CH_3	CH_2	3-Chlorophenyl	82	78	7	ND	ND	130 ± 13
27i	S	CH_3	CH_3	CH_2	4-Chlorophenyl	257	94	17	ND	ND	ND
27l	S	CH_3	CH_3	CH_2	4-Methoxyphenyl	106	83	51	ND	ND	ND
Rosi[d]						8	75	40	100	4	135 ± 8
Pio[e]						364	100	160	100	341	ND

[a] K_i (nM) is the concentration of test compound required to achieve an apparent concentration value according to the equation $K_i = IC_{50}/(1 + [L]/K_d)$, where IC_{50} is the concentration of test compound required to inhibit 50% of the specific binding of the radioligand, [L] is the concentration of the radioligand used and K_d is the dissociation constant for radioligand at the receptor.

[b] Potency (%).

[c] EC_{50} of the test compound is the concentration required to induce 50% of the maximum pioglitazone (1 μM) activity. Fold activation relative to maximum activation obtained with pioglitazone (1 μM) corresponded to 100% in PPARγ full-length PPRE system. In transactivation GAL4 chimeric PPARγ system, rosiglitazone (1 μM) is the reference substance.

[d] Rosiglitazone.

[e] Pioglitazone.

Table 3. In vivo activity of PPARγ agonists in *ob*/*ob* mice

	Antihyperglycemic activity Plasma glucose reduction (% control)		Antihyperlipidemic activity Triglycerides reduction (% control)	
	IP 10 mg/kg	PO 30 mg/kg	IP 10 mg/kg	PO 30 mg/kg
21c	−9	3	−57	−14
21h	−36	0	−48	ND
22	−32	−15	−58	−52
23	0	33	−26	−16
26	ND	−28	ND	ND
27a	ND	0	ND	ND
27c	ND	0	ND	ND
27h	ND	0	ND	ND
Rosiglitazone	−42	−61	−65	−65

potent and selective PPARγ agonists. The SAR studies of this work demonstrated that 2(3*H*)-benzothiazolone seemed to be the most potent nitrogen heterocycle of this series. Acylation at position 6 of this heterocycle induces an enhancement of both the binding affinity and the functional activity. Reduction of the benzoyl to a benzyl group improves adipocyte differentiation whereas introduction of a 2-chlorobenzoyl decreases it. This class of compounds generally maintains a high level of receptor subtype (PPARγ) selectivity but exhibits a poor oral efficacy in *ob*/*ob* mice. The acid ester **22** reduces comparable levels of glucose and triglyceride correction to rosiglitazone in the *ob*/*ob* mouse studies. These results encourage us to continue synthesis and evaluation of compounds in the chemical series with the goal of increased in vivo potency, while maintaining acceptable parameters of pharmaceutical suitability.

5. Experimental

5.1. In vitro assays

Membrane-bound PPARγ binding assay. Binding assays were performed in 96-well plates format, using a classical filtration assay with a human full-length PPARγ construct [GST-PPAR LBD (25 μg/ml)] expressed in bacteria with some modifications regarding the conditions of the experiments. The membrane-associated PPARγ was used as the biological source as previously described. Binding buffer consisted of 10 mM Tris/HCl, pH 8.2, containing 50 mM KCl and 1 mM dithiothreitol. Membrane preparations (5 μg/mL) were incubated for 180 min at 4 °C in the presence of [^{3}H]rosiglitazone [BRL49653, Amersham] (4 nM) and the tested compounds. Non-specific binding was defined using an excess of unlabeled rosiglitazone (10 μM).

Incubation was terminated by the addition of ice-cold 50 mM Tris/HCl buffer, pH 7.4, followed by rapid filtration under reduced pressure through Whatman GF/C filter plates presoaked with ice-cold buffer, followed by three successive washes with the same buffer. Radioactivity was measured in a TopCount apparatus (Packard). The receptor preparation used during these experiments presented a Bmax of 49 pmol/mg proteins and a K_d of 5.58 nM for [^{3}H]rosiglitazone. The compounds were solubilized in pure DMSO and diluted to the appropriate working concentrations (100 μM to 0.1 nM). For each compound tested, plots of ligand concentration versus DPM of radioligand bound were constructed and apparent K_i values were estimated from non-linear least-squares fit of the data assuming simple competitive binding. The details of this assay have been reported.[23]

5.2. Transactivation assays: cell culture and transfection

Compounds were screened for functional potency in a transient transfection assay performed on CV-1 cells. Cells were transiently transfected with plasmids pMCMVneo-hPPARγ and pMCMVneo-hRXRα, pGL3-PPRE X 3-tk-luc-neo. The luciferase reporter plasmid PPRE was from acyl-CoA oxidase human gene.[24] A second transactivation assay was performed on Cos7 cells in a previously established chimeric receptor system used to allow comparison on the relative transcriptional activity on the same target gene but to prevent endogenous receptor activation and heterodimerization from complicating the interpretation of results. Cos-7 cells were transiently transfected with luciferase reporter plasmid (pG5-TK-pGL3) in the presence of pGal4hPPARγ (this vector expresses chimeric proteins containing the Gal4 DNA-binding domain fused to the human PPARγ ligand binding domain coding sequence) expression vector. Plasmids pGal4-hPPARγ and pG5-TK-pGL3 were constructed as described previously.[25] Cells were seeded in 60 mm dishes at a density of 5.5×10^5 cells/dish in DMEM supplemented with 10% FCS and incubated at 37 °C for 24 h prior to transfection. Cells were transfected in OptiMEM without FCS for 3 h at 37 °C, using polyethylenimine (PEI), with reporter and expression plasmids, as stated in figure's legend. The plasmid pBluescript (Stratagene, La Jolla, CA) was used as carrier DNA to set the final amount of DNA to 5.5 μg/dish. The pCMV-*β*-galactosidase expression plasmid was cotransfected as a control for transfection efficiency. Transfection was stopped by addition of DMEM supplemented with 10% FCS and cells were then incubated at 37 °C. After 16 h, cells were trypsinized and seeded in 96-well plates at the density of 2×10^4 cells/well and incubated for 6 h in 10% FCS containing DMEM. Cells were then incubated for 24 h in DMEM containing 0.2% FCS and increasing concentrations of the compound tested or vehicle (DMSO). At the end of the experiment, cells were washed once with ice-cold PBS and the luciferase and the β-galactosidase assays were performed as described previously.[26] Cells were incubated for 24 h in the presence of indicated concentrations of the compound. Luciferase activity was measured and normalized to internal control β-galactosidase activity. Compounds which elicited on average at least 80% activation of PPARγ versus pioglitazone (PPRE) or rosiglitazone (GAL4) (positive controls) were considered full agonists. EC_{50} were estimated using Prism software (GraphPad). All transfection experiments were performed at least three times.

5.3. Adipocyte differentiation

3T3-L1 preadipocytes were cultured in Dulbecco's modified Eagle's medium supplemented with a 10% heat-inactivated fetal bovine serum (FBS), L-glutamine (5 mM) and antibiotics (streptomycin: 2 μg/ml, penicillin: 50 μU/ml, and amphotericin B: 5 ng/ml) at 37 °C in a 5% CO_2 humidified atmosphere.[27] Cells were grown to confluence and treated with palmitate (10 mM) and solvent (DMSO 0.1%, control cells), or compounds (100 nM) every two days. Adipocyte differentiation was determined by Oil Red O staining, by triglyceride quantification using the Triglycerides Enzymatic PAP150 kit from BioMérieux (Marcy-l'Etoile, France). Protein content

was determined using the DC Protein Assay System from Bio-Rad Laboratories.

5.4. In vivo models

The glucose and triglyceride-lowering activities of the compounds were tested using *ob*/*ob* mice (male or female, C57BL/6J). *Ob*/*ob* mice (10–12 weeks old) were purchased from Harlan (France). The mice were housed in a temperature controlling room (21.8–24 °C), with relative humidity of 36–80% and 12 h light/dark cycle (light 7:00 am to 7:00 pm). Mice had ad libitum access to filtered tap-water (0.22 μm filter) and irradiated pelleted laboratory chow (ref # A03-10, UAR, France) throughout the study. Compounds were prepared in 10% DMSO/15% Solutol/75% sterile water (v/v/v) prepared daily for intraperitoneal administration (5.0 mL/kg) or as suspensions in 1% HEC for oral administration (2.5 mL/kg). The mice (n = 8–12 per dose) were treated by intraperitoneal method or by gavage daily between 3.00 pm and 5:00 pm during four days. Randomization was performed on glycemia values at day 0. At day five, between 9:00 and 11:00 am, mice were weighed and blood samples were collected into heparin-containing tubes by retro-orbital puncture (500 μL/mouse) under CO_2 anesthesia. Plasma sample were prepared by centrifugation (2000*g* for 10 min) and stored at −20 °C. Mice were euthanized by cervical dislocation. For each animal, the percentage change of plasma glucose on day 5 was calculated relative to the values obtained at day zero. For triglycerides, the percentage change in plasma was calculated relative to the mean triglycerides' plasma value of the vehicle treated mice. ANOVA, followed by Dunnett's comparison test (one tailed) was used to estimate the significant difference between the plasma triglycerides values from the control group and the individual compound treated groups. The compound is considered active, at the specific dosage administrated, if the difference of plasma levels had a P value < 0.05. All compounds with a $P > 0.05$ were reported as inactive.

