N-Acyl-2-substituted-1,3-thiazolidines, a New Class of Non-narcotic Antitussive Agents: Studies Leading to the Discovery of Ethyl 2-[(2-Methoxyphenoxy)methyl]-β-oxothiazolidine-3-propanoate

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The synthesis of a novel class of antitussive agents is described. The compounds were examined for antitussive activity in guinea pig after cough induction by electrical or chemical stimulation. Ethyl 2-[(2-methoxyphenoxy)methyl]-β-oxothiazolidine-3-propanoate (BBR 2173, moguisteine, **7**) and other structurally related compounds showed a significant level of activity, comparable to that of codeine and dextromethorphan. The compounds presented in this paper are characterized by the *N*-acyl-2-substituted-1,3-thiazolidine moiety, which is a novel entry in the field of antitussive agents. The serendipitous discovery of the role played by the thiazolidine moiety in determining the antitussive effect promoted extensive investigations on these structures. This optimization process on *N*-acyl-2-substituted-1,3-thiazolidines led to the initial identification of 2-[(2-methoxypheoxy)methyl]-3-[2-(acetylthio)acetyl]-1,3-thiazolidine (**18a**) as an interesting lead compound. The careful study of the rapid and very complicated metabolism of **18a** provided further insights for the design of newer related derivatives. The observation that the metabolic oxidation on the lateral chain's sulfur of **18a** to sulfoxide maintained the antitussive properties suggested the introduction of isosteric functional groups with respect to the sulfoxide moiety. Subsequent structural modifications showed that hydrolyzable malonic residues in the 3-position of the thiazolidine ring were able to assure high antitussive activity. This optimization ultimately led to the selection of moguisteine (**7**) as the most effective and safest representative of the series. Moguisteine is completely devoid of unwanted side effects (such as sedation and addiction), and its activity was demonstrated also in clinical studies.

Introduction

Antitussive drugs are widely used in the treatment of coughs. They are particularly indicated in nonproductive cough, usually associated with different respiratory diseases varying from mild throat infections to the more serious bronchitis and asthma. Nonproductive cough is often painful and fatiguing to the patient especially during the night when, lying down, relief from this persistent reflex is greatly desired. The main ways used to inhibit the cough reflex involve either suppressing the cough center or anesthetizing the respiratory mucosa. Several drugs are available for the treatment of cough, but the number of safe and effective antitussive agents devoid of central effects or local anesthetic activity is rather limited. Opioid alkaloids still seem to be the most effective compounds available, in spite of their several well-established side effects and the risk of addiction. Codeine (**1**), the 3-methoxy derivative of (−)-morphine, is the most notable representative of the morphine family, and its major side effects, such as sedation, depression, and constipation, are well known.[1] For many years, novel antitussives have been sought through structures incorporating the essential features of codeine series.[2] Dextromethorphan (**2a**) and dimemorphan (**2b**), which have the same absolute configuration as (+)-morphine, emerged as clinically useful antitussives with fewer side effects than codeine, although they both showed potent central activity.[3] In addition, **2b** has been reported to have analgesic properties.[4] Further simplifications of the morphine nucleus provided newer antitussive agents, structural families less closely related to the morphinans. One of the most crowded class is represented by the phenothiazines among which pipazetate (**3**)[5] was shown to exhibit antitussive properties, through a central mechanism of action, together with antibronchospastic effects. Clophedianol[6] and cloperastine (**4**)[7] belong to another big class of antitussives which are bis-arylmethane/ethane derivatives provided with lateral chains containing tertiary amines. The former is reported to depress the cough center and stimulate the respiratory center. Besides, it shows antibronchospastic properties. More selectively, cloperastine does not interact with the respiratory center. In the group of 1,4-disubstituted-piperazines, eprazinone, zipeprol,[8] and dropropizine (**5**)[9] are the best known representatives. Some central nervous system (CNS) side effects were reported to be retained by zipeprol, whereas, more recently, the levorotatory isomer of dropropizine[10] showed less sedative properties than the racemate or the dextro isomer, maintaining a considerable analgesic activity. Finally, in the class of heterocyclic oxadiazoles, oxolamine (**6**)[11] emerged as one of the most active representatives. This antitussive agent was suggested to have a predominantly peripheral mechanism of action because of its major activity in tests involving a diffuse stimulation of the bronchial tree.

In this paper we disclose a new family of non-narcotic antitussive agents, namely, the *N*-acyl-2-substituted-1,3-thiazolidines, among which moguisteine (**7**) is one of the most active (Figure 1). The new compounds are structurally unrelated to any of the previously mentioned classes. Significantly enough, the compounds

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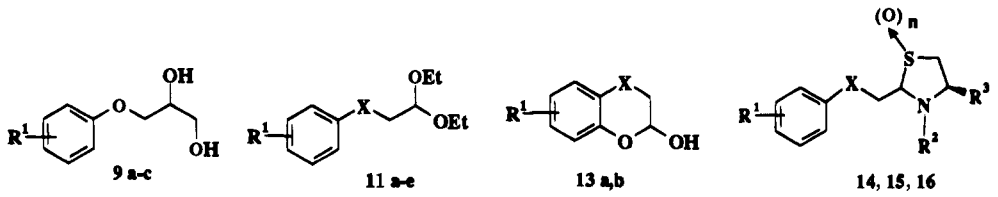
Table 1. Intermediates



no.	R^1	X	n	R^2	R^3	mp, °C	crystn solvent	yield, %	formula	anal.
9a	2-OCH_3					78–80	toluene	84	$C_{10}H_{14}O_4$	C,H
9b	4-OCH_3					54–56	Et_2O	86	$C_{10}H_{14}O_4$	C,H
9c	2-CH_3					oil		90	$C_{10}H_{14}O_3$	C,H
11a	2-OCH_3	O				oil		88	$C_{13}H_{20}O_4$	C,H
11b	4-OCH_3	O				oil		83	$C_{13}H_{20}O_4$	C,H
11c	2-CH_3	O				oil		90	$C_{13}H_{20}O_3$	C,H
11d	4-$COOCH_3$	O				oil		73	$C_{14}H_{20}O_5$	C,H
11e	2-OCH_3	S				oil		95	$C_{13}H_{20}O_3S$	C,H,S
13a		O				oil		95	$C_8H_8O_3$	C,H
13b		CH_2				oil		90	$C_9H_{10}O_2$	C,H
14a	2-OCH_3	O	0	H	H	66–67	EtOH–H_2O	76	$C_{11}H_{15}NO_2S$	C,H,N,S
14b	4-OCH_3	O	0	H	H	57–59	EtOAc	73	$C_{11}H_{15}NO_2S$	C,H,N,S
14c	2-CH_3	O	0	H	H	66–68	EtOH–H_2O	64	$C_{11}H_{15}NOS$	C,H,N,S
14d	4-$COOCH_3$	O	0	H	H	98–100	EtOH–H_2O	79	$C_{12}H_{15}NO_3S$	C,H,N,S
14e	2-OCH_3	S	0	H	H	99–100	*i*-PrOH	75	$C_{11}H_{15}NOS_2$	C,H,N,S
14f	2-OH	O	0	H	H	76–78	EtOH–H_2O	76	$C_{10}H_{13}NO_2S$	C,H,N,S
14g	2-OH	CH_2	0	H	H	99–100	*i*-PrOH	86	$C_{11}H_{15}NOS$	C,H,N,S
14h	2-OCH_3	O	0	H	COOEt	53–57	Et_2O	78	$C_{14}H_{19}NO_4S$	C,H,N,S
14i	2-OH	O	0	H	COOH	181–182	EtOH–H_2O	80	$C_{11}H_{13}NO_4S$	C,H,N,S
14j	2-OH	CH_2	0	H	COOH	182–185	EtOH–H_2O	85	$C_{12}H_{15}NO_3S$	C,H,N,S
14k	2-OH	CH_2	0	H	COOEt	100–102	EtOH–H_2O	78	$C_{14}H_{19}NO_3S$	C,H,N,S
14l	2-OCH_3	O	0	H	COOH	149–150	EtOH–H_2O	77	$C_{12}H_{15}NO_4S$	C,H,N,S
15a	2-OCH_3	O	0	$COCH_2Cl$	H	83–85	*i*-PrOH	86	$C_{13}H_{16}ClNO_3S$	C,H,Cl,N,S
15b	4-OCH_3	O	0	$COCH_2Cl$	H	51–53	MeOH	74	$C_{13}H_{16}ClNO_3S$	C,H,Cl,N,S
15c	2-CH_3	O	0	$COCH_2Cl$	H	oil		90	$C_{13}H_{16}ClNO_2S$	C,H,Cl,N,S
15d	4-$COOCH_3$	O	0	$COCH_2Cl$	H	66–68	EtOH	67	$C_{14}H_{16}ClNO_3S$	C,H,Cl,N,S
15e	2-OCH_3	S	0	$COCH_2Cl$	H	127–129	*i*-PrOH	88	$C_{13}H_{16}ClNO_2S_2$	C,H,Cl,N,S
15f	2-OH	O	0	$COCH_2Cl$	H	89–91	*i*-PrOH	81	$C_{12}H_{14}ClNO_3S$	C,H,Cl,N,S
15g	2-OH	CH_2	0	$COCH_2Cl$	H	110–112	*i*-PrOH	81	$C_{13}H_{16}ClNO_2S$	C,H,Cl,N,S
15h	2-OCH_3	O	0	$COCH_2Cl$	COOEt	94–96	Et_2O	71	$C_{16}H_{20}ClNO_5S$	C,H,Cl,N,S
15i	2-$OCOCH_2Cl$	CH_2	0	$COCH_2Cl$	H	88–89	Et_2O–$CHCl_3$	58	$C_{15}H_{17}Cl_2NO_3S$	C,H,Cl,N,S
15j	2-OCH_3	O	0	$COCH(CH_3)Br$	H	oil		90	$C_{14}H_{18}BrNO_3S$	C,H,Br,N,S
15k	2-OCH_3	O	0	$COCH_2Br$	H	84–87	EtOH–H_2O	75	$C_{13}H_{16}BrNO_3S$	C,H,Br,N,S
15l	2-OCH_3	O	0	$COCH_2I$	H	81–83	Et_2O	77	$C_{13}H_{16}INO_3S$	C,H,I,N,S
16a	2-OCH_3	O	1	$COCH_2Cl$	H	124–128	EtOH	85	$C_{13}H_{16}ClNO_4S$	C,H,Cl,N,S
16b	2-OCH_3	O	2	$COCH_2Cl$	H	68–69	AcOH–H_2O	83	$C_{13}H_{16}ClNO_5S$	C,H,Cl,N,S

[a] Elemental analyses for C,H,N,S. Alogens were within ±0.4% of the theoretical values unless otherwise stated.

discussed in this work do not require the presence of any basic residues, such as tertiary amines, as often encountered in the classical antitussive agents.

The relevant role played by the thiazolidine ring in the design of orally active antitussive agents was serendipitously discovered during a search of new expectorants related to guaiacol and guaiphenesin (Figure 2). By using this latter as a starting point, we introduced steric constraints by including the glyceryl residue into a heterocyclic ring, such as 1,3-dioxolanes. Other heterocyclic rings were also investigated, such as oxazolidines and thiazolidines. In this context, cough inhibition was tested as an undesired side effect when, surprisingly, pronounced antitussive properties unrelated to mucolysis were found to be a common characteristic of the thiazolidines under investigation. A few of them were compared with the corresponding pyrrolidine analogues in order to determine if the heterocyclic sulfur atom was necessary for pharmacological activity.

Chemistry

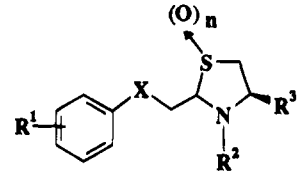
The syntheses of the new compounds[12] shown in Tables 1–3 are outlined in Schemes 1–10. Thiazolidines **14a–l** were obtained by three converging methods. The first one (Scheme 1, method A), starting from guaiphenesin (**9a**) or other 3-(aryloxy)-1,2-propanediols (**9b,c**), involves the oxidative cleavage of a 1,2-diol with sodium periodate, followed by the reaction of the crude aldehydes **10** with the appropriate 2-mercaptoethylamine derivatives.

The second method (Scheme 2, method B) involves a nucleophilic substitution of a salt of compounds **8** (phenylthiolate or aryloxy salt) with α-bromoacetaldehyde diethyl acetal to give the acetals **11** that are then converted into the desired thiazolidines in acidic media.

Method C (Scheme 3) was specifically designed for the synthesis of compounds such as **14f,g,i–k** which have a free phenolic group in the ortho position of the benzene ring. The reduction of lactones **12** to lactols **13** was easily carried out with lithium tri-*tert*-butoxyaluminum hydride in THF at 0 °C with good yields.

Thiazolidines **14a–h** were acylated by several methods using either acyl chlorides or activated carboxylic anhydrides. Scheme 4 outlines the reaction conditions which were used to obtain the 2-(α-haloacyl)-1,3-thiazolidines **15a–l**. In addition, Scheme 5 illustrates the preparation of other *N*-acyl-2-substituted-1,3-thiazolidines **20a–c** by direct coupling of **14a** or **14f** with 2-(methylsulfenyl)- or 2-(methylsulfinyl)acetic acid, in the presence of DCC as condensing agent. Mixtures of

Table 2.