5.5. Molecular modeling

Molecular modeling studies were performed using SYBYL software version 6.4[28] running on Silicon Graphics workstations. The geometry of compound **9b** was subsequently optimized using the Tripos force field[29] including the electrostatic term calculated from Gasteiger and Hückel atomic charges. The method of Powell available in Maximin2 procedure was used for energy minimization until the gradient value was smaller than 0.001 kcal/mol Å. The structure of the PPARγ ligand binding domain (LBD) was obtained from its complexed X-ray crystal structure with rosiglitazone and a fragment of src-1 coactivator available in the RCSB Protein Data Bank (2PRG).[30] The binding site cavity of the receptor was visualized using the SURFNET version 1.5 program.[31] Flexible docking of compounds into the receptor active site was performed using the FlexiDock module of SYBYL. The complexes were energy-minimized using the Powell method available in Maximin2 procedure with the MMFF94 force field[32] and a dielectric constant of 4.0 until the gradient value reached 0.05 kcal/mol Å. The anneal function was used defining around the inhibitor a hot region (10 Å) and an interesting region (15 Å).

5.6. Chemistry

Thin-layer chromatography was performed on precoated silica gel plates (60F254, Merck). Flash chromatography was performed on silica gel (Merck, 0.063–0.200 mm). Melting points were obtained with a Büchi 530 melting point apparatus and are uncorrected. Infrared spectra were recorded on a Bruker vector 22 spectrometer. ^{1}H NMR spectra were recorded on a Bruker AC 300P spectrometer (LARM, Université de Lille 2) in solutions of DMSO-d_6 or $CDCl_3$-*d* and are reported as parts per million (ppm) from downfield to tetramethylsilane.

5.6.1. General procedure for N-alkylation of 2(3*H*)-benzoxazolone or 2(3*H*)-benzothiazolone to compounds 4, 5, 16, 17c, g, h, i, l, 18, 19a, b, k. To a solution of 1.0 equiv of the appropriate benzazolonic heterocycle in DMF were added 2 equiv of potassium carbonate and the mixture was stirred for 20 min at reflux. A solution of chloro compounds (4-(2-chloroethoxy)benzaldehyde or **29**) in DMF was added dropwise and the mixture was stirred at reflux for 3 h. The solution was poured into water and the resulting solid filtered. The crude product was recrystallized from the appropriate solvent.

5.6.1.1. 4-[2-(*2*(*3H*)-Benzoxazolon-3-yl)ethoxy]benzaldehyde (4). Mp 112–113 °C (cyclohexane/toluene (1:1)) (yield 56%). IR (KBr) cm^{-1} 1700, 1750. ^{1}H NMR (DMSO) δ 4.20 (m, 2H), 4.50 (m, 2H), 7.10 (d, J = 8.6 Hz, 2H), 7.15 (t, J = 8.0 Hz, 1H), 7.25 (t, J = 7.5 Hz, 1H), 7.35 (d, J = 8.0 Hz, 1H), 7.45 (d, J = 7.5 Hz, 1H), 7.85 (d, J = 8.6 Hz, 2H), 10.00 (s, 1H).

5.6.1.2. 4-[2-(*2*(*3H*)-Benzothiazolon-3-yl)ethoxy]benzaldehyde (5). Mp 118–120 °C (EtOH) (yield 83%). IR (KBr) cm^{-1} 1670, 1700. ^{1}H NMR (DMSO) δ 4.40 (s, 4H), 7.05 (d, J = 8.8 Hz, 2H), 7.20 (t, J = 8.0 and J = 7.7 Hz, 1H), 7.40 (t, J = 7.7 Hz, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.65 (d, J = 7.7 Hz, 1H), 7.85 (d, J = 8.8 Hz, 2H), 9.90 (s, 1H).

5.6.1.3. 4-[2-(6-Benzoyl-*2*(*3H*)-benzoxazolon-3-yl)ethoxy]benzaldehyde (16). Mp 105–108 °C (toluene) (yield 50%). IR (KBr) cm^{-1} 1690, 1780. ^{1}H NMR (DMSO) δ 4.35 (t, J = 5.0 Hz, 2H), 4.45 (t, J = 5.0 Hz, 2H), 7.10 (d, J = 8.7 Hz, 2H), 7.55–7.80 (m, 8H), 7.85 (d, J = 8.7 Hz, 2H), 9.90 (s, 1H).

5.6.1.4. 4-[2-(6-Benzoyl-*2*(*3H*)-benzothiazolon-3-yl)-ethoxybenzaldehyde (17c). Mp 135–138 °C (toluene) (yield 60%). IR (KBr) cm^{-1} 1700, 1780. ^{1}H NMR (DMSO) δ 4.45 (s, 4H), 7.05 (d, J = 8.7 Hz, 2H), 7.50–7.90 (m, 9H), 8.15 (s, 1H), 9.85 (s, 1H).

5.6.1.5. 4-{2-[6-(2-Chlorobenzoyl)-*2*(*3H*)-benzothiazolon-3-yl]ethoxy}benzaldehyde (17g). Mp 168–171 °C (EtOH) (yield 70%). IR (KBr) cm^{-1} 1650, 1690. ^{1}H NMR (DMSO) δ 4.40 (s, 4H), 7.05 (d, J = 8.7 Hz, 2H), 7.50–7.85 (m, 8H), 8.10 (s, 1H), 9.85 (s, 1H).

5.6.1.6. 4-{2-[6-(3-Chlorobenzoyl)-2(3*H*)-benzothiazolon-3-yl]ethoxy}benzaldehyde (17h). Mp 162–165 °C (EtOH) (yield 50%). IR (KBr) cm^{-1} 1650, 1695. ^1H NMR (DMSO) δ 4.50 (s, 4H), 7.10 (d, $J = 8.5$ Hz, 2H), 7.60–7.90 (m, 8H), 8.20 (s, 1H), 9.85 (s, 1H).

5.6.1.7. 4-{2-[6-(4-Chlorobenzoyl)-2(3*H*)-benzothiazolon-3-yl]ethoxy}benzaldehyde (17i). Mp 190–194 °C (EtOH) (yield 50%). IR (KBr) cm^{-1} 1650, 1695. ^1H NMR (DMSO) δ 4.50 (s, 4H), 7.10 (d, $J = 8.7$ Hz, 2H), 7.60–7.85 (m, 8H), 8.15 (s, 1H), 9.85 (s, 1H).

5.6.1.8. 4-{2-[6-(4-Methoxybenzoyl)-2(3*H*)-benzothiazolon-3-yl]ethoxy}benzaldehyde (17l). Mp 149–153 °C (MeOH) (yield 75%). IR (KBr) cm^{-1} 1695. ^1H NMR (DMSO) δ 3.90 (s, 3H), 4.50 (s, 4H), 7.10 (m, 4H), 7.65 (d, $J = 8.7$ Hz, 1H), 7.70–7.80 (m, 3H), 7.85 (d, $J = 8.7$ Hz, 1H), 8.10 (s, 1H), 9.90 (s, 1H).

5.6.1.9. Dimethyl 4-[2-(6-benzoyl-)-2(3*H*)-benzoxazolon-3-yl)ethoxy]benzylidenemalonate (18). Mp 173–176 °C (diisopropyl ether) (yield 80%). IR (KBr) cm^{-1} 1725. ^1H NMR (DMSO) δ 3.75 (s, 3H), 3.85 (s, 3H), 4.35 (s, 2H), 4.45 (s, 2H), 7.00 (d, $J = 8.8$ Hz, 2H), 7.40 (d, $J = 8.8$ Hz, 2H), 7.55–7.75 (m, 9H).

5.6.1.10. Dimethyl 4-[2-(6-butyryl-2(3*H*)-benzothiazolon-3-yl)ethoxy]benzylidenemalonate (19a). Mp 154–155 °C (MeOH) (yield 50%). IR (KBr) cm^{-1} 1680, 1710, 1735. ^1H NMR (DMSO) δ 0.90 (t, $J = 7.4$ Hz, 3H), 1.65 (s, 2H), 3.00 (t, $J = 7.4$ Hz, 2H), 3.80 (s, 6H), 4.35 (t, $J = 4.6$ Hz, 2H), 4.45 (t, $J = 4.6$ Hz, 2H), 6.95 (d, $J = 8.8$ Hz, 2H), 7.40 (d, $J = 8.8$ Hz, 2H), 7.60 (d, $J = 8.4$ Hz, 1H), 7.75 (s, 1H), 8.00 (d, $J = 8.4$ Hz, 1H), 8.35 (s, 1H).

5.6.1.11. Dimethyl 4-[2-(6-hexanoyl-2(3*H*)-benzothiazolon-3-yl)ethoxy]benzylidenemalonate (19b). Mp 105–110 °C (diisopropyl ether) (yield 55%). IR (KBr) cm^{-1} 1680, 1710, 1735. ^1H NMR (DMSO) δ 0.90 (t, $J = 6.7$ Hz, 3H), 1.30 (m, 4H), 1.60 (t, $J = 6.7$ Hz, 2H), 3.00 (t, $J = 6.7$ Hz, 2H), 3.80 (s, 6H), 4.35 (t, $J = 4.5$ Hz, 2H), 4.45 (t, $J = 4.5$ Hz, 2H), 6.95 (d, $J = 8.8$ Hz, 2H), 7.40 (d, $J = 8.8$ Hz, 2H), 7.60 (d, $J = 8.6$ Hz, 1H), 7.75 (s, 1H), 8.00 (dd, $J = 8.6$ and $J = 1.6$ Hz, 1H), 8.35 (d, $J = 1.6$ Hz, 1H).

5.6.1.12. Dimethyl 4-{2-[6-(3-methoxybenzoyl)-2(3*H*)-benzothiazolon-3-yl]ethoxy}benzylidenemalonate (19k). Mp 155–160 °C (MeOH) (yield 50%). IR (KBr) cm^{-1} 1660. ^1H NMR (DMSO) δ 3.70 (s, 3H), 3.75 (s, 3H), 3.85 (s, 3H), 4.35 (s, 2H), 4.45 (s, 2H), 6.95 (d, $J = 8.7$ Hz, 2H), 7.20–7.30 (m, 3H), 7.40–7.55 (m, 4H), 7.60–7.70 (m, 2H), 8.15 (s, 1H).

5.6.2. General procedure for Knoevenagel condensation (6, 7a–c, 19 c, d, e, f, g, h, i, j, l). A solution of the appropriate aldehyde and malonate diester in toluene containing a catalytic quantity of piperidine and acetic acid was refluxed in a Dean–Stark trap for 4 days. After cooling to room temperature, toluene was evaporated under reduced pressure. The residue was purified by flash chromatography using dichloromethane as eluent and was recrystallized from an appropriate solvent.

5.6.2.1. Diethyl 4-[2-(2(3*H*)-benzoxazolon-3-yl)ethoxy]benzylidenemalonate (6). Mp 98–100 °C (cyclohexane/toluene (1:1)) (yield 80%). IR (KBr) cm^{-1} 1715, 1730, 1770. ^1H NMR (DMSO) δ 1.20–1.30 (m, 6H), 4.15–4.30 (m, 6H), 4.40 (t, $J = 4.9$ Hz, 2H), 7.00 (d, $J = 8.8$ Hz, 2H), 7.15 (t, $J = 7.8$ and $J = 7.9$ Hz, 1H), 7.25 (t, $J = 7.9$ Hz, 1H), 7.35 (d, $J = 7.8$ Hz, 1H), 7.40 (d, $J = 7.9$ Hz, 1H), 7.45 (d, $J = 8.8$ Hz, 2H), 7.65 (s, 1H).

5.6.2.2. Diethyl 4-[2-(2(3*H*)-benzothiazolon-3-yl)ethoxy]benzylidenemalonate (7a). Mp 113–114 °C (EtOH) (yield 62%). IR (KBr) cm^{-1} 1710. ^1H NMR (DMSO) δ 1.20–1.30 (m, 6H), 4.20–4.40 (m, 8H), 6.95 (d, $J = 8.8$ Hz, 2H), 7.20 (t, $J = 7.6$ Hz, 1H), 7.35–7.50 (m, 4H), 7.60–7.70 (m, 2H).

5.6.2.3. Dimethyl 4-[2-(2(3*H*)-benzothiazolon-3-yl)-ethoxy]benzylidenemalonate (7b). Mp 144–146 °C (MeOH) (yield 73%). IR (KBr) cm^{-1} 1680, 1735. ^1H NMR (DMSO) δ 3.75 (s, 3H), 3.85 (s, 3H), 4.40 (s, 4H), 6.95 (d, $J = 8.8$ Hz, 2H), 7.20 (t, $J = 7.7$ and $J = 7.5$ Hz, 1H), 7.35–7.50 (m, 4H), 7.65 (d, $J = 7.7$ Hz, 1H), 7.70 (s, 1H).

5.6.2.4. Methyl-*tert*-butyl 4-[2-(2(3*H*)-benzothiazolon-3-yl)ethoxy]benzylidenemalonate (7c). Yellow oil (yield 68%). IR (KBr) cm^{-1} 1680, 1720. ^1H NMR (DMSO) δ 1.30 (s, 9H), 3.80 (s, 3H), 4.40 (s, 4H), 6.95 (d, $J = 8.3$ Hz, 2H), 7.20 (t, $J = 7.7$ and $J = 7.5$ Hz, 1H), 7.35–7.50 (m, 4H), 7.65 (d, $J = 7.7$ Hz, 1H), 7.70 (s, 1H).

5.6.2.5. Dimethyl 4-[2-(6-benzoyl-2(3*H*)-benzothiazolon-3-yl)ethoxy]benzylidenemalonate (19c). Mp 167–170 °C (diisopropyl ether) (yield 93%). IR (KBr) cm^{-1} 1685, 1740. ^1H NMR (DMSO) δ 3.75 (s, 3H), 3.85 (s, 3H), 4.40 (s, 2H), 4.50 (s, 2H), 7.00 (d, $J = 8.6$ Hz, 2H), 7.40 (d, $J = 8.6$ Hz, 2H), 7.55–7.85 (m, 8H), 8.20 (s, 1H).

5.6.2.6. Dimethyl 4-[2-(6-(2-toluoyl)-2(3*H*)-benzothiazolon-3-yl)ethoxy]benzylidenemalonate (19d). Purified by flash chromatography using EtOAc/cyclohexane (3:7). Mp 176–178 °C (acetonitrile) (yield 30%). IR (KBr) cm^{-1} 1687, 1737. ^1H NMR ($CDCl_3$) δ 2.33 (s, 3H), 3.85 (s, 6H), 4.33 (t, $J = 4.7$ Hz, 2H), 4.40 (t, $J = 4.7$ Hz, 2H), 6.79 (d, $J = 8.8$ Hz, 2H), 7.25–7.45 (m, 7H), 7.70 (s, 1H), 7.85 (d, $J = 7.8$ Hz, 1H), 7.90 (s, 1H).

5.6.2.7. Dimethyl 4-[2-(6-(3-toluoyl)-2(3*H*)-benzothiazolon-3-yl)ethoxy]benzylidenemalonate (19e). Purified by flash chromatography using EtOAc/cyclohexane (3:7). Mp 153–154 °C (toluene) (yield 60%). IR (KBr) cm^{-1} 1687, 1737. ^1H NMR ($CDCl_3$) δ 2.45 (s, 3H), 3.85 (s, 6H), 4.35 (t, $J = 4.4$ Hz, 2H), 4.40 (t, $J = 4.4$ Hz, 2H), 6.80 (d, $J = 8.9$ Hz, 2H), 7.35–7.45 (m, 5H), 7.55 (d, $J = 7.4$ Hz, 1H), 7.60 (d, $J = 1.7$ Hz, 1H), 7.70 (s, 1H), 7.85 (dd, $J = 1.5$; 8.5 Hz, 1H), 7.95 (d, $J = 1.5$ Hz, 1H).

5.6.2.8. Dimethyl 4-[2-(6-(4-toluoyl)-*2*(*3H*)-benzothiazolon-3-yl)ethoxy]benzylidenemalonate (19f). Purified by flash chromatography using EtOAc/cyclohexane (3:7). Mp 111–112 °C (EtOH 95°) (yield 55%). IR (KBr) cm^{-1} 1680, 1725. ^1H NMR ($CDCl_3$) δ 2.45 (s, 3H), 3.85 (s, 6H), 4.35 (t, $J = 4.8$ Hz, 2H), 4.40 (t, $J = 4.8$ Hz, 2H), 6.80 (d, $J = 8.8$ Hz, 2H), 7.25–7.65 (m, 5H), 7.70 (m, 3H), 7.85 (d, $J = 8.3$ Hz, 1H), 7.90 (s, 1H).

5.6.2.9. Dimethyl 4-{2-[6-(2-chlorobenzoyl)-*2*(*3H*)-benzothiazolon-3-yl]ethoxy}benzylidenemalonate (19g). Purified by flash chromatography using EtOAc/cyclohexane (1:4). Mp 141–144 °C (MeOH) (yield 80%). IR (KBr) cm^{-1} 1685, 1725. ^1H NMR (DMSO) δ 3.60 (s, 6H), 4.30 (s, 4H), 6.80 (d, $J = 8.5$ Hz, 2H), 7.10 (d, $J = 8.5$ Hz, 2H), 7.50–7.80 (m, 8H).

5.6.2.10. Dimethyl 4-{2-[6-(3-chlorobenzoyl)-*2*(*3H*)-benzothiazolon-3-yl]ethoxy}benzylidenemalonate (19h). Mp 234–238 °C (MeOH) (yield 80%). IR (KBr) cm^{-1} 1690, 1720, 1735. ^1H NMR (DMSO) δ 3.75 (s, 3H), 3.80 (s, 3H), 4.35 (t, $J = 4.9$ Hz, 2H), 4.45 (t, $J = 4.9$ Hz, 2H), 6.95 (d, $J = 9.0$ Hz, 2H), 7.40 (d, $J = 9.0$ Hz, 2H), 7.60–7.85 (m, 7H), 8.20 (s, 1H).