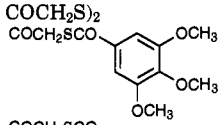
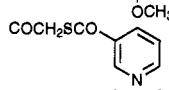
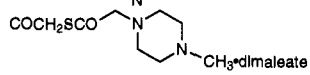
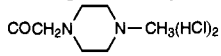
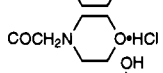
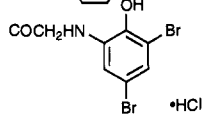
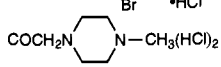
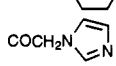
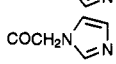
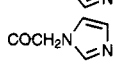
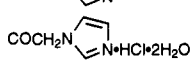
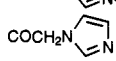
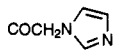
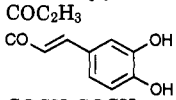
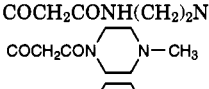
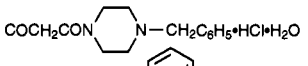
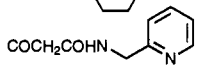
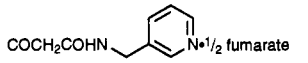
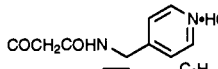
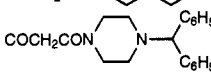
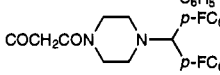
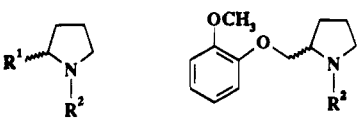
no.	R^1	X	*n*	R^2	R^3	mp, °C	crystn solvent	yield, %	formula	anal.[a]
7	2-OCH_3	O	0	$COCH_2COOCH_2CH_3$	H	60–62	EtOH–H_2O	85	$C_{16}H_{21}NO_5S$	C,H,N,S
17	2-OCH_3	O	1	$COCH_2SCOCH_3$	H	111–114	1-PrOH	68	$C_{15}H_{19}NO_5S_2$	C,H,N,S
18a	2-OCH_3	O	0	$COCH_2SCOCH_3$	H	91–92	EtOAc	82	$C_{15}H_{19}NO_4S_2$	C,H,N,S
18b	2-OCH_3	O	0	$COCH_2SCOCH_3$	COOEt	90–92	*i*-PrOH	68	$C_{18}H_{23}NO_6S_2$	C,H,N,S
18c	2-OCH_3	O	0	$COCH(CH_3)SCOCH_3$	H	101–103	Et_2O	70	$C_{16}H_{21}NO_4S_2$	C,H,N,S
18d	4-OCH_3	O	0	$COCH_2SCOCH_3$	H	101–102	EtOAc	69	$C_{15}H_{19}NO_4S_2$	C,H,N,S
18e	2-CH_3	O	0	$COCH_2SCOCH_3$	H	oil		94	$C_{15}H_{19}NO_3S_2$	C,H,N,S
18f	2-OH	O	0	$COCH_2SCOCH_3$	H	97–99	EtOH	89	$C_{14}H_{17}NO_4S_2$	C,H,N,S
18g	2-OH	CH_2	0	$COCH_2SCOCH_3$	H	oil		80	$C_{15}H_{19}NO_3S$	C,H,N,S
18h	2-$OCOCH_2$-$SCOCH_3$	CH_2	0	$COCH_2SCOCH_3$	H	oil		93	$C_{19}H_{23}NO_5S_3$	C,H,N,S
18i	2-$OCOCH_2$-$SCOCH_3$	O	0	$COCH_2SCOCH_3$	H	oil		74	$C_{18}H_{21}NO_6S_3$	C,H,N,S
19a	2-OCH_3	O	0	$COCH_2SH$	H	84–86	EtOAc	76	$C_{13}H_{17}NO_3S_2$	C,H,N,S
19b	2-OCH_3	O	0	$COCH_2S)_2$	H	50–60	DMSO–H_2O	74	$C_{26}H_{32}N_2O_6S_4$	C,H,N,S
19c	2-OCH_3	O	0		H	108–110	EtOAc–hexane	71	$C_{23}H_{27}NO_7S_2$	C,H,N,S
19d	2-OCH_3	O	0		H	88–91	Et_2O	79	$C_{19}H_{20}N_2O_4S_2$	C,H,N,S
19e	2-OCH_3	O	0		H	106–108	acetone	83	$C_{28}H_{37}N_3O_{12}S_2$	C,H,N,S
19f	2-OCH_3	O	0	$COCH_2SCOOEt$	H	64–66	*i*-PrOH	48	$C_{16}H_{21}NO_5S_2$	C,H,N,S
20a	2-OCH_3	O	0	$COCH_2SCH_3$	H	78–80	EtOAc	80	$C_{14}H_{19}NO_3S_2$	C,H,N,S
20b	2-OH	O	0	$COCH_2SCH_3$	H	68–70	EtOAc	74	$C_{13}H_{17}NO_3S_2$	C,H,N,S
20c	2-OCH_3	O	0	$COCH_2S(O)CH_3$	H	91–105	EtOAc	90	$C_{14}H_{19}NO_4S_2$	C,H,N,S
21a	2-OCH_3	O	1	$COCH_2S(O)CH_3$	H	foam		88	$C_{14}H_{19}NO_5S_2$	C,H,N,S
21b	2-OCH_3	O	1	$COCH_2S(O)_2CH_3$	H	foam		76	$C_{14}H_{19}NO_6S_2$	C,H,N,S
22a	2-OCH_3	O	0	$COCH_2NH_2$·HCl	H	182–184	Et_2O–MeOH	69	$C_{13}H_{18}N_2O_3S$·HCl	C,H,N,S
22b	2-OCH_3	O	0	$COCH_2NHCOCH_3$	H	119–120	EtOH	75	$C_{15}H_{20}N_2O_4S$	C,H,N,S
22c	2-OCH_3	O	0		H	211–215	Et_2O	69	$C_{18}H_{27}N_3O_3S$·2HCl	C,H,N,S,Cl
22d	2-OCH_3	O	0		H	183–185	acetone–Et_2O	60	$C_{17}H_{24}N_2O_4S$·HCl	C,H,N,S,Cl
22e	2-OCH_3	O	0		H	195–197	EtOH	70	$C_{20}H_{22}Br_2N_2O_4S$·HCl	C,H,N,S,Br
22f	2-OCH_3	S	0		H	200–205	acetone	82	$C_{18}H_{27}N_3O_2S_2$·2HCl	C,H,N,S,Cl
23a	2-OCH_3	O	0		H	94–96	EtOAc	86	$C_{16}H_{19}N_3O_3S$	C,H,N,S
23b	4-OCH_3	O	0		H	132–133	acetone	69	$C_{16}H_{19}N_3O_3S$	C,H,N,S
23c	4-$COOCH_3$	O	0		H	149–150	*i*-PrOH–*i*-Pr_2O	83	$C_{17}H_{19}N_3O_4S$	C,H,N,S
23d	4-COOH	O	0		H	100–105	H_2O	20	$C_{16}H_{19}N_3O_6S$·HCl·$2H_2O$	C,H,N,S
23e	2-OCH_3	S	0		H	126–128	EtOAc	87	$C_{16}H_{19}N_3O_2S_2$	C,H,N,S
23f	2-OH	O	0		H	211–214	acetone	75	$C_{15}H_{17}N_3O_3S$	C,H,N,S
24a	2-OCH_3	O	0	$COCH_2OCOCH_3$	H	89–91	Et_2O	80	$C_{15}H_{19}NO_5S$	C,H,N,S
24b	2-OCH_3	O	0	$COCH_2OCH_3$	H	76–77	*i*-PrOH	56	$C_{14}H_{19}NO_4S$	C,H,N,S
24c	2-OCH_3	O	0	$COCH_2O(CH_2)_2OEt$	H	oil		90	$C_{17}H_{25}NO_5S$	C,H,N,S
25a	2-OCH_3	O	0	$COCH_3$	H	79–81	Et_2O	95	$C_{13}H_{17}NO_3S$	C,H,N,S
25b	2-OCH_3	O	0	$COC(CH_3)_3$	H	70–72	*i*-Pr_2O	73	$C_{16}H_{23}NO_3S$	C,H,N,S
25c	2-OCH_3	O	0	COC_2H_3	H	56–58	Et_2O	90	$C_{14}H_{17}NO_3S$	C,H,N,S
25d	2-OCH_3	O	0		H	189–190	*i*-PrOH	80	$C_{20}H_{21}NO_5S$	C,H,N,S
25e	2-OCH_3	O	0	$COCH_2COCH_3$	H	61–63	Et_2O	68	$C_{15}H_{19}NO_4S$	C,H,N,S
25f	2-OCH_3	O	0	$COCH_2COCH_2CH_2CH_3$	H	oil		87	$C_{17}H_{23}NO_4S$	C,H,N,S
25g	2-OCH_3	O	0	$COCH_2COOCH_3$	H	80–82	EtOAc–hexane	85	$C_{15}H_{19}NO_5S$	C,H,N,S
25h	2-OCH_3	O	0	$COCH_2COOCH(CH_3)_2$	H	oil		70	$C_{17}H_{23}NO_5S$	C,H,N,S

Table 2 (Continued)

no.	R^1	X	n	R^2	R^3	mp, °C	crystn solvent	yield, %	formula	anal.[a]
26a	2-OCH_3	O	0	$COCOOCH_2CH_3$	H	oil		90	$C_{15}H_{19}NO_5S$	C,H,N,S
26b	2-OCH_3	O	0	$COCH_2CH_2COOCH_2CH_3$	H	56–58	Et_2O	72	$C_{17}H_{23}NO_5S$	C,H,N,S
26c	2-OH	O	0	$COCH_2COOCH_2CH_3$	H	61–63	*i*-Pr_2O	72	$C_{15}H_{19}NO_5S$	C,H,N,S
27a	2-OCH_3	O	0	$COCH_2COOH$	H	123–125	EtOAc	75	$C_{14}H_{17}NO_5S$	C,H,N,S
27b	2-OCH_3	O	0	$COCH_2CH_2COOH$	H	105–107	Et_2O–*i*-Pr_2O	80	$C_{15}H_{19}NO_5S$	C,H,N,S
27c	2-OCH_3	O	1	$COCH_2COOH$	H	134–137	acetone–MeOH	76	$C_{14}H_{17}NO_6S$	C,H,N,S
27d	2-OH	O	0	$COCH_2COOH$	H	106–108	Et_2O	78	$C_{13}H_{15}NO_5S$	C,H,N,S
28a	2-OCH_3	O	1	$COCH_2COOCH_2CH_3$	H	76–79	*i*-Pr_2O	84	$C_{16}H_{21}NO_6S$	C,H,N,S
28b	2-OCH_3	O	2	$COCH_2COOCH_2CH_3$	H	100–102	EtOAc	70	$C_{16}H_{21}NO_7S$	C,H,N,S
29	2-OCH_3	O	0	$COC(CH_3)_2COOCH_2CH_3$	H	54–56	Et_2O–hexane	65	$C_{18}H_{25}NO_5S$	C,H,N,S
30	2-OCH_3	O	1	$COC(CH_3)_2COOCH_2CH_3$	H	65–68	EtOAc–hexane	75	$C_{18}H_{25}NO_6S$	C,H,N,S
31	2-OCH_3	O	0	$COC(CH_3)_2COOH$	H	118–119	Et_2O	63	$C_{16}H_{21}NO_5S$	C,H,N,S
32a	2-OCH_3	O	0	$COCH_2CONHCH_3$	H	136–138	EtOAc	92	$C_{15}H_{20}N_2O_4S$	C,H,N,S
32b	2-OCH_3	O	0	$COCH_2CONH(CH_2)_2NEt_2$	H	58–60	Et_2O	67	$C_{20}H_{31}N_3O_4S$	C,H,N,S
32c	2-OCH_3	O	0		H	75–77	Et_2O	80	$C_{19}H_{27}N_3O_4S$	C,H,N,S
32d	2-OCH_3	O	0		H	foam		76	$C_{25}H_{31}N_3O_5S{\cdot}HCl{\cdot}H_2O$[b]	C,H,N,S,Cl
32e	2-OCH_3	O	0		H	105–107	*i*-PrOH	64	$C_{20}H_{23}N_3O_4S$	C,H,N,S
32f	2-OCH_3	O	0		H	113–115	Et_2O–MeOH	66	$C_{22}H_{25}N_3O_6S$	C,H,N,S
32g	2-OCH_3	O	0		H	54–56	Et_2O–EtOAc	88	$C_{20}H_{23}N_3O_4S{\cdot}HCl{\cdot}H_2O$[c]	C,H,N,S,Cl
32h	2-OCH_3	O	0		H	132–134	EtOAc	66	$C_{31}H_{35}N_3O_4S$	C,H,N,S
32i	2-OCH_3	O	0		H	72–75	EtOAc	44	$C_{31}H_{33}Fe_2N_3O_4S$	C,H,N,S

[a] Elemental analyses for C,H,N,S. Alogens were within ±0.4% of the theoretical values unless otherwise stated. [b] C: calcd, 55.60; found, 56.61. Cl: calcd, 6.56; found, 7.35. [c] S: calcd, 7.03; found, 6.31.

Table 3.



34 35, 36, 37, 38, 39

no.	config	R^1	R^2	mp, °C	crystn solvent	yield, %	formula[a]	$[\alpha]^{20}_D$ (*c*, solvent)
34a	*S*	CH_2OH	$COOC(CH_3)_3$	59–60	hexane	68	$C_{10}H_{19}NO_3$	−52° (2, EtOH)
34b	*R*	CH_2OH	$COOC(CH_3)_3$	59–60	hexane	71	$C_{10}H_{19}NO_3$	+52° (2, EtOH)
35a	*S*		$COOC(CH_3)_3$	65–67	hexane	47	$C_{17}H_{25}NO_4$	−67° (2, EtOH)
35b	*R*		$COOC(CH_3)_3$	65–67	hexane	48	$C_{17}H_{25}NO_4$	+68° (2, EtOH)
36a	*S*		H	oil		90	$C_{12}H_{17}NO_2$	−10° (2, EtOH)
36b	*R*		H	oil		90	$C_{12}H_{17}NO_2$	+9° (2, EtOH)
37a	*S*		$COCH_2COOC_2H_5$	oil		77	$C_{17}H_{23}NO_5$	−64° (2, EtOH)
37b	*R*		$COCH_2COOC_2H_5$	oil		79	$C_{17}H_{23}NO_5$	+64° (2, EtOH)
38a	*S*		$COCH_2Cl$	98–100	Et_2O	70	$C_{14}H_{18}ClNO_3$	−63° (2, EtOH)
38b	*R*		$COCH_2Cl$	98–100	Et_2O	65	$C_{14}H_{18}ClNO_3$	+63° (2, EtOH)
39a	*S*		$COCH_2SCOCH_3$	53–55	Et_2O	78	$C_{16}H_{21}NO_4S$	−60° (2, EtOH)
39b	*R*		$COCH_2SCOCH_3$	54–56	Et_2O	75	$C_{16}H_{21}NO_4S$	+61° (2, EtOH)

[a] Elemental analyses for C,H,N,S. Alogens were within ±0.4% of the theoretical values unless otherwise stated.

the diastereoisomeric sulfoxides such as **16a,b, 17** (Scheme 4), and **21a,b** (Scheme 5) were obtained by selective S-oxidation of the heterocyclic ring, which introduces in the new molecules another center of asymmetry. Compounds **15** and **16** underwent nucleophilic substitution with potassium thioacetate to give 2-[α-(acetylthio)acyl]-1,3-thiazolidines **18** and the sulfoxide **17**, respectively. The S–acetyl bond in **18a** was easily hydrolyzed to obtain the thiol **19a** and then, after oxidation or acylation, the compounds **19b** or **19c–f** (Scheme 4). Compounds **21a,b** were obtained by oxidizing **20a,c,** respectively (Scheme 5).

Scheme 6 describes the preparation of two other series of thiazolidines: the first contains basic residues (**22**, **23**), while the second has acyloxy or alkoxy substituents in the lateral chain of the 1,3-thiazolidinic ring (**24**). In these cases substances were prepared by two different synthetic approaches: the acylation of thiazolidine **14a** with appropriate acids led to compounds **22a** (two steps), **22b**, and **24a** (one step); the alternative pathway was the nucleophilic substitution of the chlorine atom of 2-(α-chloroacetyl)-1,3-thiazolidines **15a,b,d,e** (or the THP-protected derivative of **15f**) with different nucleophiles such as free primary or secondary amines (**22c–f**), potassium imidazolide (**23a–f**), or sodium alkoxides (**24b,c**). The 4-substituted-benzoic acid **23d** was obtained from the hydrolysis of ester **23c**.

The replacement of the thiocarbonyl fragment, -SCO-, of compound **18a** with different functionalities such as a connecting bond, alkylene groups, or carbonyl or carboxyl fragments like -CO-, -COO-, or -CON< opened the door to a series of very potent thiazolidine deriva-

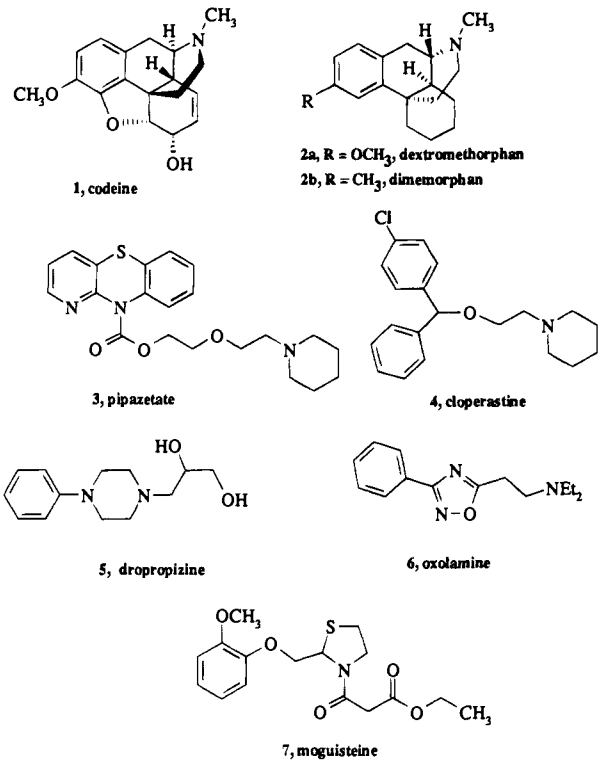


Figure 1.

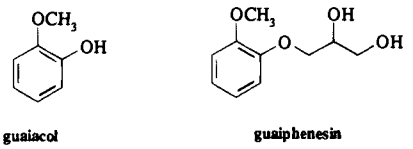
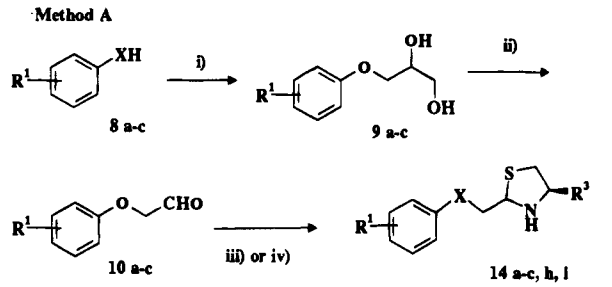


Figure 2.

Scheme 1[a]



compd	R^1
9a, 10a	2-OCH_3
9b, 10b	4-OCH_3
9c, 10c	2-CH_3

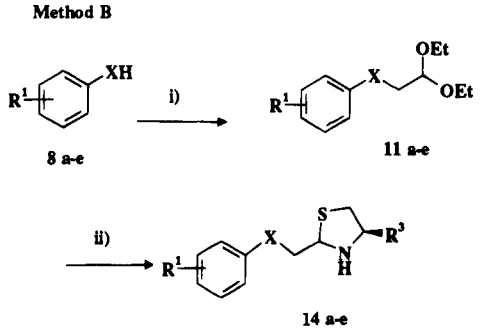
[a] (i) EtONa, EtOH, $ClCH_2CHOHCH_2OH$, rt; (ii) $NaIO_4$, H_2O, 0–5 °C; (iii) $R^3CH(NH_2)CH_2SH$·HCl, $KHCO_3$, EtOAc, H_2O, rt, or $R^3CH_2(NH_2)CH_2SH$, H_2O, EtOH, rt; (iv) $R^3CH(NH_2)CH_2SH$·HCl, AcOK, H_2O, EtOH, rt.

tives. Schemes 7 and 8 illustrate the preparation of 3-acyl-1,3-thiazolidines, whereas Scheme 9 describes the preparation of several related malonic amides.

Compounds **25a–h** and **26a–c** (Scheme 7), together with **29** (Scheme 8), were prepared from thiazolidines **14a,f** by acylation, including the use of acyl halides, 5-butyryl Meldrum's acid, diketene, or carboxylic acids in the presence of a condensing agent such as DCC.

Moguisteine (**7**) and its phenolic analogue, **26c**, were obtained in excellent yields by acylating the thiazolidine **14a** with ethyl malonyl chloride in a mixture of water and organic solvents such as toluene or EtOAc in the presence of inorganic bases such as sodium or potassium

Scheme 2[a]



compd	R^1	X
8a, 11a	2-OCH_3	O
8b, 11b	4-OCH_3	O
8c, 11c	2-CH_3	O
8d, 11d	4-$COOCH_3$	O
8e, 11e	2-OCH_3	S

[a] (i) $BrCH_2CH(OEt)_2$, K_2CO_3, NMP, Δ; (ii) (1) $R^3CH(NH_2)CH_2SH$·HCl, cat. HCl (37%), EtOH, H_2O, Δ; (2) NaOH.

bicarbonate. The free acid **27a** and the corresponding sulfoxide **27c**, sulfone **28b**, and 2,2-dimethylmalonate derivatives **30** and **31** (Scheme 8) were also prepared for comparison.

Scheme 9 summarizes the approaches used in the synthesis of malonodiamides **32a–i**: the acylation of amines by esters or the treatment of the appropriate amines with the carboxylic acid **29a** in the presence of condensing agents (such as DCC) or of an activated form (such as the *N*-hydroxysuccinimide ester or the imidazolide) of the acid itself.

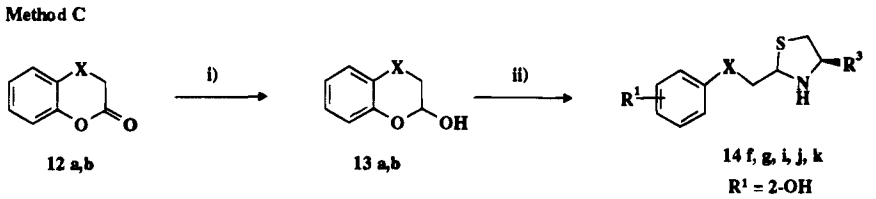
Finally pyrrolidines **38** and **40** were synthesized for comparative testing with the closely related thiazolidines **18a** and **7** (moguisteine). The enantiomeric BOC-prolines (**33a,b**) were reduced to the corresponding BOC-prolinols (**34a,b**). The subsequent activation of the latter as their tosylates followed by coupling with sodium guaiacolate gave the BOC intermediates **35a,b**, which, after deprotection, were acylated to obtain compounds **37** and **39**, each of them as a pure *R* or *S* enantiomer.

Pharmacological Results and Discussion

The antitussive activity of *N*-acyl-2-substituted-1,3-thiazolidine derivatives was investigated in male guinea pig. Two different models of induced cough were used, (a) exposure to citric acid aerosol[13] or (b) electrical stimulation of the tracheal submucosa.[14] The compounds were tested at doses of 15–30 mg/kg po, and those exhibiting interesting activity were evaluated at different doses in order to determine their ED_{50} values. Acute toxicity was determined in mice after oral administration. Details of the methods are described in the Experimental Section, and the results are summarized in Table 4. Codeine phosphate (**1**), dextromethorphan (**2a**), and dropropizine (**5**) were used as reference antitussive drugs.

The first class of compounds which showed interesting antitussive properties was that of the 2-[α-(acetylthio)-acetyl]-1,3-thiazolidines illustrated in Scheme 4. The antitussive activity appeared only in N-acylated thiazolidines, and one of the most interesting compounds of the series was **18a:** ED_{50}(chem cough) = 26 mg/kg and ED_{50}(elec cough) = 17 mg/kg. The introduction of 3-acyl residues including basic or oxygenated groups (**22–24**; Scheme 6), so commonly present in structures

Scheme 3[a]



compd	R^1	X	R^3	compd	R^1	X	R^3
12, 13a		O		**14f**	2-OH	O	H
12b, 13b		CH_2		**14g**	2-OH	CH_2	H
14a	2-OCH_3	O	H	**14h**	2-OCH_3	O	COOEt
14b	4-OCH_3	O	H	**14i**	2-OH	O	COOH
14c	2-CH_3	O	H	**14j**	2-OH	CH_2	COOH
14d	4-$COOCH_3$	O	H	**14k**	2-OH	CH_2	COOEt
14e	2-OCH_3	S	H	**14l**	2-OCH_3	O	COOH

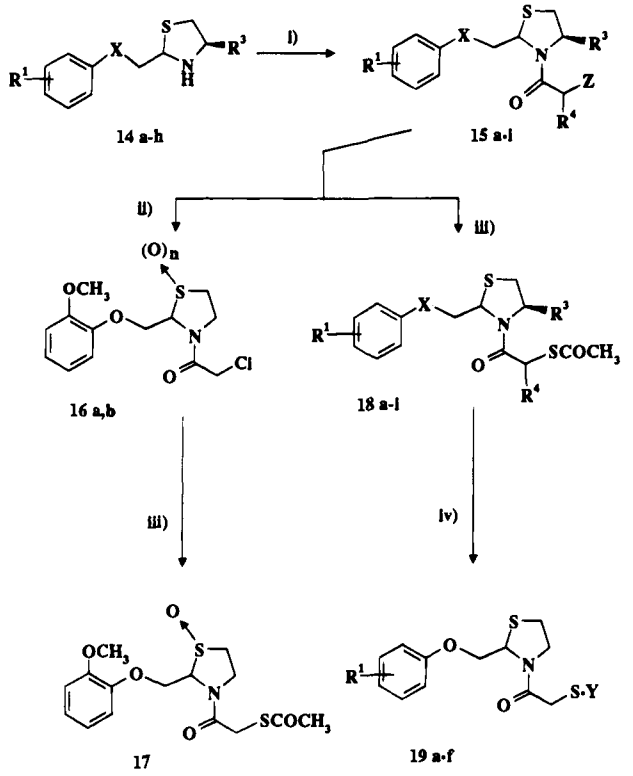
[a] (i) DIBAH, toluene, −78 °C, or (*t*-BuO)$_3$LiAlH, THF, 0 °C; (ii) $R^3CH(NH_2)CH_2SH$·HCl, AcOK, H_2O, EtOH, rt.

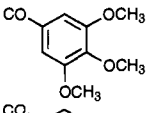
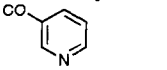
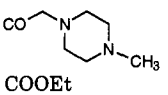
of known antitussive agents,[2,15] lowered the activity of **18a** and slightly increased the toxicity (**22a,c,d**). Among the group of imidazole derivatives (**23a−f**), the change of aromatic substituent did not improve pharmacological effectiveness. In addition, the substitution in this series of the oxygen bridge connecting aromatic and thiazolidinic rings with a sulfur atom induced a complete loss of activity (**22f, 23e**). No interesting activity was found by introducing polyoxygenated chains (**24**). In order to evaluate the importance of the different chemical functionalities present in the molecular structure of compound **18a**, some modifications were introduced. These concerned the aromatic substituent (**18e,f,i**), the X bridge (O or CH_2) connecting the aromatic and thiazolidinic rings (**18f,g**), the acidic residues of the thioester (**19c−f**), the introduction of a carboxylic group on the thiazolidinic ring (**18b**), and the alkylation of the 3-acyl substituent (**18c**). However many of these showed decreased activity. In general, 2- or 4-methoxy groups in the hydrophobic aromatic region of the molecule give rise to comparable activity (**18a** and **23a** versus **18d** and **23b**); a free phenolic group is partially effective (**18f,g, 23f**), whereas 2-methyl (**18e**) and 4-carboxy (**23d**) abolish antitussive properties.

Metabolic studies performed on **18a**[16] brought about a decisive change in both the design and final configuration of this new class of antitussive drugs. It was found that **18a** is rapidly and completely metabolized by rats to give derivatives which are predominantly eliminated by urinary excretion. Compared with **18a**, its main metabolites, **20a−c**, like the disulfide **19b**, possess at least comparable antitussive properties. Among the main metabolites, whose structures were confirmed by independent systhesis, it was interesting to observe the different pharmacological effects generated by oxidation of sulfur atoms when located in the heterocyclic ring or in the 3-acyl side chain. The oxidation of the thiazolidine ring produces a drastic reduction of the activity, whereas that of the sulfide in the lateral chain can be tolerated (compare **18a** with **17** and **20c** with **21a** in electric cough). The multistep metabolic pathway of **18a** and the experimental evidence that its metabolite **20c**, a mixture of two diastereoisomers, still retained antitussive activity caused us to evaluate the effect of simpler isosteric substituents, devoid of chirality. At first we changed the chiral sulfinyl group of **20c** with an achiral isoelectronic carbonyl group. This operation led to compound **25e** which showed only a slight decrease of potency. This renewed our interest in investigating which 3-acyl substituent would maximize the activity. Thus several acyl residues containing an alkyl or alkenyl group, carboxy esters, or amides (Schemes 7−9) were examined. Among the simplest acyl groups, the 3-acetyl derivative (**25a**) proved more toxic than **20c** whereas 3-pivalyl (**25b**) had only a low potency. No improvement was found with the alkenyl **25c,d**. The acylation of the thiazolidine ring with α,ω-bicarboxylic acids resulted in impressive and unexpected findings: although the ethyloxalyl (**26a**) and ethylsuccinyl (**26b**) amides had very poor antitussive properties, the malonyl moiety satisfied our purposes. Compound **7** (moguisteine) showed good antitussive activity [ED_{50}(chem cough) = 21 mg/kg and ED_{50}(elect cough) = 11 mg/kg], comparable with that of compounds **20c** and **18a**. Similar activity was seen in the phenol derivative **26c**, while a reduced antitussive effect was observed for the 3-oxohexanoyl derivative **25f**. Moguisteine (**7**) is rapidly metabolized in animals and humans[23] to the corresponding carboxylic acid **27a** and partially oxidized to give the mixture of diastereoisomeric sulfoxides **27c**. Only in the rat were small amounts of compound **27d**, the phenolic derivative of **27a**, detectable. All of these carboxylic acids showed similar activity in the chemical model for cough, whereas no pharmacological effect was observed in the electrical stimulation test for **27a**. Acceptable activity was detected also for compound **29**, the 2,2-dimethylmalonic derivative of **7**, although the corresponding acid **31** showed a lower activity. In contrast to the thiazolidine series of **18a**, for the malonamide congeners, the first S-oxidation of the heterocyclic ring (**28a**) does not significantly compromise the antitussive property of **7** but the sulfonyl derivative **28b** was found to be considerably less active. Neutral and basic malonodiamides were also investigated (Scheme 9) with the aim of slowing down the metabolic transformation. Interesting activity was observed in this series even if it did not result in a compound more active than **7** in both cough tests. The simplest amide, **32a**, showed a good ED_{50} value in the chemical test but considerably lower activity in the electric test, whereas the (*N,N*-diethylamino)ethylamide **32b** was quite toxic. Other basic amides showed better results. Among these compounds, **32c,g** showed the best antitussive effects even if they appeared less safe than **7**.

Bulky lipophilic benzyl or benzhydryl groups in the piperazine residue (**32d,h,i**) reduce the activity, whereas the picolylamine isomers of **32g** have a pharmacological profile similar to that of the parent compounds (**32e,f**). The antitussive profiles of pyrrolidines **39a,b** and **37a,b**,

Scheme 4[a]

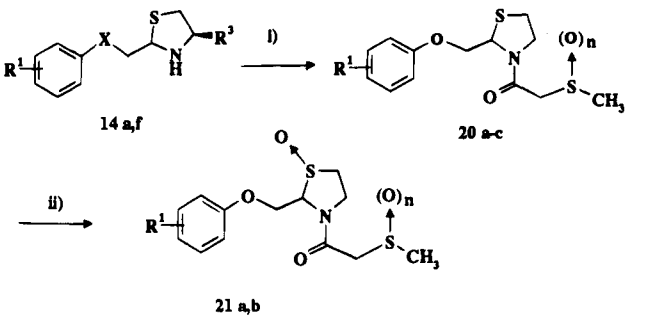


compd	R^1	X	R^3	R^4	Z	n	Y
15a	2-OCH_3	O	H	H	Cl		
15b	4-OCH_3	O	H	H	Cl		
15c	2-CH_3	O	H	H	Cl		
15d	4-$COOCH_3$	O	H	H	Cl		
15e	2-OCH_3	S	H	H	Cl		
15f	2-OH	O	H	H	Cl		
15g	2-OH	CH_2	H	H	Cl		
15h	2-OCH_3	O	COOEt	H	Cl		
15i	2-$OCOCH_2Cl$	O	H	H	Cl		
15j	2-OCH_3	O	H	CH_3	Br		
15k	2-OCH_3	O	H	H	Br		
15l	2-OCH_3	O	H	H	I		
16a						1	
16b						2	
18a	2-OCH_3	O	H	H			
18b	2-OCH_3	O	COOEt	H			
18c	2-OCH_3	O	H	CH_3			
18d	4-OCH_3	O	H	H			
18e	2-CH_3	O	H	H			
18f	2-OH	O	H	H			
18g	2-OH	CH_2	H	H			
18h	2-$OCOCH_2SAc$	CH_2	H	H			
18i	2-$OCOCH_2SAc$	O	H	H			
19a	2-OCH_3						H
19b	2-OCH_3						(single bond)$_2$
19c	2-OCH_3						
19d	2-OCH_3						
19e	2-OCH_3						
19f	2-OCH_3						COOEt

[a] (i) $R^4CHZCOCl$, Et_3N, acetone or CH_2Cl_2, 0–5 °C, or $KHCO_3$, EtOAc, H_2O, 0 °C to rt, or 1. $R^4CHZCOOH$, $(CH_3)_3CCOCl$, TEA, THF; 2. **14**, THF; (ii) $NaIO_4$, EtOH, H_2O, or MCPBA, CH_2Cl_2; (iii) CH_3COSK, acetone, rt; (iv) 1. NH_4OH, DME; 2. DMSO, Δ, or YCl, Et_3N, CH_2Cl_2, 0 °C to rt.

isosteric carba analogues of compounds **18a** and moguisteine, are only slightly modified, which indicates that the presence of a sulfur atom in the heterocyclic five-membered ring does not seem to be an essential requirement for the pharmacological activity. No difference was recorded between *R* and *S* enantiomers.

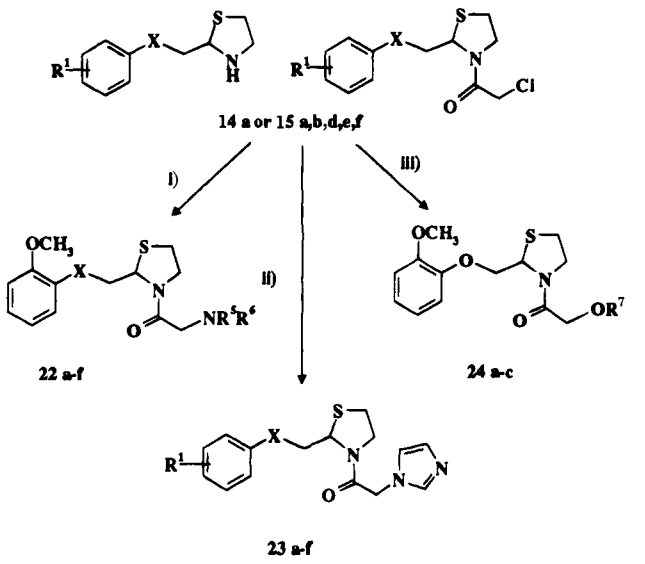
Scheme 5[a]

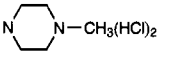
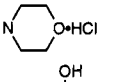
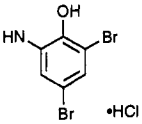
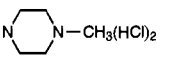


compd	R^1	n
20a	2-OCH_3	0
20b	2-OH	0
20c	2-OCH_3	1
21a	2-OCH_3	1
21b	2-OCH_3	2

[a] (i) CH_3SCH_2COOH or $CH_3S(O)CH_2COOH$, DCC, EtOAc or DME, rt; (ii) $NaIO_4$, EtOH, H_2O, or MCPBA, CH_2Cl_2.

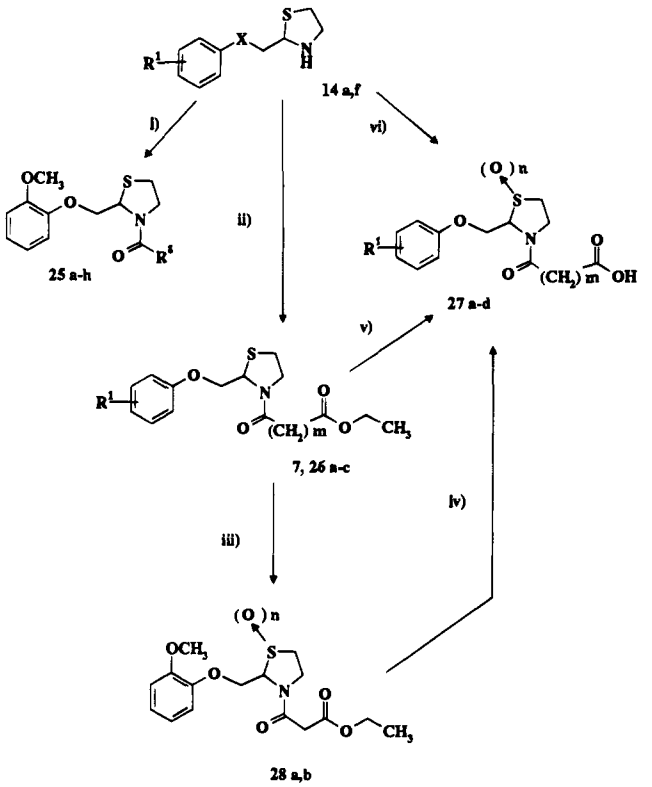
Scheme 6[a]

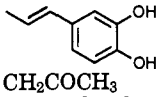


compd	R^1	X	compd	X	NR^5R^6	R^7
14a, 15a	2-OCH_3	O	**22a**	O	NH_2·HCl	
14b, 15b	4-CH_3	O	**22b**	O	$NHCOCH_3$	
14d, 15d	4-$COOCH_3$	O	**22c**	O		
14e, 15e	2-OCH_3	S	**22d**	O		
14f, 15f	2-OH	O	**22e**	O		
23a	2-OCH_3	O	**22f**	S		
23b	4-OCH_3	O	**24a**			$COCH_3$
23c	4-$COOCH_3$	O	**24b**			CH_3
23d	4-COOH	O	**24c**			CH_2CH_2-OCH_2CH_3
23e	2-OCH_3	S				
23f	2-OH	O				

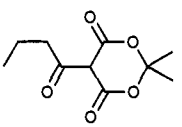
[a] (i) 1. **14a**, $OCHNHCH_2COOH$ or $CH_3CONHCH_2COOH$, DCC, DMF, rt; 2. MeOH, HCl(g), rt; or 1. **15**, R^5R^6NH, K_2CO_3, CH_3CN, Δ; (ii) 1. imidazole, *t*-BuOK, *t*-BuOH; 2. **15**, Δ; 3. **23c**, KOH, H_2O, EtOH, Δ; or 1. **15f**, DHP, PTSA, 15 °C; 2. imidazole, *t*-BuOK, *t*-BuOH, Δ; 3. HCl(g), MeOH, 15 °C; (iii) R^7OCH_2COCl, Et_3N, CH_2Cl_2, 0 °C to rt; or 1. R^7OH, NaH, 5 °C, **15a**, THF, 5 °C to rt.