5.6.2.11. Dimethyl 4-{2-[6-(4-chlorobenzoyl)-*2*(*3H*)-benzothiazolon-3-yl]ethoxy}benzylidenemalonate (19i). Mp 232–235 °C (MeOH) (yield 60%). IR (KBr) cm^{-1} 1680, 1710, 1720. ^1H NMR (DMSO) δ 3.75 (s, 3H), 3.80 (s, 3H), 4.35 (s, 2H), 4.45 (s, 2H), 6.95 (d, $J = 8.8$ Hz, 2H), 7.40 (d, $J = 8.8$ Hz, 2H), 7.60–7.80 (m, 7H), 8.15 (s, 1H).

5.6.2.12. Dimethyl 4-{2-[6-(3,5-dichlorobenzoyl)-*2*(*3H*)-benzothiazolon-3-yl]ethoxy}benzylidenemalonate (19j). Mp 199–200 °C (acetonitrile) (yield 50%). IR (KBr) cm^{-1} 1690, 1715, 1735. ^1H NMR ($CDCl_3$) δ 3.85 (s, 6H), 4.35 (t, $J = 4.9$ Hz, 2H), 4.45 (t, $J = 4.9$ Hz, 2H), 6.80 (d, $J = 8.8$ Hz, 2H), 7.35 (d, $J = 8.8$ Hz, 2H), 7.40 (d, $J = 8.4$ Hz, 1H),7.60–7.65 (m, 3H), 7.70 (s, 1H), 7.80 (dd, $J = 8.4$, 1.8 Hz, 1H), 7.90 (d, $J = 1.8$ Hz, 1H).

5.6.2.13. Dimethyl 4-{2-[6-(4-methoxybenzoyl)-*2*(*3H*)-benzothiazolon-3-yl]ethoxy}benzylidenemalonate (19l). Mp 144–145 °C (EtOAc) (yield 60%). IR (KBr) cm^{-1} 1660. ^1H NMR (DMSO) δ 3.70 (s, 3H), 3.75 (s, 3H), 3.85 (s, 3H), 4.35 (s, 2H), 4.45 (s, 2H), 6.95 (d, $J = 8.7$ Hz, 2H), 7.20–7.30 (m, 3H), 7.40–7.55 (m, 4H), 7.60–7.70 (m, 2H), 8.15 (s, 1H).

5.6.3. General procedure for the synthesis of benzylmalonates (8, 9a–c, 20, 21a–l). A solution of benzylidenemalonate diester in a mixture of the appropriate alcohol (MeOH or EtOH), 1,4-dioxane and THF (2:5, 2:5, 1:5) was stirred in the presence of 10% palladium on charcoal under an atmosphere of hydrogen at room temperature until reaction was completed as juged by TLC (24–48 h). The solution was filtered through Celite and the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel or was recrystallized from the appropriate solvent.

5.6.3.1. Diethyl 4-[2-(*2*(*3H*)-benzoxazolon-3-yl)ethoxy]-benzylmalonate (8). Mp 68–70 °C (cyclohexane/toluene (9:1)) (yield 88%). IR (KBr) cm^{-1} 1730, 1770. ^1H NMR (DMSO) δ 0.95–1.15 (m, 6H), 3.00 (d, $J = 7.9$ Hz, 2H), 3.75 (t, $J = 7.9$ Hz, 1H), 3.95–4.15 (m, 4H), 4.20 (d, $J = 4.2$ Hz, 4H), 6.80 (d, $J = 8.5$ Hz, 2H), 7.05–7.15 (m, 3H), 7.25 (t, $J = 7.8$ Hz, 1H), 7.35 (d, $J = 7.8$ Hz, 1H), 7.40 (d, $J = 7.8$ Hz, 1H). Anal. Calcd for $C_{23}H_{25}NO_7$: C, 64.63; H, 5.90; N, 3.28. Found: C, 64.42; H, 5.78; N, 3.38.

5.6.3.2. Diethyl 4-[2-(*2*(*3H*)-benzothiazolon-3-yl)ethoxy]benzylmalonate (9a). Purified by flash chromatography using CH_2Cl_2. Yellow oil (yield 80%). IR (KBr) cm^{-1} 1730. ^1H NMR (DMSO) δ 3.95–1.15 (m, 6H), 3.00 (d, $J = 7.9$ Hz, 2H), 3.75 (t, $J = 7.9$ Hz, 1H), 3.95–4.15 (m, 4H), 4.25 (t, $J = 5.0$ Hz, 2H), 4.40 (t, $J = 5.0$ Hz, 2H), 6.80 (d, $J = 8.6$ Hz, 2H), 7.10 (d, $J = 8.6$ Hz, 2H), 7.20 (t, $J = 7.8$ Hz, 1H), 7.40 (t, $J = 7.8$ Hz, 1H), 7.50 (d, $J = 7.8$ Hz, 1H), 7.65 (d, $J = 7.8$ Hz, 1H). Anal. Calcd for $C_{23}H_{25}NO_6S$: C, 62.29; H, 5.68; N, 3.16. Found: C, 62.48; H, 5.54; N, 3.19.

5.6.3.3. Dimethyl 4-[2-(*2*(*3H*)-benzothiazolon-3-yl)-ethoxy]benzylmalonate (9b). Mp 67–70 °C (diisopropyl ether) (yield 85%). IR (KBr) cm^{-1} 1670, 1730, 1745. ^1H NMR (DMSO) δ 3.00 (d, $J = 7.9$ Hz, 2H), 3.60 (s, 6H), 3.80 (t, $J = 7.9$ Hz, 1H), 4.20 (s, 2H), 4.35 (s, 2H), 6.75 (d, $J = 8.7$ Hz, 2H), 7.10 (d, $J = 8.7$ Hz, 2H), 7.20 (t, $J = 7.9$ Hz, 1H), 7.40 (t, $J = 7.9$ Hz, 1H), 7.50 (d, $J = 7.9$ Hz, 1H), 7.65 (d, $J = 7.9$ Hz, 1H). Anal. Calcd for $C_{21}H_{21}NO_6S$: C, 60.71; H, 5.09; N, 3.37. Found: C, 61.12; H, 4.98; N, 3.56.

5.6.3.4. Methyl-tertiobutyl 4-[2-(*2*(*3H*)-benzothiazolon-3-yl)ethoxy]benzylmalonate (9c). Purified by flash chromatography using cyclohexane/EtOAc (7:3). Yellow oil (yield 30%). IR (KBr) cm^{-1} 1680, 1720. ^1H NMR (DMSO) δ 1.30 (s, 9H), 3.00 (d, $J = 7.5$ Hz, 2H), 3.55–3.70 (m, 4H), 4.20 (s, 2H), 4.35 (s, 2H), 6.75 (d, $J = 8.3$ Hz, 2H), 7.10 (d, $J = 8.3$ Hz, 2H), 7.20 (t, $J = 7.3$ and $J = 8.0$ Hz, 1H), 7.35 (t, t, $J = 7.3$ and $J = 7.7$ Hz, 1H), 7.45 (d, $J = 8.0$ Hz, 1H), 7.65 (d, $J = 7.7$ Hz, 1H). Anal. Calcd for $C_{24}H_{27}NO_6S$: C, 63.00; H, 5.95; N, 3.06. Found: C, 63.24; H, 6.01; N, 3.10.

5.6.3.5. Dimethyl 4-[2-(6-benzoyl-*2*(*3H*)-benzoxazolinon-3-yl)ethoxy]benzylmalonate (20). Purified by flash chromatography using cyclohexane/EtOAc (4:1). Mp 120–123 °C (MeOH) (yield 40%). IR (KBr) cm^{-1} 1740, 1750. ^1H NMR (DMSO) δ 3.00 (d, $J = 7.7$ Hz, 2H), 3.60 (s, 6H), 3.70 (t, $J = 7.7$ Hz, 1H), 4.30 (s, 4H), 6.80 (d, $J = 8.5$ Hz, 2H), 7.10 (d, $J = 8.5$ Hz, 2H), 7.50–7.80 (m, 8H). Anal. Calcd for $C_{28}H_{25}NO_8$: C, 66.79; H, 5.00; N, 2.78. Found: C, 66.87; H, 5.03; N, 2.82.

5.6.3.6. Dimethyl 4-[2-(6-butyryl-*2*(*3H*)-benzothiazolinon-3-yl)ethoxy]benzylmalonate (21a). Purified by flash chromatography using acetone/toluene/cyclohexane (2:3:5). Mp 74–75 °C (diisopropyl ether) (yield 80%). IR (KBr) cm^{-1} 1680, 1735. ^1H NMR (DMSO) δ 0.90

(t, J = 7.3 Hz, 3H), 1.65 (m, 2H), 3.00 (m, 4H), 3.60 (s, 6H), 3.80 (t, J = 8.0 Hz, 1H), 4.25 (t, J = 4.8 Hz, 2H), 4.40 (t, J = 4.8 Hz, 2H), 6.75 (d, J = 8.3 Hz, 2H), 7.05 (d, J = 8.3 Hz, 2H), 7.60 (d, J = 8.6 Hz, 1H), 8.00 (d, J = 8.0 Hz, 1H), 8.35 (s, 1H). Anal. Calcd for $C_{25}H_{27}NO_7S$: C, 64.73; H, 4.85; N, 2.70. Found: C, 64.79; H, 4.78; N, 2.63.