Scheme 7[a]



compd	R^8	compd	R^1	m	n
25a	CH_3	**7**	2-OCH_3	1	
25b	$C(CH_3)_3$	**26a**	2-OCH_3	0	
25c	C_2H_3	**26b**	2-OCH_3	2	
25d		**26c**	2-OH	1	
25e	CH_2COCH_3	**27a**	2-OCH_3	1	0
25f	$CH_2COCH_2CH_2CH_3$	**27b**	2-OCH_3	2	0
25g	CH_2COOCH_3	**27c**	2-OCH_3	1	1
25h	$CH_2COOCH(CH_3)_2$	**27d**	2-OH	1	0
		28a			1
		28b			2

[a] (i) R^8COCl, Et_3N, CH_2Cl_2, 0 °C to rt, or



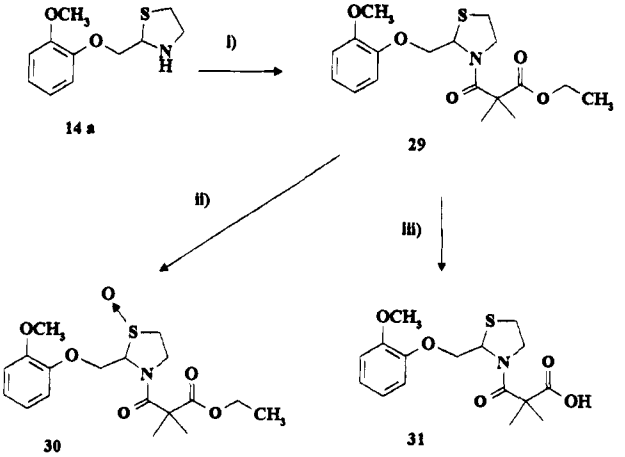
EtOAc, Δ, or R^8COOH, DCC, CH_2Cl_2, 0 °C to rt, or diketene, acetone, rt; (ii) $EtOCO(CH_2)_mCOCl$, $KHCO_3$, H_2O, EtOAc or toluene, 0 °C to rt; (iii) MCPBA, CH_2Cl_2, 0 °C or rt; (iv) 1. NaOH (0.25 N), 0 °C; 2. HCl (2 N); (v) 1. NaOH, EtOH; 2. H_2SO_4, rt; 3. **27a**, MCPBA, CH_2Cl_2, 5–10 °C; (vi) succinic anhydride, toluene, cat. DMAP, Δ.

Nevertheless, in spite of their LD_{50} > 1000 mg/kg (po; mice), a marked hypokinesia, never observed with thiazolidine compounds, was detected in the pyrrolidine series, suggesting a potential central sedative effect.

Conclusion

The syntheses and the pharmacological evaluation of a new series of antitussive 2-substituted-3-acyl-1,3-thiazolidines are discussed. Compound **7** (moguisteine) is one of the most potent and safe compounds, whose activity is comparable with that of codeine (**1**) and dextromethorphan (**2a**) but higher than that of dropropizine (**5**). It was selected for development and submitted to a profound pharmacological, toxicological, and clinical evaluation.[17] When tested in another experimental model of cough (guinea pig), the antitussive profile of moguisteine (**7**) was further confirmed. This happened either in the model of cough induced by mechanical stimulation of the trachea[18] [ED_{50} = 23 mg/kg po (12.3–33.69); codeine: ED_{50} = 26.4 mg/kg po (18.6–34.1)] or in the cough induced by capsaicin aerosol[19] [ED_{50} = 19 mg/kg po (12.1–26.5); codeine: ED_{50} = 15.2 mg/kg po (6.2–35.8)]. A thorough inves-

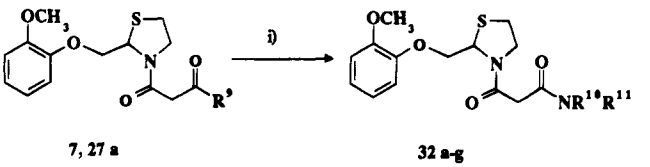
Scheme 8[a]

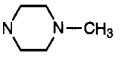
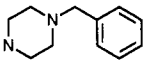
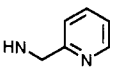
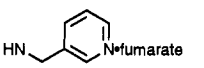
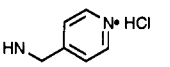
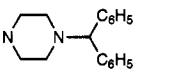
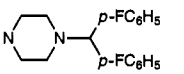


compd	R^1	X
14a	2-OCH_3	O
14b	4-OCH_3	O
14c	2-CH_3	O
14d	4-$COOCH_3$	O
14e	2-OCH_3	O
14f	2-OH	O
14g	2-OH	CH_2

[a] (i) $EtOCOC(CH_3)_2COCl$, $KHCO_3$, H_2O, EtOAc or toluene, 0 °C to rt; (ii) MCPBA, CH_2Cl_2, 0 °C or rt; (iii) (1) NaOH (1 N), EtOH, 8 h, 40 °C; (2) H_2SO_4.

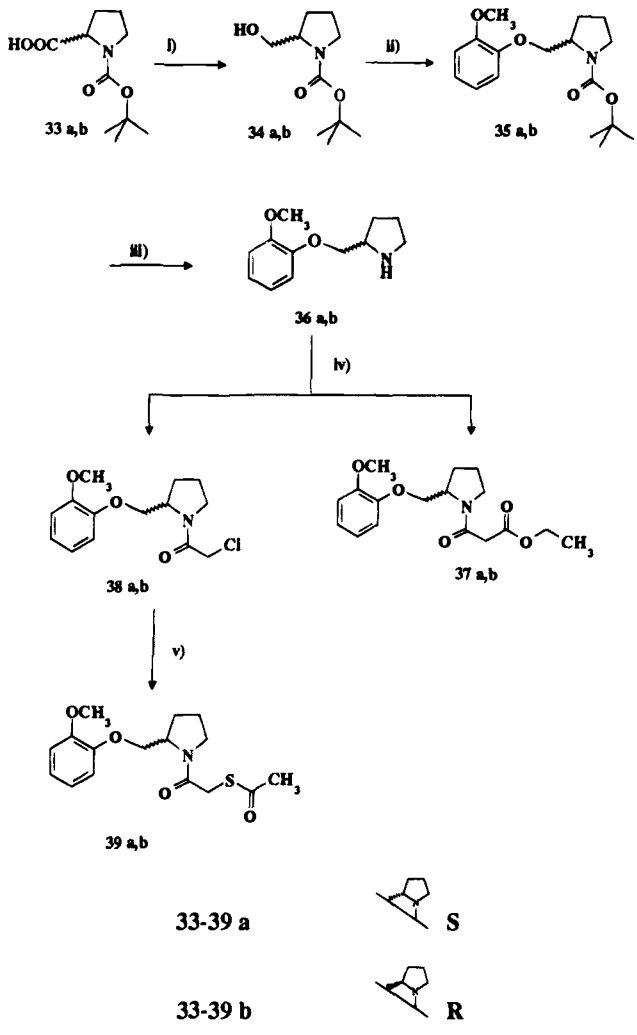
Scheme 9[a]



compd	R^9	$NR^{10}R^{11}$
7	OEt	
27a	OH	
32a		$NHCH_3$
32b		$NHCH_2CH_2N(CH_2CH_3)_2$
32c		
32d		
32e		
32f		
32g		
32h		
32i		

[a] (i) **7**, $R^{10}R^{11}NH$, EtOH, Δ; or **1**. **27a**, *N*-OH-succinimide, MEI, THF, 0–5 °C, or CDI, THF, 0–5 °C; **2**. $R^{10}R^{11}NH$, toluene or THF, Δ, or **27a**, $R^{10}R^{11}NH$, DCC, CH_2Cl_2, 0 °C to rt; **3**. HCl(g), Et_2O.

Scheme 10[a]



[a] (i) 1. EtOCOCl, Et_3N, THF, −5−0 °C; **2**. $NaBH_4$, THF, rt; (ii) 1. TsCl, pyridine, CH_2Cl_2, rt; **2**. guaiacol, DMSO, NaH, 80 °C; (iii) CF_3COOH, CH_2Cl_2, rt; (iv) $ClCH_2COCl$, TEA, acetone or $EtOCOCH_2COCl$, $KHCO_3$, H_2O, EtOAc, rt; (v) CH_3COSK, acetone, rt.

tigation demonstrated that moguisteine does not act on the cough center and is devoid of CNS effects. Actually, after intracerebroventricular injection, it did not display antitussive properties and distribution studies with labeled compound showed that it does not cross the blood brain barrier. Moreover it does not interact with opiate receptors but possibly acts on the irritant receptors in the tracheobronchial tree.[20] In addition it showed remarkable airway anti-inflammatory properties.[20,21] No toxic effects were detected in the preclinical toxicological evaluation of the substance.[22] Extensive pharmacokinetics and metabolic studies were performed,[23] and clinical trials proved moguisteine to be effective as an antitussive agent in humans.[24]

Experimental Section

General. Melting points were determined with a Buchi 535 instrument in open capillary tubes, and the data are uncorrected. Infrared spectra (IR) were recorded on a Perkin Elmer 297 infrared spectrophotometer. ^1H NMR spectra were recorded on a Varian 60 MHz or a Bruker 200 MHz spectrometer, and chemical shifts are reported in parts per million (δ) downfield from the internal standard Me_4Si. Optical rotations were registered with a Perkin Elmer 241 polarimeter. Microanalyses were carried out by Redox snc, Cologno Monzese (MI), Italy. Analyses are indicated by symbols of the elements, and the analytical values are within ±0.4% of the theoretical value. For thin layer chromatography (TLC), precoated Kieselgel 60 F254 (Merck 5554 or 5719) layers were applied using the following mixtures of eluents: A, EtOAc/hexane (1:1); B, EtOAc; C, $CHCl_3$/hexane (8:2), D, CH_2Cl_2; E, $CHCl_3$/acetone/MeOH/TEA (3:4:1:2); F, EtOAc/MeOH (8:2); G, CH_2Cl_2/MeOH (10:2); H, EtOAc/$CHCl_3$ (1:1); I, EtOAc/MeOH (20:1); L, *i*-Pr_2O/EtOH (4:1); M, $CHCl_3$/MeOH/AcOH (8:2:0.3); N, EtOAc/MeOH/NH_4OH (10:2:0.5). For column chromatography, Kieselgel 60 adsorbent (70−230 mesh) was used. The HPLC analyses were carried out with a Perkin Elmer analytical instrument composed of a Rheodine 7125 injection valve, a binary LC pump 250, an LC 95 UV−vis spectrometer, and a Spectra Physics integrator. Mass spectral analyses were conducted on a Finnigan MAT 312 mass spectrometer. All compounds displayed NMR spectra fully in accord with their proposed structures. The procedures presented below are representative of all the syntheses used.

Cough Induced by Citric Acid Aerosol in the Guinea Pig. Male guinea pigs (350−400 g) were put into a Perspex box (20 × 12 × 14 cm) and exposed to a 7.5% citric acid aerosol for 5 min;[13] during this period, the number of coughs (14−22) was recorded and considered as a basal value. Twenty-four hours later, after overnight fasting with water ad libitum, guinea pigs (6−8 animals/dose) were randomly treated by gavage with test compounds dissolved in water or suspended in 0.5% methyl cellulose solution (2 mL/kg) 1 h before reexposure to the citric acid aerosol. Antitussive activity was evaluated for each guinea pig as the reduction of the number of coughs in comparison with the control basal value.

Cough Induced by Electrical Stimulation of the Guinea Pig Trachea. Under general anesthesia (ketamine, 10 mg/kg im, and xylazine, 3 mg/kg im), an isolated electrode (Awg 32-Habia) was wrapped around the trachea at about 1.5 cm above bifurcation.[14] The indifferent electrode (a stainless steel clip) was fixed on the dorsal skin. Forty-eight hours from the surgical implant, the fasted-overnight guinea pigs, with water ad libitum, were assessed for tussive threshold to electrical stimulation by the determination of the minimum voltage (range of 4−10 V) required to elicit cough with the following stimulus conditions: square wave pulses of 0.6 ms, 40 Hz, 10 s of train duration (Stimulator S; Ugo Sachs Elektronik, Germany). The number of coughs (7−12) during the electrical stimulation was recorded for each guinea pig and considered as a basal value. The guinea pigs were then randomized into different experimental groups (6−8 animals/dose) and treated by gavage with compounds dissolved in water or suspended in a 0.5% solution of methyl cellulose (2 mL/kg). Antitussive activity was evaluated for each guinea pig as the reduction of the number of coughs in comparison with the control basal value.

Acute Toxicity. Groups of six Swiss mice of both sexes were treated by gavage with test compounds at different doses up to 1000 mg/kg. Compounds were dissolved in water or suspended in 0.5% carboxymethyl cellulose solution (volume of administration: 10 mL/kg). Animals were observed during 1−7 days, and the number of deaths was recorded.

Statistical Analysis. ED_{50} values, corresponding to the dose that reduces the number of coughs by 50%, were determined according to Cochran and Snedecor.[25] LD_{50} values were determined by logit transformation.[26]

2-[(2-Methoxyphenoxy)methyl]-1,3-thiazolidine (14a; Method B). A mixture of guaiacol (**8a**; 1 kg, 8.05 mol), 2-bromoacetaldehyde diethyl acetal (1.82 kg, 9.23 mol), and potassium carbonate (1.22 kg, 8.83 mol) in *N*-methylpyrrolidone (NMP; 5 L) was heated at 150 °C for 5 h. The reaction mixture was cooled to room temperature, and precipitated inorganic salts were filtered off and washed with NMP. The organic solution was concentrated in vacuo, and the residue was distilled (115 °C, 2 Torr) to yield 1.7 kg (88%) of 2-(2-methoxyphenoxy)acetaldehyde diethyl acetal (**11a**) as a colorless oil: TLC (eluent A) R_f 0.8; ^1H NMR ($CDCl_3$) δ 1.5 (t, 6H, J = 7 Hz), 3.6−3.8 (m, 4H), 3.85 (s, 3H), 4.1 (d, 2H, J = 5 Hz), 4.9 (t, 1H, J = 5 Hz), 6.8−7 (br s, 4H); ^{13}C NMR ($CDCl_3$) δ 10.51 (CH_3), 55.83 (OCH_3), 62.62 (CH_2O), 69.91 ($ArCH_2O$), 100.62 (CHNS), 112, 114.32, 120.78, 121.59 (CHaro), 148.2, 149.64 (COaro); IR ($CHCl_3$) 1595, 1507, 1456, 1256, 1229, 1127, 1074, 744 cm^{-1}.

A solution of **11a** (570 g, 2.37 mol) and cysteamine hydrochloride (299 g, 2.63 mol) in a mixture of ethanol (1.5 L) and water (0.5 L) was treated with 37%, w/w, HCl (12 g, 0.12 mol) and refluxed for 4 h. After cooling to 30 °C, the reaction mixture was slowly added to a cooled 0.5 N NaOH solution (6 L). A yellowish precipitate was collected by filtration and recrystallized from EtOH/H_2O (1:2) to yield 2-[(2-methoxyphenoxy)methyl]-1,3-thiazolidine (**14a**) as 406 g (76%) of a fluffy white solid. Compound **14a** can be also crystallized from EtOAc or *i*-PrOH: mp 66–67 °C; TLC (eluent B) R_f 0.5; ^{1}H NMR ($CDCl_3$) δ 2.2 (s, 1NH), 2.8–3.1 (m, 2H), 3.3 (m, 2H), 3.85 (s, 3H), 4–4.15 (m, 2H), 5.0 (dd, 1H), 6.8–7 (br s, 4H); ^{13}C NMR ($CDCl_3$) δ 35.17 (CH_2S), 51.46 (CH_2N), 55.8 (OCH_3), 69.5 (CHNS), 71.14 (CH_2O), 100.62 (CH), 111.96, 114.74, 120.71, 121.89 (CHaro), 147.9, 149.79 (COaro); IR (KBr) 3319, 1600, 1510, 1420, 1260, 1220, 1120, 1020, 745 cm^{-1}.

2-[(4-Methoxyphenoxy)methyl]-1,3-thiazolidine (14b; Method A). Under a nitrogen atmosphere, 4-methoxyphenol (**8b**; 50 g, 0.4 mol) was added portionwise to a solution of sodium ethoxide in EtOH previously prepared from sodium (9.73 g, 0.42 mol) and absolute EtOH (400 mL). After 30 min at room temperature, 3-chloro-1,2-propanediol (36.8 mL, 0.44 mol) was added dropwise to the reaction mixture which was refluxed for 4 h and stirred overnight at room temperature. The reaction mixture was then filtered and the solvent removed in vacuo. The crude residue was dissolved in EtOAc, washed with water, dried (sodium sulfate), and concentrated to dryness. The residual oil was crystallized from ethyl ether to yield 68 g (86%) of 3-(4-methoxyphenoxy)-1,2-propanediol (**9b**) as a white solid: mp 54–56 °C; TLC (eluent C) R_f 0.5; ^{1}H NMR ($CDCl_3$/DMSO-d_6) δ 3.6 (m 1H), 3.7 (s, 3H), 3.85 (br s, 4H), 6.8–7 (br s, 4H), 7.7 (s, 2OH).

To a solution of sodium periodate (44.8 g, 0.21 mol) in water (400 mL) cooled to 0–5 °C was added compound **9b** (40 g, 0.21 mol) portionwise, under vigorous stirring, in about 90 min, keeping the temperature under 10 °C. After 1 h at 10 °C, any possible excess of $NaIO_4$ was decomposed with ethylene glycol (0.6 g), and 30 min later at room temperature, the reaction mixture was treated with sodium sulfate (20 g) and extracted with EtOAc (3 × 200 mL). Combined extracts, containing 2-(4-methoxyphenoxy)acetaldehyde (**11b**), were washed with brine (2 × 100 mL) and treated with a solution of cysteamine hydrochloride (23.8 g, 0.21 mol) in water (100 mL) and with $KHCO_3$ (21 g, 0.21 mol) in four portions. After 4 h at room temperature, the organic layer was separated, washed with water, and dried (sodium sulfate). The solvent was partially removed under reduced pressure until a volume of about 100 mL. After dilution with hexane (100 mL), 34.5 g (73%) of 2-[(4-methoxyphenoxy)methyl]-1,3-thiazolidine (**14b**) was recovered by filtration: mp 57–59 °C; TLC (eluent B) R_f 0.5; ^{1}H NMR ($CDCl_3$) δ 2.2 (s, NH), 2.8–3.1 (m, 2H), 3.3 (t, 2H, J = 6 Hz), 3.6 (m, 1H), 3.75 (s, 3H), 3.9–4.1 (m, 2H), 4.9 (dd, 1H, X portion of ABX system), 6.8–7 (m, 4H); IR (KBr) 3250, 1600, 1510, 1460, 1230, 1020, 820, 780 cm^{-1}.

2-[(4-Methoxythiophenoxy)methyl]-1,3-thiazolidine (14e; Method B). According to the procedure described for the preparation of **14a** but using 2-methoxythiophenol (14 g, 0.1 mol) as starting material, 2-(2-methoxythiophenoxy)-acetaldehyde diethyl acetal (**11e**) was obtained in quantitative yield, and without additional purification, it was used to prepare 2-[(4-methoxythiophenoxy)methyl]-1,3-thiazolidine (**14e**) which was recrystallized from *i*-PrOH to yield 18.1 g (75%) of a white powder: mp 99–100 °C; TLC (eluent B) R_f 0.55; ^{1}H NMR ($CDCl_3$) δ 2.2 (s, NH), 2.85 (m, 2H), 3.0–3.3 (m, 4H), 3.8 (s, 3H), 4.65 (t, 1H, J = 6 Hz), 6.7–7.4 (m, 4H).

2-[(2-Hydroxyphenoxy)methyl]-1,3-thiazolidine (14f; Method C). Chloroacetyl chloride (88 mL, 1.1 mol) was added dropwise to a stirred solution of catechol (110 g, 1 mol) and TEA (280 mL, 2 mol) in CH_2Cl_2 (1 L) cooled to 0–5 °C. The reaction mixture was refluxed for 4 h and then poured into water. The organic layer was washed with water (2 × 200 mL), dried (sodium sulfate), and decolored (charcoal). The solvent was removed in vacuo and the residual oil crystallized from ethyl ether to give 105 g (70%) of 1,4-benzodioxan-2-one (**12a**): mp 53–55 °C; TLC (eluent C) R_f 0.75; ^{1}H NMR ($CDCl_3$) δ 4.55 (s, 2H), 7 (s, 4H).

Under a nitrogen atmosphere, a solution of diisobutylaluminum hydride (DIBAL-H; 1.2 M) in toluene (401 mL, 0.48 mol) was added dropwise (1 h) to a solution of 1,4-benzodioxan-2-one (**12a**; 67 g, 0.45 mol) in dry toluene (750 mL) cooled to −70 °C. After about 1 h (TLC: eluent A, R_f 0.5) at the same temperature, a solution of 2-propanol in toluene (2 M, 470 mL) was dropped in the reaction mixture, keeping the temperature under −60 °C. Then the temperature was allowed to rise to 0 °C by adding an aqueous solution of NaH_2PO_4 (30%, 90 mL) and sodium sulfate (150 g). The reaction mixture was stirred overnight at room temperature. Salts were filtered off and washed with EtOAc (300 mL) and CH_2Cl_2 (300 mL). Combined filtered solution and washings were concentrated to dryness to yield 64.5 g (95%) of 2-hydroxy-1,4-benzodioxan (**13a**) as a pale yellow oil which was directly used in the next step: ^{1}H NMR ($CDCl_3$) δ 3.9 (d, 2H, J = 2 Hz), 5.3 (t, 1H, J = 2 Hz), 6.7 (s, 4H).

Compound **13a** (26.5 g, 0.17 mol) dissolved in EtOH (130 mL) was treated with a solution of cysteamine hydrochloride (20.5 g, 0.18 mol) in water (26.5 mL). Then potassium acetate (18 g, 0.18 mol) was added in one portion to the stirred reaction mixture. After 2 h at room temperature, the reaction mixture was poured onto a saturated solution of $NaHCO_3$ (340 mL), and the resultant white precipitates were collected by filtration, washed with water and ethanol, and recrystallized from EtOH/water (1:2) to yield 27.3 g (76%) of 2-[(2-hydroxyphenoxy)methyl]-1,3-thiazolidine (**14f**): mp 76–78 °C; TLC (eluent A) R_f 0.25; ^{1}H NMR ($CDCl_3$) δ 2.7–3.6 (m, 4H), 3.7–4.2 (m, 2H, AB portion of ABX system, J_{AB} = 16 Hz, J_{AX} = 0 Hz, J_{BX} = 7 Hz), 4.7–5.0 (dd, 1H, X portion of ABX system), 5.0–6.0 (br s, OH + NH), 6.7–7.0 (m, 4H).

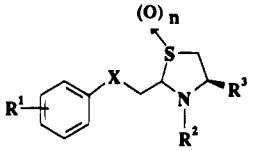
2-[(2-Hydroxyphenyl)ethyl]-1,3-thiazolidine (14g; Method C). Under a nitrogen atmosphere, dihydrocoumarin (**12b**; 240 g, 1.62 mol) in dry THF (molecular sieves, 3 Å, 0.3 L) was added dropwise to a stirred slurry of lithium tri-*tert*-butoxyaluminohydride (commercial grade or prepared according to Brown's procedure;[27] 422 g, 1.62 mol) in THF (2.8 L) cooled to 0–5 °C. The addition rate was regulated in order not to overcome 5 °C. The reaction mixture was further stirred for 90 min at 0 °C, and 8 N H_2SO_4 (400 mL) was cautiously dropped into it without exceeding 5 °C. After about 1 h at room temperature, the resultant white precipitates were filtered off and washed with THF (0.3 L). Combined filtered solution and washings were concentrated to dryness to yield 219 g (90%) of 2-hydroxy-2*H*-3,4-dihydro-1-benzopyran (**13b**) as a pale yellow oil which was directly used in the following step: TLC (eluent D) R_f 0.3; ^{1}H NMR ($CDCl_3$) δ 1.7–2.1 (m, 2H), 2.6–3 (m, 2H) 3.7 (m, OH), 5.5 (t, 1H, J = 3 Hz), 6.6–7.1 (m, 4H).

According to the procedure for the preparation of compound **14a**, 2-hydroxy-2*H*-3,4-dihydro-1-benzopyran (**13b**; 30 g, 0.2 mol) afforded 2-[(2-hydroxyphenyl)ethyl]-1,3-thiazolidine (**14g**) which was crystallized from *i*-PrOH to yield 36 g (86%) of a white solid: mp 99–100 °C; TLC (eluent B) R_f 0.45; ^{1}H NMR ($CDCl_3$) δ 1.8–2.3 (m, 2H), 2.5–3.2 (m, 5H), 3.3–3.7 (m, 1H), 4.2 (dd, 1H), 5.0–6.0 (br s, OH + NH), 6.7–7.2 (m, 4H).

Ethyl 2-[(2-Methoxyphenoxy)methyl]-1,3-thiazolidine-4-carboxylate (14h; Method A). To a solution of sodium periodate (101 g, 0.47 mol) in water (1000 mL) cooled to 0–5 °C was added 3-(4-methoxyphenoxy)-1,2-propanediol (**9a**, guaiphenesin; 89.2 g, 0.45 mol) portionwise, under vigorous stirring, in about 90 min and keeping the temperature under 10 °C. After 1 h at 10 °C, excess $NaIO_4$ was decomposed with ethylene glycol (1.5 g). Thirty minutes later at room temperature, the reaction mixture was filtered and collected precipitates were suspended again in cool demineralized water (250 mL), stirred for a further 30 min, and filtered again to give 85 g of a wet solid which was air dried affording a 95% yield of 2-(2-methoxyphenoxy)acetaldehyde (**10a**) which was directly used in the next step without further purification: mp 57–58 °C; TLC (eluent A) R_f 0.4; ^{1}H NMR ($CDCl_3$) δ 3.85 (s, 3H), 4.5 (s, 2H), 6.7–7.1 (m, 5H), 9.65 (s, 1H).

Compound **10a** (20 g, 0.12 mol) was dissolved in EtOH (200 mL) and treated with L-cysteine ethyl ester hydrochloride (22.3 g, 0.12 mol) and a solution of potassium acetate (11.8 g, 0.12 mol) in demineralized water (30 mL) at room temperature. After 2 h the solvent was partially removed under vacuum

Table 4.



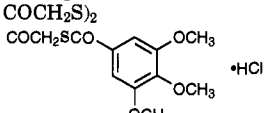
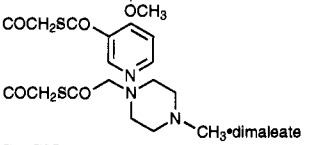
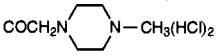
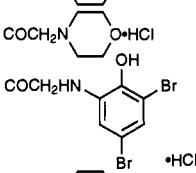
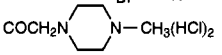
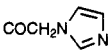
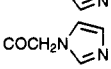
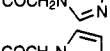
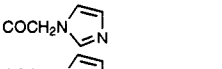
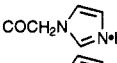
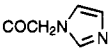
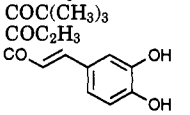
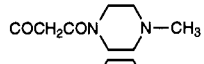
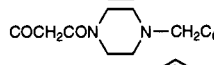
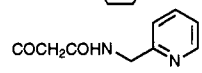
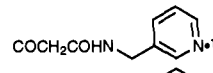
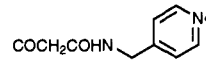
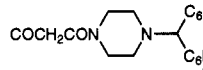
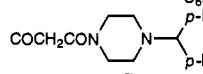
no.	R^1	X	n	R^2	R^3	irritant aerosol-induced coughing ED_{50}, % inhibn (mg/kg po), guinea pig	electrically induced coughing ED_{50}, % inhibn (mg/kg po), guinea pig	LD_{50} (mg/kg po), mice
7	2-OCH_3	O	0	$COCH_2COOCH_2CH_3$	H	21	11	>1000
14a	2-OCH_3	O	0	H	H	*b*	*a*	>1000
14f	2-OH	O	0	H	H	*b*	*a*	>1000
14h	2-OCH_3	O	0	H	COOEt	*a*	*b*	757
14i	2-OH	O	0	H	COOH	*a*	*b*	>1000
14j	2-OH	CH_2	0	H	COOH	*a*	45	>1000
17	2-OCH_3	O	1	$COCH_2SCOCH_3$	H	*a*	*b*	620
18a	2-OCH_3	O	0	$COCH_2SCOCH_3$	H	26	17	>1000
18b	2-OCH_3	O	0	$COCH_2SCOCH_3$	COOEt	*a*	*b*	672
18c	2-OCH_3	O	0	$COCH(CH_3)SCOCH_3$	H	*a*	*b*	>1000
18d	4-OCH_3	O	0	$COCH_2SCOCH_3$	H	*b*	19	>1000
18e	2-CH_3	O	0	$COCH_2SCOCH_3$	H	*a*	29 (15)	>1000
18f	2-OH	O	0	$COCH_2SCOCH_3$	H	60	*/b*	>1000
18g	2-OH	CH_2	0	$COCH_2SCOCH_3$	H	61	*b*	>1000
18h	2-$OCOCH_2SCOCH_3$	CH_2	0	$COCH_2SCOCH_3$	H	*a*	*b*	>1000
18i	2-$OCOCH_2SCOCH_3$	O	0	$COCH_2SCOCH_3$	H	*a*	*b*	>1000
19a	2-OCH_3	O	0	$COCH_2SH$	H	*a*	*b*	*b*
19b	2-OCH_3	O	0	$COCH_2S)_2$	H	*b*	18	*b*
19c	2-OCH_3	O	0		H	*a*	*b*	>1000
19d	2-OCH_3	O	0		H	*a*	*b*	>1000
19e	2-OCH_3	O	0		H	*a*	*b*	>1000
19f	2-OCH_3	O	0	$COCH_2SCOOEt$	H	*a*		*b*
20a	2-OCH_3	O	0	$COCH_2SCH_3$	H	*b*	21	*b*
20b	2-OH	O	0	$COCH_2SCH_3$	H	*b*	28	>1000
20c	2-OCH_3	O	0	$COCH_2S(O)CH_3$	H	25	10	>1000
21a	2-OCH_3	O	1	$COCH_2S(O)CH_3$	H	*b*	25 (15)	>1000
21b	2-OCH_3	O	1	$COCH_2S(O)_2CH_3$	H	*b*	28 (15)	>1000
22a	2-OCH_3	O	0	$COCH_2NH_2 \cdot HCl$	H	57	*b*	585
22b	2-OCH_3	O	0	$COCH_2NHCOCH_3$	H	40	*b*	>1000
22c	2-OCH_3	O	0		H	*b*	*a*	818
22d	2-OCH_3	O	0		H	*a*	*b*	612
22e	2-OCH_3	O	0		H	*b*	20 (15)	>1000
22f	2-OCH_3	S	0		H	*a*	*b*	*b*
23a	2-OCH_3	O	0		H	50	*b*	966
23b	4-OCH_3	O	0		H	48	*b*	>1000
23c	4-$COOCH_3$	O	0		H	62	*b*	>1000
23d	4-COOH	O	0		H	*a*	*b*	>1000
23e	2-OCH_3	S	0		H	*a*	*b*	958
23f	2-OH	O	0		H	*b*	27 (30)	*b*
24a	2-OCH_3	O	0	$COCH_2OCOCH_3$	H	*b*	25 (30)	>1000
24c	2-OCH_3	O	0	$COCH_2O(CH_2)_2OEt$	H	*a*	*b*	916
25a	2-OCH_3	O	0	$COCH_3$	H	46	*b*	552
25b	2-OCH_3	O	0	$COC(CH_3)_3$	H	*b*	24 (15)	>1000
25c	2-OCH_3	O	0	COC_2H_3	H	74	*b*	718
25d	2-OCH_3	O	0		H	*a*	*b*	>1000
25e	2-OCH_3	O	0	$COCH_2COCH_3$	H	30	26	>1000
25f	2-OCH_3	O	0	$COCH_2COCH_2CH_2CH_3$	H	42	*b*	*b*
26a	2-OCH_3	O	0	$COCOOCH_2CH_3$	H	*a*	*b*	>1000
26b	2-OCH_3	O	0	$COCH_2CH_2COOCH_2CH_3$	H	24 (30)	*b*	>1000

Table 4 (Continued)

no.	R^1	X	n	R^2	R^3	irritant aerosol-induced coughing ED_{50}, % inhibn (mg/kg po), guinea pig	electrically induced coughing ED_{50}, % inhibn (mg/kg po), guinea pig	LD_{50} (mg/kg po), mice
26c	2-OH	O	0	$COCH_2COOCH_2CH_3$	H	20	*b*	>1000
27a	2-OCH_3	O	0	$COCH_2COOH$	H	20	*a*	>1000
27c	2-OCH_3	O	1	$COCH_2COOH$	H	20	*b*	>1000
27d	2-OH	O	0	$COCH_2COOH$	H	25	*b*	>1000
28a	2-OCH_3	O	1	$COCH_2COOCH_2CH_3$	H	27	28	>1000
28b	2-OCH_3	O	2	$COCH_2COOCH_2CH_3$	H	28 (30)	*a*	>1000
29	2-OCH_3	O	0	$COC(CH_3)_2COOCH_2CH_3$	H	61 (30)	48 (30)	>1000
31	2-OCH_3	O	0	$COC(CH_3)_2COOH$	H	34 (30)	21 (30)	>1000
32a	2-OCH_3	O	0	$COCH_2CONHCH_3$	H	21	22 (30)	>1000
32b	2-OCH_3	O	0	$COCH_2CONH(CH_2)_2NEt_2$	H	56 (30)	*a*	250
32c	2-OCH_3	O	0		H	27	*b*	880
32d	2-OCH_3	O	0		H	41 (30)	*b*	681
32e	2-OCH_3	O	0		H	26	64 (15)	*b*
32f	2-OCH_3	O	0		H	57 (30)	*b*	677
32g	2-OCH_3	O	0		H	23	13	707
32h	2-OCH_3	O	0		H	66 (30)	44 (15)	>1000
32i	2-OCH_3	O	0		H	26 (30)	32 (15)	>1000
37a				$COCH_2COOC_2H_5$		48 (30)	*b*	>1000
37b				$COCH_2COOC_2H_5$		41 (30)	*b*	>1000
39a				$COCH_2SCOCH_3$		52 (30)	*b*	>1000
39b				$COCH_2SCOCH_3$		48 (30)	*b*	>1000
1, codeine phosphate						29	14	
2a, dextromethorphan						48	16	
5, dropropizine						144	32	

[a] Inhibition <20% at 30 mg/kg po, guinea pig. [b] Not tested.

and the residue was poured into 5% $NaHCO_3$ and extracted with EtOAc (2 × 200 mL). Combined extracts were washed with water, dried (sodium sulfate), and concentrated to dryness. The oily residue was crystallized from Et_2O to yield 27.8 g (78%) of ethyl 2-[(2-methoxyphenoxy)methyl]-1,3-thiazolidine-4-carboxylate (**14h**): mp 53–57 °C; TLC (eluent A) R_f 0.6; ^1H NMR ($CDCl_3$) δ 1.3 (t, 3H, J = 7 Hz), 2.85 (br s, NH), 3.0–3.4 (m, 2H), 3.85 (s, 3H), 4.0–4.5 (m, 4H), 4.6 (m, 1H), 4.9 (t, 1H, J = 4 Hz), 6.9 (br s, 4H).