5.6.3.7. Dimethyl 4-[2-(6-hexanoyl-*2*(*3H*)-benzothiazolon-3-yl)ethoxy]benzylmalonate (21b). Mp 76–80 °C (hexane) (yield 65%). IR (KBr) cm^{-1} 1665, 1700, 1740. ^1H NMR (DMSO) δ 0.90 (t, J = 6.8 Hz, 3H), 1.25–1.40 (m, 4H), 1.60 (t, J = 6.8 Hz, 2H), 2.95–3.05 (m, 4H), 3.60 (s, 6H), 3.80 (t, J = 7.8 Hz, 1H), 4.25 (t, J = 4.9 Hz, 2H), 4.40 (t, J = 4.9 Hz, 2H), 6.75 (d, J = 8.0 Hz, 2H), 7.05 (d, J = 8.0 Hz, 2H), 7.60 (d, J = 8.6 Hz, 1H), 8.00 (d, J = 8.6 Hz, 1H), 8.35 (s, 1H). Anal. Calcd for $C_{27}H_{31}NO_7S$: C, 63.14; H, 6.08; N, 2.73. Found: C, 63.28; H, 6.14; N, 2.67.

5.6.3.8. Dimethyl 4-[2-(6-benzoyl-*2*(*3H*)-benzothiazolon-3-yl)ethoxy]benzylmalonate (21c). Mp 65–67 °C (MeOH) (yield 85%). IR (KBr) cm^{-1} 1675, 1730. ^1H NMR (DMSO) δ 3.00 (d, J = 7.9 Hz, 2H), 3.60 (s, 6H), 3.80 (t, J = 7.9 Hz, 1H), 4.25 (s, 2H), 4.45 (s, 2H), 6.80 (d, J = 8.3 Hz, 2H), 7.10 (d, J = 8.3 Hz, 2H), 7.50–7.90 (m, 7H), 8.20 (s, 1H). Anal. Calcd for $C_{28}H_{25}NO_7S$: C, 64.73; H, 4.85; N, 2.70. Found: C, 64.79; H, 4.78; N, 2.63.

5.6.3.9. Dimethyl 4-[2-(6-(2-toluoyl)-*2*(*3H*)-benzothiazolon-3-yl)ethoxy]benzylmalonate (21d). Purified by flash chromatography using EtOAc/cyclohexane (1:4). Mp 92–94 °C (EtOH) (yield 80%). IR (KBr) cm^{-1} 1675, 1730. ^1H NMR ($CDCl_3$) δ 2.33 (s, 3H), 3.15 (d, J = 7.7 Hz, 2H), 3.60 (t, J = 7.9 Hz, 1H), 3.70 (s, 6H), 4.25 (t, J = 4.6 Hz, 2H), 4.35 (t, J = 4.6 Hz, 2H), 6.70 (d, J = 8.6 Hz, 2H), 7.05 (d, J = 8.6 Hz, 2H), 7.25–7.35 (m, 3 H),7.35–7.40 (m, 2H), 7.85 (d, J = 7.8 Hz, 1H), 7.90 (s, 1H). Anal. Calcd for $C_{29}H_{27}NO_7S$: C, 65.28; H, 5.10; N, 2.62. Found: C, 65.35; H, 5.04; N, 2.58.

5.6.3.10. Dimethyl 4-[2-(6-(3-toluoyl)-*2*(*3H*)-benzothiazolon-3-yl)ethoxy]benzylmalonate (21e). Purified by flash chromatography using cyclohexane/EtOAc (7:3). Mp 96–97 °C (EtOH) (yield 45%). IR (KBr) cm^{-1} 1670, 1740. ^1H NMR ($CDCl_3$) δ 2.45 (s, 3H), 3.15 (d, J = 8 Hz, 2H), 3.60 (t, J = 7.6 Hz, 1H), 3.70 (s, 6H), 4.25 (t, J = 5.2 Hz, 2H), 4.40 (t, J = 5.2 Hz, 2H), 6.70 (d, J = 8.3 Hz, 2H), 7.05 (d, J = 8.3 Hz, 2H), 7.30 (d, J = 8.3 Hz, 2H), 7.40 (d, J = 8.3 Hz, 1H), 7.70 (d, J = 8.3 Hz, 2H), 7.85 (dd, J = 8.7, 1.6 Hz, 1H), 7.90 (d, J = 1.6 Hz, 1H). Anal. Calcd for $C_{29}H_{27}NO_7S$: C, 65.28; H, 5.10; N, 2.62. Found: C, 65.12; H, 5.21; N, 2.53.

5.6.3.11. Dimethyl 4-[2-(6-(4-toluoyl)-*2*(*3H*)-benzothiazolon-3-yl)ethoxy]benzylmalonate (21f). Purified by flash chromatography using cyclohexane/EtOAc (7:3). Mp 85–86 °C (95% EtOH) (yield 55%). IR (KBr) cm^{-1} 1675, 1730. ^1H NMR ($CDCl_3$) δ 2.45 (s, 3H), 3.15 (d, J = 7.7 Hz, 2H), 3.60 (t, J = 8.1 Hz, 1H), 3.70 (s, 6H), 4.25 (t, J = 4.9 Hz, 2H), 4.30 (t, J = 4.9 Hz, 2H), 6.70 (d, J = 8.6 Hz, 2H), 7.05 (d, J = 8.6 Hz, 2H), 7.40–7.45 (m, 3H), 7.55 (d, J = 7.2 Hz, 1H), 7.60 (m, 1H), 7.85 (dd, J = 8.6, 1.8 Hz, 1H), 7.95 (d, J = 1.3 Hz, 1H). Anal. Calcd for $C_{29}H_{27}NO_7S$: C, 65.28; H, 5.10; N, 2.62. Found: C, 65.24; H, 5.14; N, 2.71.

5.6.3.12. Dimethyl 4-{2-[6-(2-chlorobenzoyl)-*2*(*3H*)-benzothiazolon-3-yl]ethoxy}benzylmalonate (21g). Purified by flash chromatography using EtOAc/cyclohexane (1:4). Mp 104–108 °C (diisopropyl ether) (yield 80%). IR (KBr) cm^{-1} 1670, 1690, 1730, 1750. ^1H NMR (DMSO) δ 3.00 (d, J = 8.0 Hz, 2H), 3.60 (s, 6H), 3.80 (t, J = 8.0 Hz, 1H), 4.25 (t, J = 4.9 Hz, 2H), 4.40 (t, J = 4.9 Hz, 2H), 6.75 (d, J = 8.2 Hz, 2H), 7.05 (d, J = 8.2 Hz, 2H), 7.50–7.65 (m, 5H), 7.75 (dd, J = 8.6 and J = 1.6 Hz, 1H), 8.15 (d, J = 1.6 Hz, 1H). Anal. Calcd for $C_{28}H_{24}ClNO_7S$: C, 60.70; H, 4.37; N, 2.53. Found: C, 60.87; H, 4.50; N, 2.45.

5.6.3.13. Dimethyl 4-{2-[6-(3-chlorobenzoyl)-*2*(*3H*)-benzothiazolon-3-yl]ethoxy}benzylmalonate (21h). Mp 90–94 °C (MeOH) (yield 80%). IR (KBr) cm^{-1} 1660, 1690, 1720, 1740. ^1H NMR (DMSO) δ 3.00 (d, J = 7.9 Hz, 2H), 3.60 (s, 6H), 3.80 (t, J = 7.9 Hz, 1H), 4.25 (t, J = 4.8 Hz, 2H), 4.40 (t, J = 4.8 Hz, 2H), 6.80 (d, J = 8.5 Hz, 2H), 7.10 (d, J = 8.5 Hz, 2H), 7.60–7.85 (m, 6H), 8.10 (s, 1H). Anal. Calcd for $C_{28}H_{24}ClNO_7S$: C, 60.70; H, 4.37; N, 2.53. Found: C, 60.75; H, 4.23; N, 2.47.

5.6.3.14. Dimethyl 4-{2-[6-(4-chlorobenzoyl)-*2*(*3H*)-benzothiazolon-3-yl]ethoxy}benzylmalonate (21i). Purified by flash chromatography using EtOAc/cyclohexane (1:4). Mp 80–85 °C (MeOH) (yield 50%). IR (KBr) cm^{-1} 1660, 1680, 1740. ^1H NMR (DMSO) δ 3.00 (d, J = 7.8 Hz, 2H), 3.60 (s, 6H), 3.80 (t, J = 7.87 Hz, 1H), 4.25 (t, J = 4.7 Hz, 2H), 4.40 (t, J = 4.7 Hz, 2H), 6.75 (d, J = 8.4 Hz, 2H), 7.10 (d, J = 8.4 Hz, 2H), 7.60–7.80 (m, 6H), 8.15 (s, 1H). Anal. Calcd for $C_{28}H_{24}ClNO_7S$: C, 60.70; H, 4.37; N, 2.53. Found: C, 60.91; H, 4.51; N, 2.42.