2-[(2-Methoxyphenoxy)methyl]-1,3-thiazolidine-4-carboxylic Acid (14l; Method A). 2-(2-Methoxyphenoxy)acetaldehyde (**10a**; 20 g. 0.12 mol) was dissolved in EtOH (250 mL) and treated with a solution of L-cysteine (14.5 g, 0.12 mol) in demineralized water (100 mL) at room temperature. After 2 h white precipitates were filtered off, washed with EtOH, and dried to yield 25 g (77%) of 2-[(2-methoxyphenoxy)methyl]-1,3-thiazolidine-4-carboxylic acid (**14l**): mp 149–150 °C; TLC (eluent E) R_f 0.5; ^1H NMR (DMSO-d_6) δ 2.5–3.3 (m, 2H), 3.7 (s, 3H), 3.7–4.0 (m, 2H), 4.1 (t, 1H, J = 4 Hz), 4.75 + 4.95 (2t, 1H), 6.9 (br s, 4H), 7–7.5 (br s, NH + COOH).

2-[(2-Methoxyphenoxy)methyl]-3-[2-(acetylthio)acetyl]-1,3-thiazolidine 1-Oxide (17). Chloroacetyl chloride (189 mL, 2.43 mol) was added dropwise to a solution of compound **14a** (463 g, 2.05 mol) and triethylamine (342 mL, 2.46 mol) in acetone (2400 mL) cooled at 0–5 °C. After 1 h at the same temperature, the reaction mixture was cautiously diluted with water (2500 mL). This induced the crystallization of 2-[(2-methoxyphenoxy)methyl]-3-(2-chloroacetyl)-1,3-thiazolidine (**15a**) which was crystallized from *i*-PrOH to yield 530 g (86%) of a white solid: mp 83–85 °C; TLC (eluent H) R_f 0.85; ^1H NMR ($CDCl_3$) δ 2.9–3.3 (m, 2H), 3.8 (s, 3H), 3.6–4.1 (m, 4H), 4.6 (br s, 2H), 5.5 (br t, 1H, J = 6 Hz), 6.85 (br s, 4H); IR (KBr) 2927, 1645, 1500, 1254, 1121, 745 cm^{-1}.

To a solution of 2-[(2-methoxyphenoxy)methyl]-3-(2-chloroacetyl)-1,3-thiazolidine (**15a**; 5 g, 16.6 mmol) in CH_2Cl_2 (70 mL) cooled to 0–5 °C was dropped 3-chloroperoxybenzoic acid (85%, 3.7 g, 18.3 mmol) dissolved in CH_2Cl_2 within about 30 min. After an additional half-hour, the reaction mixture was poured into aqueous $NaHCO_3$ (5%) and the organic layer was washed with water and dried (sodium sulfate). The solvent was removed in vacuo, and the residual oil was chromatographed on silica gel using EtOAc as eluent. Fractions were monitored by TLC, and those containing mostly major product were combined and evaporated to give a crude solid (5.19 g) which was recrystallized from EtOH (20 mL) to give 4.5 g (85%) of 2-[(2-methoxyphenoxy)methyl]-3-(2-chloroacetyl)-1,3-thiazolidine 1-oxide (**16a**) as a white solid: mp 124–128 °C; TLC (eluent I) R_f 0.45; ^1H NMR ($CDCl_3$) δ 2.9–3.3 (m, 2H), 3.8 (s, 3H), 3.5–4.6 (m, 6H), 5.35 (br t, 1H), 6.85 (br s, 4H).

The following substitution reaction with potassium thioacetate was carried out as described in the preparation of compound **18a** to yield a 68% of 2-[(2-methoxyphenoxy)-methyl]-3-[2-(acetylthio)acetyl]-1,3-thiazolidine 1-oxide (**17**) after crystallization from *i*-PrOH: mp 111–114 °C; TLC (eluent I) R_f 0.4; ^1H NMR ($CDCl_3$) δ 2.35 (br s, 3H), 2.9–3.6 (m, 2H), 3.75 (s 3H), 3.6–4.6 (m, 6H), 5.3 (br t, 1H), 6.85 (br s, 4H); IR (KBr) 2927, 1680, 1630, 1490, 1244, 1220, 1060, 740 cm^{-1}.

2-[(2-Methoxyphenoxy)methyl]-3-[2-(acetylthio)acetyl]-1,3-thiazolidine (18a). Under a nitrogen atmosphere, potassium thioacetate (189 g, 1.62 mol) was added to a stirred solution of intermediate **15a** (450 g, 1.5 mol) in acetone (3000 mL) containing charcoal (65 g) and kept at room temperature. After an additional 1 h of stirring, charcoal and precipitated KCl were filtered off and the solution was diluted with demineralized water (4000 L). A pale brown solid precipitated and was filtered and washed with water. The wet crude solid was dissolved in EtOAc (1500 mL), and the solution was dried (sodium sulfate), decolored again (charcoal), concentrated to one-half of its volume, and cooled to 5–10 °C for 2 h. The crystallized product was collected by filtration and dried to yield 453 (82%) of 2-[(2-methoxyphenoxy)methyl]-3-[2-(acetylthio)acetyl]-1,3-thiazolidine (**18a**) as a white solid: mp 91–92 °C: TLC (eluent A) R_f 0.4; ^1H NMR ($CDCl_3$) δ 2.35 (br s, 3H), 2.9–3.3 (m, 2H), 3.7 (s, 3H), 3.3–4.4 (m, 6H), 5.6 (t, 1H, J = 6 Hz), 6.85 (br s, 4H); IR (KBr) 2927, 1670, 1639, 1500, 1254, 1220, 1121, 750 cm^{-1}.

Ethyl 2-[(2-Methoxyphenoxy)methyl]-3-[2-(acetylthio)acetyl]-1,3-thiazolidine-4-carboxylate (18b). Chloroacetyl chloride (3.1 mL, 4.03 mmol) in CH_2Cl_2 (10 mL) was added dropwise to a solution of compound **14h** (10 g, 3.36 mmol) and triethylamine (5.6 mL, 4.03 mmol) in CH_2Cl_2 (200 mL) cooled at 0–5 °C. After 4 h at the same temperature, the reaction mixture was cautiously poured onto 5% $NaHCO_3$ and the organic layer washed with water, dried (sodium sulfate), and concentrated to dryness. The residual oil was crystallized from Et_2O to yield 9 g (71%) of ethyl 2-[(2-methoxyphenoxy)methyl]-3-(2-chloroacetyl)-1,3-thiazolidine-4-carboxylate (**15h**) as a white solid: mp 94–96 °C; TLC (eluent A) R_f 0.75; ^{1}H NMR ($CDCl_3$) δ 0.9 (t, 3H, J = 7.5 Hz), 3.1 (d, 2H, J = 8 Hz), 3.7 (s, 3H), 3.7–4.1 (m, 4H), 4.6 (br s, 2H), 4.9 (t, 1H, J = 8 Hz), 5.35 (br t, 1H), 6.8 (br s, 4H).

Following the same procedure described for the preparation of compound **18a**, but using compound **15h** as starting material, ethyl 2-[(2-methoxyphenoxy)methyl]-3-[2-(acetylthio)acetyl]-1,3-thiazolidine-4-carboxylate (**18b**) was obtained from *i*-PrOH with a 68% yield: mp 90–92 °C; TLC (eluent A) R_f 0.7; ^{1}H NMR ($CDCl_3$) δ 1.1 (t, 3H, J = 7.5 Hz), 2.35 (br s, 3H), 3.3 (d, 2H J = 8 Hz), 3.7 (s, 3H), 3.7–4.3 (m, 6H), 5.05 (t, 1H, J = 8 Hz), 5.65 (t, 1H, J = 7 Hz), 6.8 (br s, 4H).

2-[2-(Methoxyphenoxy)methyl]-3-[2-(acetylthio)propionyl]-1,3-thiazolidine (18c). Following the same procedure described in the preparation of compound **18a** but using 2-bromopropionyl chloride, instead of 2-chloroacetyl chloride, 2-[(2-methoxyphenoxy)methyl]-3-[2-(acetylthio)propionyl]-1,3-thiazolidine (**18c**) was prepared in a 70% yield: mp 101–103 °C; TLC (eluent A) R_f 0.4; ^{1}H NMR ($CDCl_3$) δ 1.5 (br d, 3H), 2.3 (s, 3H), 2.8–3.3 (m, 2H), 3.8 (s, 3H), 3.3–4.4 (m, 5H), 5.6 (m, 1H), 6.85 (br s, 4H); IR (KBr) 2910, 1690, 1640, 1500, 1250, 1220, 1121, 740 cm^{-1}.

2-[(2-Hydroxyphenoxy)methyl]-3-[2-(acetylthio)acetyl]-1,3-thiazolidine (18f). While cooling to 0–5 °C, a solution of chloroacetyl chloride (15.9 mL, 0.2 mol) in EtOAc (30 mL) was added dropwise to a stirred mixture of compound **14f** (42.2 g, 0.2 mol), dissolved in EtOAc (450 mL) and $KHCO_3$ (21 g, 0.21 mol) suspended in water (50 mL). After about 30 min at the same temperature, the reaction mixture was diluted with water (250 mL) and the organic layer separated from the aqueous one. After washing with additional water (2 × 100 mL), the EtOAc solution was dried (sodium sulfate) and concentrated to dryness. The residual brown oil was crystallized from 2-PrOH (100 mL) to yield 46.8 g (81%) of 2-[(2-hydroxyphenoxy)methyl]-3-(2-chloroacetyl)-1,3-thiazolidine (**15f**) as a white solid: mp 89–91 °C; TLC (eluent A) R_f 0.6; ^{1}H NMR ($CDCl_3$) δ 2.9–3.3 (m, 2H), 3.6–4.1 (m, 4H), 4.6 (br s, 2H), 5.5 (br t, 1H, J = 6 Hz), 6.4 (br s, OH), 6.85 (br s, 4H).

Under a nitrogen atmosphere, potassium thioacetate (20.1 g, 0.17 mol) was added to a stirred solution of intermediate **15f** (45 g, 0.16 mol) in acetone (300 mL) kept at room temperature. After a further 1 h of stirring, the reaction mixture was diluted with demineralized water (400 L). A pale brown solid precipitated and was filtered and washed with water. The wet crude solid was dissolved in hot EtOH (150 mL), and the solution was decolored (charcoal) and cooled to 5–10 °C for 2 h. The crystallized product was collected by filtration and dried to yield 46.6 (89%) of 2-[(2-hydroxyphenoxy)methyl]-3-[2-(acetylthio)acetyl]-1,3-thiazolidine (**18f**) as a white solid: mp 97–99 °C; TLC (eluent A) R_f 0.5; ^{1}H NMR ($CDCl_3$) δ 2.3 (br s, 3H), 2.9–3.3 (m, 2H), 3.3–4.3 (m, 6H), 5.6 (t, 1H, J = 6 Hz), 6.4 (br s, OH), 6.75 (br s, 4H); IR (KBr) 2900, 1670, 1639, 1500, 1250, 1220, 720, 760 cm^{-1}.

3,3′-(2,2′-Dithiodiacetyl)bis[2-[(2-methoxyphenoxy)methyl]-1,3-thiazolidine] (19b). Under a nitrogen atmosphere, a solution of 2-[(2-methoxyphenoxy)methyl]-3-[2-(acetylthio)acetyl]-1,3-thiazolidine (**18a**; 341 g, 1 mol) in ethylene glycol dimethyl ether (1500 mL) was treated with NH_4OH (28%, 200 mL), added dropwise in about 30 min at room temperature. After about 20 min most of the solvent was removed under reduced pressure of nitrogen and the residue was partitioned between EtOAc (1500 mL) and water (1000 mL). The double-layer solution was acidified with hydrocloric acid (6 N) until pH 3 was reached. Then the organic layer was separated, washed with water, dried (sodium sulfate), and concentrated to a small volume. By removing solvent, a white solid crystallized and was collected by filtration and dried under vacuum to give 227 g (76%) of 2-[(2-methoxyphenoxy)methyl]-3-(2-mercaptoacetyl)-1,3-thiazolidine (**19a**): mp 84–86 °C; TLC (eluent A) R_f 0.4; ^{1}H NMR ($CDCl_3$) δ 2.1 (t, J = 7 Hz, SH), 2.8–3.6 (m, 4H), 3.7 (s, 3H), 3.7–4.5 (m, 4H), 5.6 (br t, 1H), 6.85 (br s, 4H); IR (KBr) 2927, 2500, 1640, 1500, 1240, 1220, 1020, 740 cm^{-1}.

Compound **19a** (15 g, 0.05 mol) was dissolved in DMSO (30 mL) and heated to 80 °C for 16 h and then to 120 °C for an additional 4 h. The reaction mixture was cooled to room temperature and slowly dropped into ice-cooled water (800 mL). A pale brown solid precipitated and was collected by filtration, washed with water, and dried in vacuo to yield 11 g (74%) of 3,3′-(2,2′-dithiodiacetyl)bis[2-[(2-methoxyphenoxy)methyl]-1,3-thiazolidine] (**19b**) as a mixture of diastereoisomers which were not separable on TLC: mp 50–60 °C; TLC (eluent A) R_f 0.3; ^{1}H NMR ($CDCl_3$) δ 2.8–3.4 (m, 2 × 2H), 3.8 (br s, 2 × 3H), 3.4–4.5 (m, 2 × 6H), 5.6 (br t, 2 × 1H), 6.85 (br s, 2 × 4H); IR (KBr) 2927, 1635, 1490, 1240, 1220, 1105, 1020, 740 cm^{-1}.

2-[(2-Methoxyphenoxy)methyl]-3-[2-[(3,4,5-trimethoxybenzoyl)thio]acetyl]-1,3-thiazolidine (19c). Under a nitrogen atmosphere, an ice-cooled solution of 2-[(2-methoxyphenoxy)methyl]-3-(2-mercaptoacetyl)-1,3-thiazolidine (**19a**; 6 g, 20 mmol) and TEA (3.2 mL, 23 mmol) in CH_2Cl_2 (60 mL) was dropwise treated with a solution of 3,4,5-trimethoxybenzoyl chloride (5.3 g, 23 mmol) in the same solvent (40 mL). After an additional 1 h at 10 °C and 30 min at room temperature, the reaction mixture was poured onto $NaHCO_3$ (5%, 100 mL). The organic layer was washed with water (2 × 50 mL), dried (sodium sulfate), and concentrated to dryness. The residual oil was chromatographed on silica gel (110 g) using the mixture hexane/EtOAc (2:1) as eluent. Fractions were monitored by TLC, and those containing mostly major product were combined and evaporated to give a crude oil (10 g) which was dissolved in EtOAc (10 mL). By diluting the obtained solution with hexane (30 mL), a white solid precipitated and was collected by filtration and dried to give 7 g (71%) of 2-[(2-methoxyphenoxy)methyl]-3-[2-[(3,4,5-trimethoxybenzoyl)thio]acetyl]-1,3-thiazolidine (**19c**); mp 108–110 °C; TLC (eluent A) R_f 0.5; ^{1}H NMR ($CDCl_3$) δ 2.9–3.3 (m, 2H), 3.7 (s, 3H), 3.85 (br s, 9H), 3.7–4.4 (m, 6H), 5.7 (br t, 1H), 6.8 (br s, 4H), 7.2 (br s, 2H); IR (KBr) 2900, 1660, 1640, 1490, 1240, 1240, 1205, 1120, 1005, 740 cm^{-1}.

2-[(2-Methoxyphenoxy)methyl]-3-[2-(methylthio)acetyl]-1,3-thiazolidine (20a). To a solution of compound **14a** (100 g, 0.44 mol) in EtOAc (500 mL) was added (methylthio)acetic acid (49 g, 0.46 mol). While stirring at room temperature, a solution of DCC (95 g, 0.46 mol) in EtOAc (200 mL) was dropped in about 40 min. During the addition, a fluffy solid precipitated and the temperature rose to 35 °C. After a further 1 h of stirring at room temperature, *N,N′*-dicyclohexylurea was removed by filtration and the filtered solution was washed with demineralized water (2 × 50 mL), $NaHCO_3$ (5%, 2 × 50 mL), and demineralized water again (2 × 50 mL). After drying (sodium sulfate), the solution was partially concentrated under vacuum to a volume of about 250 mL. By cooling, a white crystalline precipitate was formed, collected by filtration, and dried to yield 110 g (80%) of 2-[(2-methoxyphenoxy)methyl]-3-[2-(methylthio)acetyl]-1,3-thiazolidine (**20a**): mp 78–80 °C; TLC (eluent A) R_f 0.5; ^{1}H NMR ($CDCl_3$) δ 2.15 (br s, 3H), 2.7–3.6 (m, 4H), 3.8 (s, 3H), 3.7–4.3 (m, 4H), 5.6 (br t, 1H), 6.85 (br s, 4H); IR (KBr) 2922, 1652, 1510, 1252, 1227, 1123, 1021, 745 cm^{-1}.

2-[(2-Hydroxyphenoxy)methyl]-3-[2-(methylthio)acetyl]-1,3-thiazolidine (20b). Following the same procedure described in the preparation of compound **20a** but starting from 2-[(2-hydroxyphenoxy)methyl]-1,3-thiazolidine (**14f**), 2-[(2-hydroxyphenoxy)methyl]-3-[2-(methylthio)acetyl]-1,3-thiazolidine (**20b**) was obtained in a 74% yield. Compound **20b** was crystallized from EtOAc: mp 68–70 °C; TLC (eluent A) R_f 0.5; ^{1}H NMR ($CDCl_3$) δ 2.2 (s, 3H), 2.9–3.5 (m, 4H), 3.6–4.4 (s, 4H), 5.8 (t, 1H), 6.9 (br s, 4H); IR (KBr) 3000–3500, 2922, 1634, 1504, 1265, 1242, 1213, 1186, 1123, 1031, 1018, 741 cm^{-1}.

2-[(2-Methoxyphenoxy)methyl]-3-[2-(methylsulfinyl)-acetyl]-1,3-thiazolidine (20c). Hydrogen peroxide (36%, w/v, 93 mL, 1 mol) was dropped into a solution of (methylthio)-acetic acid (100 g, 0.94 mol) in EtOH (250 mL) cooled at 10–15 °C. The addition was regulated in order to not overcome 30 °C. After 2 h at room temperature, the reaction mixture was treated with Pd/C (10%, 1 g) and heated to 35 °C for 30 min to destroy the excess of H_2O_2. Then the catalyst was filtered off and the solvent removed in vacuo. The residual oil was crystallized from acetone (200 mL) to yield 105 g (91%) of (methylsulfinyl)acetic acid: mp 84–86 °C; ^{1}H NMR ($CDCl_3$, DMSO-d_6) δ 2.6 (s, 3H), 3.7 (s, 2H), 11.3 (s, COOH).

To a solution of compound **14a** (113 g, 0.5 mol) in ethylene glycol dimethyl ether (DME; 1000 mL) was added (methylsulfinyl)acetic acid (61 g, 0.5 mol), and the reaction mixture was warmed to 30 °C. Then a solution of DCC (104 g, 0.5 mol) in DME (240 mL) was dropped in about 1 h and the temperature raised to 40 °C. After an additional 1.5 h at 40 °C, demineralized water (40 mL) was added, and 30 min later, precipitates were filtered off and washed with DME. The clear solution was concentrated in vacuo, and the oily residue was dissolved in hot (60 °C) EtOAc (1000 mL). The hot solution was filtered again on a glass fiber filter, concentrated to one-third of its volume, and diluted with *tert*-butyl methyl ether (300 mL). The resultant white precipitates were filtered and dried to yield 149 g (90%) of 2-[(2-methoxyphenoxy)methyl]-3-[2-(methylsulfinyl)acetyl]-1,3-thiazolidine (**20c**) as a mixture of two diastereoisomers: mp 91–105 °C; TLC (eluent F) R_f 0.4 (one spot); ^{1}H NMR ($CDCl_3$, DMSO-d_6) δ 2.7 (br s, 3H), 2.9–3.2 (m, 2H), 3.8 (s, 3H), 3.9–4.1 (m, 2H), 4.4 (br s, 2H), 5.3–5.7 (m, 1H), 6.85 (br s, 4H); IR (KBr) 2927, 1641, 1510, 1254, 1121, 1024 (ν S=O), 747 cm^{-1}.

After two crystallizations from EtOAc (15/1 mL/g), one diastereoisomer was obtained in a 31% yield: mp 115–117 °C; ^{1}H NMR ($CDCl_3$, DMSO-d_6) δ 5.5 (t, 1H). The second diastereoisomer was recovered from mother liquors of the first crystallization after concentration to one-third of its volume and one further crystallization from EtOAc (15/1 mL/g) in a 23% yield: mp 95–97 °C; ^{1} NMR ($CDCl_3$, DMSO-d_6) δ 5.45 (t, 1H).

2-[(2-Methoxyphenoxy)methyl]-3-[2-(methylsulfinyl)-acetyl]-1,3-thiazolidine 1-Oxide (21a). To a cooled solution (0–5 °C) of 2-[(2-methoxyphenoxy)methyl]-3-[2-(methylthio)-acetyl]-1,3-thiazolidine (**20a**; 31.3 g, 0.1 mol) in ethanol (2400 mL) was added a solution of sodium periodate (47 g, 0.22 mol) in demineralized water (400 mL) dropwise. The reaction mixture was stirred for a further 24 h at 5–10 °C. After the addition of ethylene glycol (3 mL) and 2 h of stirring at room temperature, precipitated salts were filtered and the obtained solution was concentrated to dryness in vacuo. The oily residue was chromatographed (silica gel) using 10% MeOH in EtOAc to remove less polar impurities and 33% MeOH in EtOAc to elute the reaction product yielding, after solvent removal, 30.4 g (88%) of 2-[(2-methoxyphenoxy)methyl]-3-[2-methylsulfinyl)acetyl]-1,3-thiazolidine 1-oxide (**21a**) as a white amorphous and hygroscopic solid composed of a mixture (90/10) of two diastereoisomers: TLC (eluent G) R_f 0.58 + 054 (two spots); ^{1}H NMR ($CDCl_3$) δ 2.7 (2 s, 3H), 3.3–3.4 (m, 1H), 3.8 (s, 3H), 3.8–4.1 (m, 3H), 4.1–4.4 (m, 4H), 5.45 (m, 1H), 6.7–7.0 (m, 4H); IR (KBr) 2910, 1640, 1500, 1250, 1125, 1015 (ν S=O), 740 cm^{-1}.

A high stationary phase/substrate weight rate (silica gel 60, 230–400 mesh, 100/1, w/w) allowed the separation of diastereoisomers. **I°**: ^{1}H NMR ($CDCl_3$) δ 3.3–3.4 (m, 1H), 3.8 (s, 3H), 3.8–4.1 (m, 3H), 4.1–4.4 (m, 4H), 5.45 (m, 1H). **II°**: ^{1}H NMR ($CDCl_3$) δ 3.1 (m, 2H), 3.4 (m, 1H), 3,8 (s, 3H), 3.7–4.1 (m, 1H), 4.2 (m, 1H), 4.4 (m, 1H), 4.45–5.0 (m, 2H), 5.45, 5.85 (m, 1H).

2-[(2-Methoxyphenoxy)methyl]-3-[2-(methylsulfonyl)-acetyl]-1,3-thiazolidine 1-Oxide (21b). A solution of 3-chloroperoxybenzoic acid (85%, 9.5 g, 46.5 mmol) in CH_2Cl_2 (150 mL), dried (sodium sulfate) and then filtered, was added dropwise to a cooled solution (0–5 °C) of compound **20a** (4.7 g, 15 mmol) in CH_2Cl_2 (70 mL). After about 4 h at the same temperature, the reaction mixture was poured into 10% $KHCO_3$ and the organic layer washed again with 10% $KHCO_3$ and water. After drying (sodium sulfate), the solvent was removed under vacuum and the residual oil was chromatographed (silica gel, 2.5% MeOH in CH_2Cl_2) to yield 4.1 g (76%) of 2-[(2-methoxyphenoxy)methyl]-3-[2-(methylsulfonyl)acetyl]-1,3-thiazolidine 1-oxide (**21b**) as a white amorphous and hygroscopic solid: TLC (eluent G) R_f 0.52 (apparently one spot); ^{1}H NMR ($CDCl_3$) δ 3.15 (br s, 3H), 3.3–3.4 (m, 1H), 3.8 (s, 3H), 3.8–4.1 (m, 3H), 4.1–4.4 (m, 4H), 5.6 (m, 1H), 6.7–7.0 (m, 4H); IR (KBr) 2910, 1640, 1500, 1300 (ν SO_2), 1260, 1220, 1125, 1025 (ν S=O), 740 cm^{-1}.

2-[(2-Methoxyphenoxy)methyl]-3-[2-(4-methyl-1-piperazinyl)acetyl]-1,3-thiazolidine Dihydrochloride (22c). To a solution of 2–[(2-methoxyphenoxy)methyl]-3-(2-chloroacetyl)-1,3-thiazolidine (**15a**, 20 g, 66 mmol) in CH_3CN (120 mL) cooled to 10–15 °C were added potassium carbonate (9.16 g, 66 mmol) and 4-methylpiperazine (6.8 g, 68 mmol). After about 4 h at room temperature, inorganic salts were filtered off and the solvent was mostly removed under vacuum. The oily residue was taken up with EtOAc (150 mL), and the resultant solution was washed with water (2 × 50 mL), dried (sodium sulfate), and concentrated to dryness. The residue was chromatographed using the mixture EtOAc/MeOH (9:1) as eluent. Fractions were monitored by TLC, and those containing mostly major product were combined and evaporated to give a crude pale yellow oil (21 g) which was dissolved in diethyl ether (150 mL). The solution was cooled to 10 °C, and ethereal HCl (2.5 M, 53 mL, 132 mmol) was dropped into the stirred solution. A white precipitate was formed and collected by filtration under nitrogen to yield 20 g (69%) of 2-[(2-methoxyphenoxy)methyl]-3-[2-(4-methyl-1-piperazinyl)-acetyl]-1,3-thiazolidine dihydrochloride (**22c**): mp 210–215 °C; TLC (eluent E) R_f 0.5; ^{1}H NMR ($CDCl_3$, DMSO-d_6) δ 2.9 (s, 3H), 2.9–3.3 (m, 2H), 3.8 (br s, 3H), 3.4–4.4 (m, 12H), 4.3–4.6 (m, 2H), 4.6–5.2 (br m, 2HCl), 5.6 (m, 1H), 6.9 (br s, 4H).

2-[(4-Methoxyphenoxy)methyl]-3-(2-imidazolylacetyl)-1,3-thiazolidine (23b). Following the same procedure described in the preparation of compound **15a** but starting from 2-[(4-methoxyphenoxy)methyl]-1,3-thiazolidine (**14b**), 2-[(4-methoxyphenoxy)methyl]-3-(2-chloroacetyl)-1,3-thiazolidine (**15b**) was obtained in a 74% yield from MeOH: mp 51–53 °C; TLC (eluent A) R_f 0.6; ^{1}H NMR (DMSO-d_6) δ 3.0–3.3 (m, 2H), 3.6 (s, 3H), 3.6–4.1 (m, 4H), 4.4 (br s, 2H), 5.5 (br t, 1H, J = 6 Hz), 6.85 (br s, 4H).

Under a nitrogen atmosphere, potassium *tert*-butoxide (49.7 g, 0.44 mol) was suspended in dry (molecular sieves, 3 Å) *t*-BuOH (860 mL). Imidazole (29.5 g, 0.43 mol) was cautiously added to the suspension which was heated to 40 °C for 20 min. Then compound **15b** (108 g, 0.36 mol) was added to the reaction mixture in a single portion. Temperature rose to 60 °C, and stirring was continued further for 30 min. The mixture was poured onto ice-cooled water (1800 mL), and the precipitate was filtered and washed with water. The wet crude product was dissolved in hot acetone (1000 mL), and the solution was decolored with charcoal. The hot filtered solution was cooled and stirred for about 2 h. The crystallized solid was collected by filtration and dried to yield 83 g (69%) of 2-[(4-methoxyphenoxy)methyl]-3-(2-imidazolylacetyl)-1,3-thiazolidine (**23b**) as a white powder: mp 132–133 °C; TLC (eluent G) R_f 0.4; ^{1}H NMR (DMSO-d_6) δ 3.0–3.3 (m, 2H), 3.7 (s, 3H), 3.6–4.3 (m, 4H), 5.0 (br s, 2H), 5.5 (t, 1H, J = 6 Hz), 6.6 (br s, 5H), 6.8 (br s, 1H), 7.2 (br s, 1H); IR (KBr) 2926, 1665, 1607, 1512, 1258, 1115, 855, 770 cm^{-1}.

2-[(2-Methoxyphenoxy)methyl]-3-(2-acetoxyacetyl)-1,3-thiazolidine (24a). Following the same procedure described for the preparation of compound **15a** but using acetoxyacetyl chloride instead of chloroacetyl chloride and CH_2Cl_2 as solvent, 2-[(2-methoxyphenoxy)methyl]-3-(2-acetoxyacetyl)-1,3-thiazolidine (**24a**) was obtained from Et_2O in a 80% yield: mp 89–91 °C; TLC (eluent H) R_f 0.47; ^{1}H NMR ($CDCl_3$) δ 2.1 (s, 3H), 2.9–3.3 (m, 2H), 3.8 (s, 3H), 3.6–4.1 (m, 4H), 4.5 (br s, 2H), 5.4 (m, 1H), 6.8 (br s, 4H); IR (KBr) 2920, 1740, 1650, 1500, 1250, 1230, 1110, 740 cm^{-1}.

2-[(2-Methoxyphenoxy)methyl]-3-acetyl-1,3-thiazolidine (25a). Following the same procedure described for the preparation of compound **15f** but using 2-[(2-methoxyphenoxy)-methyl]-1,3-thiazolidine (**14a**) as starting material and acetyl chloride, instead of chloroacetyl chloride, as the acylating agent, 2-[(2-methoxyphenoxy)methyl]-3-acetyl-1,3-thiazolidine

(**25a**) was prepared and crystallized from Et_2O with a global yield of 95%: mp 79–81 °C; TLC (eluent B) R_f 0.5; ^1H NMR ($CDCl_3$) δ (two amide conformers, 1:1) 2.15, 2.35 (2 s, 3 + 3H), 3.0, 3.35 (2 m, 1 + 3H), 3.8 (s + m, 3 + 1H), 3.4–4.1 (m, 1H), 4.0, 4.25 (d + m, 2 + 2H), 4.65 (m, 1H), 4.9, 5.2 (t + dd, 1 + 1H), 6.85 (m, 4H); IR (KBr) 2920, 1650, 1505, 1260, 1220, 1121, 750 cm^{-1}.

2-[(2-Methoxyphenoxy)methyl]-3-(3-oxobutyryl)-1,3-thiazolidine (25e). To a solution of compound **14a** (4.5 g, 20 mmol) in acetone (25 mL) cooled to 0–5 °C was added diketene (1.9 mL, 25 mmol) diluted with acetone (4 mL) dropwise within 30 min. Then the temperature was allowed to rise to 20 °C, and after an additional hour, the reaction mixture was partitioned between $KHCO_3$ (5%, 100 mL) and EtOAc (100 mL). The organic layer was subsequently washed with water, dried (sodium sulfate), and concentrated to dryness. The residue was chromatographed on silica gel using the mixture EtOAc/hexane (1:2) as eluent. Fractions were monitored by TLC, and those containing mostly major product were combined and evaporated to give a crude pale yellow oil (4.8 g) which crystallized from ethyl ether (30 mL) to yield 4.2 g (68%) of 2-[(2-methoxyphenoxy)methyl]-3-(3-oxobutyryl)-1,3-thiazolidine (**25e**) as a white solid: mp 61–63 °C; TLC (eluent A) R_f 0.5; ^1H NMR ($CDCl_3$) δ (two amide conformers, 3:1) 1.9, 2.2 (2 s, 3H), 2.9–3.2 (m, 2H), 3.8 (br s, 3H), 3.3–4.4 (m, 6H), 5.0–5.6 (m, 1H), 6.85 (br s, 4H); IR (KBr) 2926, 1713, 1651, 1505, 1250, 1224, 1123, 1020, 743 cm^{-1}.