5.6.3.15. Dimethyl 4-{2-[6-(3,5-dichlorobenzoyl)-*2*(*3H*)-benzothiazolon-3-yl]ethoxy}benzyl malonate (21j). Purified by flash chromatography using EtOAc/cyclohexane (3:7). Mp 100–101 °C (EtOH 95°) (yield 80%). IR (KBr) cm^{-1} 1690, 1730, 1760. ^1H NMR ($CDCl_3$) δ 3.15 (d, J = 8.0 Hz, 2H), 3.60 (t, J = 7.5 Hz, 1H), 3.70 (s, 6H), 4.25 (t, J = 5.2 Hz, 2H), 4.40 (t, J = 5.2 Hz, 2H), 6.70 (d, J = 8.5 Hz, 2H), 7.10 (d, J = 8.5 Hz, 2H), 7.45 (d, J = 8.9 Hz, 1H), 7.60 (d, J = 2.3 Hz, 1H), 7.65 (d, J = 1.5 Hz, 2H), 7.80 (d, J = 8.5 Hz, 1H), 7.90 (s, 1H). Anal. Calcd for $C_{28}H_{23}Cl_2NO_7S$: C, 57.15; H, 3.94; N, 2.38. Found: C, 57.24; H, 4.03; N, 2.30.

5.6.3.16. Dimethyl 4-{2-[6-(3-methoxybenzoyl)-*2*(*3H*)-benzothiazolon-3-yl]ethoxy}benzyl malonate (21k). Purified by flash chromatography using EtOAc/cyclohexane (1:4). Mp 136–139 °C (MeOH) (yield 70%). IR (KBr) cm^{-1} 1680, 1730. ^1H NMR (DMSO) δ 3.00 (d, J = 7.8 Hz, 2H), 3.60 (s, 6H), 3.80 (t, J = 7.8 Hz, 1H),

3.85 (s, 3H), 4.25 (t, J = 5.0 Hz, 2H), 4.40 (t, J = 5.0 Hz, 2H), 6.75 (d, J = 8.7 Hz, 2H), 7.10 (d, J = 8.7 Hz, 2H), 7.25–7.30 (m, 3H), 7.50 (t, J = 8.7 and J = 7.7 Hz, 1H), 7.65 (d, J = 8.7 Hz, 1H), 7.80 (dd, J = 8.4 and J = 1.8 Hz, 1H), 8.15 (d, J = 1.8 Hz, 1H). Anal. Calcd for $C_{29}H_{27}NO_8S$: C, 63.38; H, 4.95; N, 2.55. Found: C, 63.47; H, 5.03; N, 2.46.

5.6.3.17. Dimethyl 4-{2-[6-(4-methoxybenzoyl)-*2*(*3H*)-benzothiazolon-3-yl]ethoxy}benzyl malonate (21l). Mp 114–117 °C (MeOH) (yield 75%). IR (KBr) cm^{-1} 1685, 1745. ^1H NMR (DMSO) δ 3.00 (d, J = 7.9 Hz, 2H), 3.60 (s, 6H), 3.80 (t, J = 7.9 Hz, 1H), 3.90 (s, 3H), 4.25 (t, J = 4.7 Hz, 2H), 4.40 (t, J = 4.7 Hz, 2H), 6.80 (d, J = 8.3 Hz, 2H), 7.05–7.15 (m, 4H), 7.60 (d, J = 8.6 Hz, 1H), 7.70–7.85 (m, 3H), 8.10 (s, 1H). Anal. Calcd for $C_{29}H_{27}NO_8S$: C, 63.38; H, 4.95; N, 2.55. Found: C, 63.44; H, 4.88; N, 2.61.

5.6.4. General procedure for partial hydrolysis of diesters 11a–b, 22. To a solution of 1 equiv of **11a**, **11b** or **21c** in EtOH or MeOH was added 1.0 equiv of potassium hydroxide. The mixture was stirred for 3 days at room temperature, and then the solvent was evaporated under reduced pressure. The residue was then purified as outlined below.

5.6.4.1. 2-(Ethoxycarbonyl)-3-{4-[2-(*2*(*3H*)-benzothiazolon-3-yl)ethoxy]phenyl}propionic acid (11a). Purified by flash chromatography using EtOAc/cyclohexane (7:3). Yellow oil (yield 62%). IR (KBr) cm^{-1} 1680, 1730. ^1H NMR (DMSO) δ 1.10 (s, 3H), 2.95 (d, J = 8.0 Hz, 2H), 3.60 (t, J = 8.0 Hz, 1H), 4.00 (q, J = 7.2 Hz, 2H), 4.20 (t, J = 5.2 Hz, 2H), 4.35 (t, J = 5.2 Hz, 2H), 6.75 (d, J = 8.5 Hz, 2H), 7.10 (d, J = 8.5 Hz, 2H), 7.20 (t, J = 7.8 and J = 7.3 Hz, 1H), 7.35 (t, J = 7.8 and J = 7.3 Hz, 1H), 7.45 (d, J = 7.8 Hz, 1H), 7.65 (d, J = 7.8 Hz, 1H), 12.60 (s, 1H). Anal. Calcd for $C_{21}H_{21}NO_6S$: C, 60.71; H, 5.09; N, 3.37. Found: C, 60.85; H, 5.14; N, 3.26.

5.6.4.2. 2-(Methoxycarbonyl)-3-{4-[2-(*2*(*3H*)-benzothiazolon-3-yl)ethoxy]phenyl}propionic acid (11b). Purified by flash chromatography using EtOAc/cyclohexane (7:3). Mp 30–34 °C (yield 30%). IR (KBr) cm^{-1} 1670, 1730, 2980. ^1H NMR (DMSO) δ 3.00 (d, J = 8.4 Hz, 2H), 3.50 (s, 3H), 3.60 (t, J = 8.4 Hz, 1H), 4.20 (t, J = 5.3 Hz, 2H), 4.40 (t, J = 5.3 Hz, 2H), 6.70 (d, J = 8.6 Hz, 2H), 7.10 (d, J = 8.6 Hz, 2H), 7.20 (t, J = 7.6 and J = 1.4 Hz, 1H), 7.40 (t, J = 7.6 and J = 1.4 Hz, 1H), 7.50 (d, J = 7.6 and J = 1.4 Hz, 1H), 7.70 (d, J = 7.6 and J = 1.4 Hz, 1H), 13.00 (s, 1H). Anal. Calcd for $C_{20}H_{19}NO_6S$: C, 59.84; H, 4.77; N, 3.49. Found: C, 60.02; H, 4.87; N, 3.33.

5.6.4.3. 2-(Methoxycarbonyl)-3-{4-[2-(6-benzoyl-*2*(*3H*)-benzothiazolon-3-yl)ethoxy]phenyl} propionic acid (22). Purified by flash chromatography using CH_2Cl_2/MeOH (9:1). Mp 144 °C (yield 65%). IR (KBr) cm^{-1} 1685, 1735, 3420. ^1H NMR (DMSO) δ 2.90 (d, J = 6.4 Hz, 2H), 3.50–3.60 (m, 4H), 4.25 (t, J = 4.9 Hz, 2H), 4.40 (t, J = 4.9 Hz, 2H), 6.75 (d, J = 8.7 Hz, 2H), 7.05 (d, J = 8.7 Hz, 2H), 7.55–7.80 (m, 7H), 8.15 (s, 1H). Anal. Calcd for $C_{27}H_{23}NO_7S$: C, 64.15; H, 4.59; N, 2.77. Found: C, 64.22; H, 4.69; N, 2.65.

5.6.5. 2-(Ethoxycarbonyl)-3-{4-[2-(2(3*H*)-benzoxazolon-3-yl)ethoxy]phenyl}propionic acid (10). One equivalent of an aqueous solution of 2 N NaOH was added to a solution of **8** in EtOH/THF (3:1) at 0 °C. The mixture was stirred for 3 days at room temperature, and then the solvent was evaporated under reduced pressure. The residue was then purified as outlined below. Purified by flash chromatography using EtOAc/cyclohexane (4:1). Yellow oil (yield 64%). IR (KBr) cm^{-1} 1745, 1790. ^1H NMR (DMSO) δ 1.10 (s, 3H), 2.85–3.00 (m, 2H), 3.60 (t, J = 7.8 Hz, 1H), 4.00 (q, J = 7.2 Hz, 2H), 4.25 (d, J = 4.3 Hz, 4H), 6.80 (d, J = 8.1 Hz, 2H), 7.05–7.20 (m, 3H), 7.25 (t, J = 7.5 and J = 7.8 Hz, 1H), 7.35 (d, J = 7.8 Hz, 1H), 7.40 (d, J = 7.5 Hz, 1H), 13.00 (s, 1H). Anal. Calcd for $C_{21}H_{21}NO_7$: C, 63.15; H, 5.30; N, 3.51. Found: C, 63.27; H, 5.24; N, 3.58.

5.6.6. General procedure for hydrolysis of benzylmalonates to diacids (12, 13 and 23). Two equivalents of a 2 N aqueous solution of NaOH were added to a solution of **8**, **9b** or **21c** in EtOH/THF (5:1). Then, the mixture was stirred for 2–4 days at room temperature. After evaporation of the solvents, water was added to the residue, and the mixture was acidified with dilute hydrochloric acid to pH 1. The precipitate was collected by filtration, washed with water, and Et_2O and recrystallized from the appropriate solvent.

5.6.6.1. 4-[2-(*2*(*3H*)-Benzoxazolon-3-yl)ethoxy]benzylmalonic acid (12). Mp 118–120 °C (cyclohexane) (yield 30%). IR (KBr) cm^{-1} 1710, 1785. ^1H NMR (DMSO) δ 2.95 (d, J = 7.5 Hz, 2H), 3.50 (t, J = 7.5 Hz, 1H), 4.25 (m, 4H), 6.80 (d, J = 8.5 Hz, 2H), 7.05–7.15 (m, 3H), 7.25 (t, J = 7.8 and J = 7.5 Hz, 1H), 7.35 (d, J = 7.8 Hz, 1H), 7.40 (d, J = 7.8 Hz, 1H), 12.50 (s, 2H). Anal. Calcd for $C_{19}H_{17}NO_7$: C, 61.45; H, 4.61; N, 3.77. Found: C, 61.64; H, 4.49; N, 3.82.

5.6.6.2. 4-[2-(*2*(*3H*)-Benzothiazolon-3-yl)ethoxy]-benzylmalonic acid (13). Mp 179–181 °C (acetonitrile) (yield 20%). IR (KBr) cm^{-1} 1680, 1730. ^1H NMR (DMSO) δ 2.95 (s, 2H), 3.60 (t, J = 7.9 Hz, 1H), 4.20 (t, J = 5.4 Hz, 2H), 4.35 (t, J = 5.4 Hz, 2H), 6.75 (d, J = 8.6 Hz, 2H), 7.10 (d, J = 8.6 Hz, 2H), 7.20 (t, J = 7.6 and J = 7.4 Hz, 1H), 7.35 (t, J = 7.9 and J = 7.4 Hz, 1H), 7.45 (d, J = 7.6 Hz, 1H), 7.65 (d, J = 7.9 Hz, 1H), 12.10 (s, 2H). Anal. Calcd for $C_{19}H_{17}NO_6S$: C, 58.91; H, 4.42; N, 3.62. Found: C, 59.06; H, 4.39; N, 3.65.

5.6.6.3. 4-[2-(6-Benzoyl-*2*(*3H*)-benzothiazolon-3-yl)-ethoxy]benzylmalonic acid (23). Purified by flash chromatography using CH_2Cl_2/MeOH (9:1). Mp 120 °C (yield 65%). IR (KBr) cm^{-1} 1675, 1705, 1740, 3000. ^1H NMR (DMSO) δ 2.90 (d, J = 7.6 Hz, 2H), 3.50 (t, J = 7.6 Hz, 1H), 4.20 (s, 2H), 4.40 (s, 2H), 6.80 (d, J = 7.9 Hz, 2H), 7.10 (d, J = 7.9 Hz, 2 H), 7.55–7.80 (m, 7H), 8.15 (s, 1H), 12.70 (s, 2H). Anal. Calcd for

$C_{26}H_{21}NO_7S$: C, 62.53; H, 4.31; N, 2.85. Found: C, 62.59; H, 4.40; N, 2.78.

5.6.7. General procedure for reduction of carbonyls to hydroxymethyles (24 and 25). To a solution of 1 equiv of **20** or **21c** in MeOH was added 0.5 equiv of sodium borohydride. The mixture was stirred at room temperature for 24 h and then the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography or recrystallized from the appropriate solvent.

5.6.7.1. Dimethyl 4-{2-[6-(phenylhydroxymethyl)-*2*(*3H*)-benzoxazolon-3-yl]ethoxy}benzyl malonate (24). Mp 84–87 °C (diisopropyl ether) (yield 65%). IR (KBr) cm^{-1} 1745, 1475. ^1H NMR (DMSO) δ 3.00 (d, $J = 8.0$ Hz, 2H), 3.60 (s, 6H), 3.80 (t, $J = 8.0$ Hz, 1H), 4.15 (t, $J = 5.0$ Hz, 2H), 4.25 (t, $J = 5.0$ Hz, 2H), 5.75 (d, $J = 5.0$ Hz, 1H), 6.00 (d, $J = 5.0$ Hz, 1H), 6.80 (d, $J = 8.3$ Hz, 2H), 7.05 (d, $J = 8.3$ Hz, 2H), 7.15–7.40 (m, 8H). Anal. Calcd for $C_{28}H_{27}NO_8$: C, 66.53; H, 5.38; N, 2.77. Found: C, 66.63; H, 5.29; N, 2.85.

5.6.7.2. Dimethyl 4-{2-[6-(phenylhydroxymethyl)-*2*(*3H*)-benzothiazolon-3-yl]ethoxy}benzyl malonate (25). Purified by flash chromatography using EtOAc/cyclohexane (1:3). Mp 153–156 °C (MeOH) (yield 40%). IR (KBr) cm^{-1} 1635, 1730, 3430. ^1H NMR (DMSO) δ 3.00 (d, $J = 8.2$ Hz, 2H), 3.55 (s, 6H), 3.75 (t, $J = 8.2$ Hz, 1H), 4.20 (t, $J = 5.0$ Hz, 2H), 4.30 (t, $J = 5.0$ Hz, 2H), 5.70 (d, $J = 4.0$ Hz, 1H), 6.00 (d, $J = 4.0$ Hz, 1H), 6.70 (d, $J = 8.7$ Hz, 2H), 7.05 (d, $J = 8.7$ Hz, 2H), 7.20–7.40 (m, 7H), 7.65 (s, 1H). Anal. Calcd for $C_{28}H_{27}NO_7S$: C, 64.48; H, 5.22; N, 2.69. Found: C, 66.38; H, 5.51; N, 2.74.

5.6.8. General procedure for reduction of carbonyls to methylenes (26, 27a, b, c, e, g, h, i, l). To a solution of 1 equiv of **20** or **21a–l** in trifluoroacetic acid were added 2.5 equiv of triethylsilane. The mixture was stirred at room temperature for 24–72 h, then water was added and the mixture was extracted with Et_2O. The organic layers were dried over magnesium sulfate and the solvent was evaporated under reduced pressure. The crude product was either purified by flash chromatography or recrystallized from the appropriate solvent.

5.6.8.1. Dimethyl 4-[2-(6-benzyl-*2*(*3H*)-benzoxazolon-3-yl)ethoxy]benzylmalonate (26). Mp 73–75 °C (petroleum ether) (yield 80%). IR (KBr) cm^{-1} 1730, 1745, 1785. ^1H NMR (DMSO) δ 3.00 (d, $J = 8.0$ Hz, 2H), 3.60 (s, 6H), 3.80 (t, $J = 8.0$ Hz, 1H), 4.00 (s, 2H), 4.15 (t, $J = 5.0$ Hz, 2H), 4.25 (t, $J = 5.0$ Hz, 2H), 6.80 (d, $J = 8.5$ Hz, 2H), 7.05–7.35 (m, 10H). Anal. Calcd for $C_{28}H_{27}NO_7$: C, 68.70; H, 5.56; N, 2.86. Found: C, 68.78; H, 5.52; N, 2.91.

5.6.8.2. Dimethyl 4-[2-(6-butyl-*2*(*3H*)-benzothiazolon-3-yl)ethoxy]benzylmalonate (27a). Mp 73–74 °C (hexane) (yield 70%). IR (KBr) cm^{-1} 1675, 1730, 1740. ^1H NMR (DMSO) δ 0.90 (t, $J = 8.2$ Hz, 3H), 1.30 (m, 2H), 1.55 (m, 2H), 2.60 (t, $J = 7.8$ Hz, 2H), 3.00 (d, $J = 7.7$ Hz, 2H), 3.60 (s, 6H), 3.80 (t, $J = 7.7$ Hz, 1H), 4.20 (t, $J = 4.6$ Hz, 2H), 4.35 (t, $J = 4.6$ Hz, 2H), 6.75 (d, $J = 8.4$ Hz, 2H), 7.05 (d, $J = 8.4$ Hz, 2H), 7.20 (d, $J = 8.4$ Hz, 1H), 7.35 (d, $J = 8.4$ Hz, 1H), 7.50 (s, 1H). Anal. Calcd for $C_{25}H_{29}NO_6S$: C, 63.67; H, 6.20; N, 2.97. Found: C, 63.82; H, 6.34; N, 2.79.

5.6.8.3. Dimethyl 4-[2-(6-hexyl-*2*(*3H*)-benzothiazolon-3-yl)ethoxy]benzylmalonate (27b). Mp 40–45 °C (hexane/petroleum ether (1:1)) (yield 78%). IR (KBr) cm^{-1} 1655, 1740. ^1H NMR (DMSO) δ 0.90 (t, $J = 6.7$ Hz, 3H), 1.30 (s, 6H), 1.50–1.60 (m, 2H), 2.60 (t, $J = 7.6$ Hz, 2H), 3.00 (d, $J = 7.8$ Hz, 2H), 3.60 (s, 6H), 3.80 (t, $J = 7.8$ Hz, 1H), 4.20 (t, $J = 5.0$ Hz, 2H), 4.30 (t, $J = 5.0$ Hz, 2H), 6.75 (d, $J = 8.5$ Hz, 2H), 7.10 (d, $J = 8.5$ Hz, 2H), 7.20 (d, $J = 8.5$ Hz, 1H), 7.35 (d, $J = 8.5$ Hz, 1H), 7.50 (s, 1H). Anal. Calcd for $C_{27}H_{33}NO_6S$: C, 64.91; H, 6.66; N, 2.80. Found: C, 65.05; H, 6.51; N, 2.74.

5.6.8.4. Dimethyl 4-[2-(6-benzyl-*2*(*3H*)-benzothiazolon-3-yl)ethoxy]benzylmalonate (27c). Purified by flash chromatography using EtOAc/cyclohexane (1:4). Mp 78–81 °C (MeOH) (yield 40%). IR (KBr) cm^{-1} 1690, 1740. ^1H NMR (DMSO) δ 3.00 (d, $J = 7.7$ Hz, 2H), 3.60 (s, 6H), 3.80 (t, $J = 7.7$ Hz, 1H), 3.95 (s, 2H), 4.20 (s, 2H), 4.30 (s, 2H), 6.75 (d, $J = 8.3$ Hz, 2H), 7.10 (d, $J = 8.3$ Hz, 2H), 7.15–7.30 (m, 6H), 7.40 (d, $J = 8.6$ Hz, 1H), 7.55 (s, 1H). Anal. Calcd for $C_{28}H_{27}NO_6S$: C, 66.52; H, 5.38; N, 2.77. Found: C, 66.43; H, 5.35; N, 2.80.

5.6.8.5. Dimethyl 4-[2-(6-(3-methylbenzyl)-*2* (*3H*)-benzothiazolon-3-yl)ethoxy]benzylmalonate (27e). Purified by flash chromatography using EtOAc/cyclohexane (3:7). Mp 102–103 °C (diisopropyl ether) (yield 80%). IR (KBr) cm^{-1} 1690, 1740. ^1H NMR ($CDCl_3$) δ 2.33 (s, 3H), 3.15 (d, $J = 8.1$ Hz, 2H), 3.60 (t, $J = 7.6$ Hz, 1H), 3.70 (s, 6H), 3.95 (s, 2H), 4.20 (t, $J = 5.3$ Hz, 2H), 4.30 (t, $J = 5.3$ Hz, 2H), 6.75 (d, $J = 9.1$ Hz, 2H), 7.0–7.10 (m, 5H), 7.15–7.20 (m, 4H). Anal. Calcd for $C_{29}H_{29}NO_6S$: C, 67.03; H, 5.63; N, 2.70. Found: C, 67.12; H, 5.54; N, 2.82.

5.6.8.6. Dimethyl 4-{2-[6-(2-chlorobenzyl)-*2*(*3H*)-benzothiazolon-3-yl]ethoxy}benzylmalonate (27g). Mp 92–96 °C (petroleum ether) (yield 80%). IR (KBr) cm^{-1} 1685, 1725, 1745. ^1H NMR (DMSO) δ 3.00 (d, $J = 8.1$ Hz, 2H), 3.60 (s, 6H), 3.80 (t, $J = 8.1$ Hz, 1H), 4.10 (s, 2H), 4.20 (t, $J = 5.0$ Hz, 2H), 4.30 (t, $J = 5.0$ Hz, 2H), 6.75 (d, $J = 8.5$ Hz, 2H), 7.10 (d, $J = 8.5$ Hz, 2H), 7.20–7.45 (m, 6H), 7.50 (s, 1H). Anal. Calcd for $C_{28}H_{26}ClNO_6S$: C, 62.27; H, 4.85; N, 2.59. Found: C, 62.41; H, 4.71; N, 2.65.

5.6.8.7. Dimethyl 4-{2-[6-(3-chlorobenzyl)-*2*(*3H*)-benzothiazolon-3-yl]ethoxy}benzylmalonate (27h). Mp 82–86 °C (petroleum ether) (yield 80%). IR (KBr) cm^{-1} 1670, 1730, 1740. ^1H NMR (DMSO) δ 3.00 (d, $J = 8.0$ Hz, 2H), 3.60 (s, 6H), 3.75 (t, $J = 8.0$ Hz, 1H), 3.95 (s, 2H), 4.20 (t, $J = 4.7$ Hz, 2H), 4.30 (t, $J = 4.7$ Hz, 2H), 6.75 (d, $J = 8.5$ Hz, 2H), 7.10 (d, $J = 8.5$ Hz, 2H), 7.20–7.45 (m, 6H), 7.55 (s, 1H). Anal. Calcd for $C_{28}H_{26}ClNO_6S$: C, 62.27; H, 4.85; N, 2.59. Found: C, 62.31; H, 4.77; N, 2.55.

5.6.8.8. Dimethyl 4-{2-[6-(4-chlorobenzyl)-2(*3H*)-benzothiazolon-3-yl]ethoxy}benzylmalonate (27i). Purified by flash chromatography using EtOAc/cyclohexane (1:4). Mp 40–45 °C (petroleum ether) (yield 60%). IR (KBr) cm^{-1} 1660, 1735. ^1H NMR (DMSO) δ 3.00 (d, $J = 8.0$ Hz, 2H), 3.60 (s, 6H), 3.80 (t, $J = 8.0$ Hz, 1H), 4.00 (s, 2H), 4.20 (t, $J = 4.7$ Hz, 2H), 4.30 (t, $J = 4.7$ Hz, 2H), 6.75 (d, $J = 8.4$ Hz, 2H), 7.10 (d, $J = 8.4$ Hz, 2H), 7.20–7.40 (m, 6H), 7.50 (s, 1H). Anal. Calcd for $C_{28}H_{26}ClNO_6S$: C, 62.27; H, 4.85; N, 2.59. Found: C, 62.39; H, 4.82; N, 2.63.

5.6.8.9. Dimethyl 4-{2-[6-(4-methoxybenzyl)-2 (*3H*)-benzothiazolon-3-yl]ethoxy}benzylmalonate (27l). Mp 112–113 °C (MeOH) (yield 70%). IR (KBr) cm^{-1} 1670, 1730, 1740. ^1H NMR (DMSO) δ 3.00 (d, $J = 8.2$ Hz, 2H), 3.60 (s, 6H), 3.70 (s, 3H), 3.80 (t, $J = 8.2$ Hz, 1H), 3.90 (s, 2H), 4.20 (t, $J = 4.5$ Hz, 2H), 4.35 (t, $J = 4.5$ Hz, 2H), 6.75 (d, $J = 8.7$ Hz, 2H), 6.85 (d, $J = 8.2$ Hz, 2H), 7.05 (d, $J = 8.2$ Hz, 2H), 7.15 (d, $J = 8.7$ Hz, 2H), 7.25 (d, $J = 8.5$ Hz, 1H), 7.40 (d, $J = 8.5$ Hz, 1H), 7.50 (s, 1H). Anal. Calcd for $C_{29}H_{29}NO_7S$: C, 65.03; H, 5.46; N, 2.62. Found: C, 65.15; H, 5.57; N, 2.54.

5.6.9. Dimethyl 4-hydroxybenzylidenemalonate (28).
(1) To dry THF (140 mL) at 0 °C was added titane tetrachloride[33] (9.0 mL, 82 mmol) diluted with carbon tetrachloride (25 mL) under a nitrogen atmosphere. Then were added a solution of 4-hydroxybenzaldehyde (5.0 g, 41 mmol) in THF (25 mL), a solution of dimethyl malonate (5.7 mL, 49 mmol) in THF (10 mL), and finally a solution of pyridine (13.2 mL, 164 mmol) in THF (25 mL). The mixture was stirred for 15 h at room temperature and then water was added. The mixture was extracted twice with EtOAc and the organic layers were washed with a solution of sodium bicarbonate, dried over magnesium sulfate, and solvent was evaporated under reduced pressure. The crude product was recrystallized from isopropanol to give **28**. Mp 154–157 °C (yield 65%). IR (KBr) cm^{-1} 3335, 1735. ^1H NMR (DMSO) δ 3.80 (s, 6H), 6.85 (d, $J = 8.5$ Hz, 2H), 7.35 (d, $J = 8.5$ Hz, 2H), 7.65 (s, 1H), 12.25 (s, 1H).
(2) Compound **28** was also synthesized using the following procedure.[34] To a solution of 4-hydroxybenzaldehyde (5.0 g, 41 mmol) in MeOH (10 mL) were added dimethyl malonate (4.7 mL, 41 mmol) and a solution of piperidine (0.4 mL, 4 mmol) in MeOH (1.2 mL). The mixture was stirred for 8 h at room temperature. The precipitate was collected by filtration and was recrystallized from isopropanol to give **28** (yield 65%).

5.6.10. Dimethyl 4-(2-Chloroethoxy)benzylidenemalonate (29). To a solution of **28** (2.5 g, 11 mmol) in DMF (100 mL) were added potassium carbonate (2.9 g, 21 mmol) and 1-bromo-2-chloroethane (2.0 mL, 32 mmol). The mixture was stirred at 60–80 °C for 3 h and then water was added. The solution was extracted with Et_2O (2×40 mL) and the organic extracts were dried over magnesium sulfate and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography using EtOAc/cyclohexane (1:9) as eluent and then recrystallized from MeOH to give **29**. Mp 63–67 °C (yield 70%). IR (KBr) cm^{-1} 1710. ^1H NMR (DMSO) δ 3.85 (m, 8H), 4.30 (t, $J = 5.7$ Hz, 2H), 6.90 (d, $J = 6.8$ Hz, 2H), 7.40 (d, $J = 6.8$ Hz, 2H), 7.75 (s, 1H).

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