Ethyl 2-[(2-Methoxyphenoxy)methyl]-β-oxo-1,3-thiazolidine-3-propionate (7). A solution of ethyl malonyl chloride[28] (680 g, 4.2 mol) in EtOAc[29] (0.66 L) was added dropwise to a stirred and ice-cooled mixture of compound **14a** (960 g, 4.26 mol) in EtOAc (4.3 L) and $KHCO_3$ (471 g, 4.7 mol) in demineralized water (0.93 L). After about 1.5 h at the same temperature, the aqueous layer was discharged and the organic one was washed with water, dried (magnesium sulfate), decolored (charcoal), and concentrated in vacuo to a global weight of about 2 kg. The clear solution was cooled to 0–5 °C and diluted with hexane (0.5 L). Two hours later the crystallized product was collected by filtration and washed with a mixture of EtOAc/hexane (1:9, 0.3 L). The crude wet solid was recrystallized from the mixture EtOH/water (1:1, 4 mL/g) to yield 1.23 kg (85%) of ethyl 2-[(2-methoxyphenoxy)-methyl]-β-oxo-1,3-thiazolidine-3-propionate (**7**) as a white solid: mp 60–62 °C; TLC (eluent A) R_f 0.4; ^1H NMR ($CDCl_3$) δ 1.2–1.4 (m, 3H), 2.9–3.2, 3.3–3.5 (m, 2H), 3.45, 3.95 (2 d, 2H), 3.3–4.7 (m, 2H), 3.85 (s, 3H), 4.1–4.4 (m, 4H), 5.4, 5.7 (2 dd, 1H), 6.8–7 (m, 4H); ^{13}C NMR (DMSO-d_6, 130 °C)δ 13.15 (CH_3), 28.63 (CH_2S), 41.56 ($COCH_2CO$), 47.73 (CH_2N), 55.8 (OCH_3), 59.85 (OCH_2CH_3), 60.39 (CHNS), 71.33 (CH_2O), 113.48, 114.92, 120.54, 121.41 (CHaro), 147.86, 149.43 (COaro), 163.90 (CON), 166.32 (COO); IR (KBr) 3063, 1738, 1660, 1593, 1510, 1429, 1250, 1210, 1020, 739 cm^{-1}; MS (EI) $M^{\cdot+}$ = 339; HPLC (5 μm Li-Chrospher RP8, 125 × 4 mm; CH_3CN:KH_2PO_4, 0.01 M buffer, pH 4.5, 3:7, 1.5 mL/min, 275 nm) t_R 11 min.

Ethyl 2-[(2-Methoxyphenoxy)methyl]-α-oxo-1,3-thiazolidine-3-acetate (26a). Following the same procedure described for the preparation of compound **7** but using ethyl oxalyl chloride, instead of ethyl malonyl chloride, ethyl 2-[(2-methoxyphenoxy)methyl]-α-oxo-1,3-thiazolidine-3-acetate (**26a**) was synthesized as an oily substance in a 90% yield: TLC (eluent A) R_f 0.36; ^1H NMR ($CDCl_3$) δ 1.0–1.4 (2 t, 3H), 2.9–3.3 (m, 2H), 3.3–4.4 (m, 6H), 3.85 (s, 3H), 5.4–5.7 (2 t, 1H), 6.8–7 (m, 4H); IR (KBr) 3063, 1740, 1660, 1600, 1500, 1260, 1220, 1020, 750 cm^{-1}.

Ethyl 2-[(2-Methoxyphenoxy)methyl]-γ-oxo-1,3-thiazolidine-3-butyrate (26b). Following the same procedure described for the preparation of compound **7** but using ethyl succinyl chloride, instead of ethyl malonyl chloride, ethyl 2-[(2-methoxyphenoxy)methyl]-γ-oxo-1,3-thiazolidine-3-butyrate (**26b**) was obtained in a 72% yield after crystallization from ethyl ether: mp 56–58 °C; TLC (eluent A) R_f 0.45; ^1H NMR ($CDCl_3$) δ 1.3 (t, 3H), 2.7 (br s, 4H) 2.9–3.3 (m, 2H), 3.4–4.4 (m, 6H), 3.85 (s, 3H), 5.4–5.7 (m, 1H), 6.8–7 (m, 4H).

Ethyl 2-[(2-Hydroxyphenoxy)methyl]-β-oxo-1,3-thiazolidine-3-propionate (26c). Following the same procedure described for the preparation of compound **7** but using 2-[(2-hydroxyphenoxy)methyl]-1,3-thiazolidine (**14f**) as starting material, instead of **14a**, ethyl 2-[(2-hydroxyphenoxy)methyl]-β-oxo-1,3-thiazolidine-3-propionate (**26c**) was obtained in a 72% yield after crystallization from isopropyl ether: mp 61–63 °C; TLC (eluent A) R_f 0.35; ^1H NMR ($CDCl_3$) δ 1.2 (t, 3H, J = 7 Hz), 3.0–3.3 (br t, 2H), 3.5 (br s, 2H), 3.7–4.1 (m, 2H), 4.0–4.3 (m, 4H), 5.7 (br t, 1H), 6.5 (br s, OH), 6.8–7 (m, 4H).

2-[(2-Methoxyphenoxy)methyl]-β-oxo-1,3-thiazolidine-3-propionic Acid (27a). NaOH (1 N, 77 mL) was added to a stirred suspension of 2-[(2-methoxyphenoxy)methyl]-β-oxo-1,3-thiazolidine-3-propionate (**7**; 25 g, 77 mmol) in EtOH (250 mL). Within the next 60 min, a complete solution was obtained with subsequent precipitation of a white solid. After one further hour, the suspension was cooled to 0–5 °C, and 30 min later, precipitated salts were collected by filtration. The wet solids were dissolved in demineralized water (100 mL), and the solution was acidified with 2 N H_2SO_4 to pH 2 (about 40 mL). During the acidification, a white precipitate of 2-[(2-methoxyphenoxy)methyl]-β-oxo-1,3-thiazolidine-3-propionic acid (**27a**) precipitated. The resultant crude product was collected by filtration and crystallized from EtOAc (200 mL) to give, after drying, 18 g (75%) of a white powder: mp 123–125 °C; TLC (eluent I) R_f 0.5; ^1H NMR ($CDCl_3$) δ 3.0–3.5 (m, 2H), 3.4–3.6 (m, 2H), 3.5–4.2 (m, 2H), 3.8, 3.85 (2 s, 3H), 3.9–4.7 (m, 2H), 5.35, 5.7 (2 dd, 1H), 6.7–7 (m, 4H), 11–13 (COOH); IR (KBr) 3500, 2964, 2582, 1735, 1599, 1505, 1441, 1252, 1230, 1026, 740 cm^{-1}.

2-[(2-Methoxyphenoxy)methyl]-β-oxo-1,3-thiazolidine-3-propionic Acid 1-Oxide (27c). To a stirred solution of compound **27a** (3.1 g, 10 mmol) in CH_2Cl_2 (60 ml), cooled to 5–10 °C, was added 3-chloroperoxybenzoic acid (55%, 5.9 g, 10 mmol) portionwise in about 30 min. After about 2 h at 10 °C, solvent was removed under reduced pressure and the solid residue was treated with acetone (40 mL). The suspension was heated to reflux for 10 min and then cooled down and filtered. The collected solid was once again suspended in hot MeOH (40 °C, 40 mL) and then filtered to give, after drying 2.5 g (76%) of 2-[(2-methoxyphenoxy)methyl]-β-oxo-1,3-thiazolidine-3-propionic acid 1-oxide (**27c**) as a white solid: mp 134–137 °C; TLC (eluent M) R_f 0.4; ^1H NMR (DMSO-d_6) δ 3.1–4.1 (m, 4H), 3.65, 3.8 (2 s, 3H), 4.1–4.5 (m, 4H), 5.3, 5.5 (2 m, 1H), 6.7–7 (m, 4H), 12.7 (br s, COOH); IR (KBr) 2964, 2584, 1724, 1665, 1509, 1259, 1222, 1027, 996 (ν SO), 745 cm^{-1}.

2-[(2-Hydroxyphenoxy)methyl]-β-oxo-1,3-thiazolidine-3-propionic Acid (27d). The alkaline hydrolysis of compound **26c** according to the procedure described in the preparation of compound **27a** allowed the synthesis of 2-[(2-hydroxyphenoxy)methyl]-β-oxo-1,3-thiazolidine-3-propionic acid (**27d**) in a 78% yield after crystallization from ethyl ether: mp 106–108 °C; TLC (eluent I) R_f 0.3; ^1H NMR ($CDCl_3$, DMSO-d_6) δ 2.9–3.2 (m, 2H), 3.5 (br s, 2H), 3.6–4.4 (m, 4H), 5.4–5.7 (m, 1H), 6.7–7.0 (m, 4H), 9.0–9.5 (br s, COOH); IR (KBr) 3300, 2950, 2582, 1760, 1645, 1520, 1441, 1280, 1230, 1150, 760 cm^{-1}.

Ethyl 2-[(2-Methoxyphenoxy)methyl]-β-oxo-1,3-thiazolidine-3-propionate 1-Oxide (28a). 3-Chloroperoxybenzoic acid (55%, 9.7 g, 31 mmol) was added portionwise under stirring to a solution of 2-[(2-methoxyphenoxy)methyl]-β-oxo-1,3-thiazolidine-3-propionate (**7**; 10 g, 29.4 mmol) in CH_2Cl_2 (100 mL) cooled to 0 °C. After 2 h at the same temperature, the reaction mixture was poured onto $KHCO_3$ (5%, 100 mL). The organic layer was separated and washed again with $KHCO_3$ (5%) and then with water (3 × 50 mL). After drying (sodium sulfate), the solvent was removed under vacuum and the resultant oil (10 g) was triturated in isopropyl ether (80 mL) to give 8.8 g (84%) of the diastereoisomeric mixture of ethyl 2-[(2-methoxyphenoxy)methyl]-β-oxo-1,3-thiazolidine-3-propionate 1-oxide (**28a**) as a white solid: mp 76–79 °C; TLC (eluent L) R_f 0.33 + 0.25 (two spots, 4:1); ^1H NMR ($CDCl_3$) δ 1.15 (t, 3H, J = 7 Hz), 3.0–3.6 (m, 2H), 3.5 (br s, 2H), 3.85 (s, 3H), 3.7–4.6 (m, 6H), 5.35 (m, 1H), 6.8–7 (m, 4H); IR (KBr) 2980, 1750, 1660, 1605, 1510, 1260, 1215, 1050 (ν SO), 1020, 750 cm^{-1}.

A high stationary phase/substrate rate (silica gel 60, 230–400 mesh, 100/1, w/w) allowed the separation of diastereoisomers. **I°**: R_f 0.33; mp 87–89 °C. **II°**: R_f 0.25; mp 92–94 °C.

Ethyl 2-[(2-Methoxyphenoxy)methyl]-β-oxo-1,3-thiazolidine-3-propionate 1,1-Dioxide (28b). Following the procedure reported in the preparation of compound **28a** but using 2.2 mol equiv of 3-chloroperoxybenzoic acid after about 16 h at room temperature, a similar workup gave a crude oil which was purified by column chromatography (EtOAc/$CHCl_3$, 1:9, as eluent). After crystallization from EtOAc (10 mL/g of oily residue), ethyl 2-[(2-methoxyphenoxy)methyl]-β-oxo-1,3-thiazolidine-3-propionate 1,1-dioxide (**28b**) was obtained in 70% yield: mp 100–102 °C; TLC (eluent A) R_f 0.3; ^{1}H NMR ($CDCl_3$) δ 1.2 (t, 3H, J = 8 Hz), 3.3–4.6 (m, 8H), 3.5 (br s, 2H), 3.8 (s, 3H), 5.1 (m, 1H), 6.8–7 (m, 4H); IR (KBr) 3019, 1738, 1661, 1593, 1331 (ν_{as} SO_2), 1256, 1228, 1124 (ν_{sim} SO_2), 1029, 750 cm^{-1}.

Ethyl 2-[(2-Methoxyphenoxy)methyl]-α,α-dimethyl-β-oxo-1,3-thiazolidine-3-propionate (29). Using the same procedure described for the synthesis of compound **7** but using ethyl 2,2-dimethylmalonyl chloride,[30] instead of ethyl malonyl chloride, ethyl 2-[(2-methoxyphenoxy)methyl]-α,α-dimethyl-β-oxo-1,3-thiazolidine-3-propionate (**29**) was obtained in a 65% yield, after crystallization from hexane/ethyl ether, 9:1: mp 54–56 °C; TLC (eluent A) R_f 0.45; ^{1}H NMR ($CDCl_3$) δ 1.2 (t, 3H, J = 7 Hz), 1.4 (br s, 3H), 2.9–3.0 (m, 1H), 3.25–3.35 (m, 1H), 3.5–3.9 (m, 2H), 3.8 (s, 3H), 4.1–4.4 (m, 4H), 5.75 (t, 1H), 6.8–7 (m, 4H); IR (KBr) 2984, 1732, 1646, 1593, 1505, 1256, 1226, 1020, 750 cm^{-1}.

2-[(2-Methoxyphenoxy)methyl]-α,α-dimethyl-β-oxo-1,3-thiazolidine-3-propionic Acid (31). The alkaline hydrolysis of compound **29** according to the procedure described in the preparation of compound **27a** but heating the reaction mixture for 8 h at room temperature allowed to obtain 2-[(2-methoxyphenoxy)methyl]-α,α-dimethyl-β-oxo-1,3-thiazolidine-3-propionic acid (**31**) in a 63% yield after crystallization from ethyl ether: mp 118–119 °C; TLC (eluent I) R_f 0.7; ^{1}H NMR ($CDCl_3$) δ 1.35–1.4 (2 s, 3H), 2.8–3.2 (m, 2H), 3.8 (br s, 3H), 3.6–4.2 (m, 4H), 5.7 (br t, 1H), 6.7–7.0 (m, 4H), 9.5 (br s, COOH); IR (KBr) 3300, 2950, 1760, 1600, 1495, 1250, 1225, 1170, 1020, 750 cm^{-1}.

***N*-Methyl 2-[(2-Methoxyphenoxy)methyl]-β-oxo-1,3-thiazolidine-3-propanamide (32a).** Ethyl 2-[(2-methoxyphenoxy)methyl]-β-oxo-1,3-thiazolidine-3-propionate (**7**; 5 g, 0.15 mol) was added to an ethanolic solution of methylamine (33%, 50 mL, 0.4 mol), and the resultant solution was heated at 40 °C for 20 h. Then reaction mixture was poured onto NaH_2PO_4 (20%, 100 mL), and ethanol was partially removed under reduced pressure. The product was extracted with CH_2Cl_2 (3 × 50 mL), and combined extracts were washed with water, dried (sodium sulfate), and concentrated to dryness. The residue was triturated in hot EtOAc (15 mL) to yield 4.5 g (92%) of *N*-methyl 2-[(2-methoxyphenoxy)methyl]-β-oxo-1,3-thiazolidine-3-propionamide (**32a**) as a white solid: mp 136–138 °C; TLC (eluent I) R_f 0.4; ^{1}H NMR ($CDCl_3$, DMSO-d_6) δ 2.7, 2.75 (2 s, 3H), 2.9–3.7 (m + s, 4H), 3.8 (br s, 3H), 3.6–4.3 (m, 4H), 5.6 (m, 1H), 6.9 (br s, 4H), 7.9 (br s, NH); IR (KBr) 3275, 3092, 2950, 1656, 1628, 1591, 1504, 1251, 1222, 1023, 745 cm^{-1}.

2-[(2-Methoxyphenoxy)methyl]-3-[1,3-dioxo-3-(4-methyl-1-piperazinyl)propanyl]-1,3-thiazolidine (32c). Under a nitrogen atmosphere, 1,1′-carbonyldiimidazole (12.9 g, 77 mmol) was portionwise added in about 30 min to a stirred solution of 2-[(2-methoxyphenoxy)methyl]-β-oxo-1,3-thiazolidine-3-propionic acid (**27a**; 20 g, 64.2 mmol) in THF (300 mL) cooled to 0–5 °C. At the end of the addition, the temperature was brought to 40 °C and stirring was continued further for 2 h. The reaction mixture was cooled down to 0–5 °C, and the intermediate imidazolide precipitated as a white solid which was collected by filtration, washed with cold THF (20 mL), and dried affording 20.2 g of a stable derivative: mp 123–125 °C; ^{1}H NMR (DMSO-d_6) δ 2.8–3.2 (m, 2H), 3.7 (br s, 2H), 3.6–4.2 (m, 4H), 4.0 (br s, 3H), 5.5 (br t, 1H), 6.7–7.0 (m, 4H), 7.15 (s, 2H), 7.9 (s, 1H).

The imidazolide (9 g, 24.9 mmol) was added portionwise within about 30 min to a warm (50 °C) solution of 1-methylpiperazine (2.76 mL, 24.9 mmol) in toluene (90 mL). After an additional 30 min at the same temperature, the reaction mixture was cooled to room temperature and poured onto demineralized water (200 mL). The organic layer was washed again with water (3 × 50 mL), dried (sodium sulfate), and concentrated to dryness to give 10 g of an oil which crystallized from Et_2O (100 mL). 2-[(2-Methoxyphenoxy)methyl]-3-[1,3-dioxo-3-(4-methyl-1-piperazinyl)propanyl]-1,3-thiazolidine (**32c**) was obtained in an 80% yield (6.8 g): mp 75–77 °C; TLC (eluent F) R_f 0.2; ^{1}H NMR ($CDCl_3$) δ 2.1–2.4 (m, 7H), 2.8–3.2 (m, 2H), 3.2–3.55 (m, 6H), 3.6 (br s, 3H), 3.6–4.2 (m, 4H), 5.4 (m, 1H), 6.5 (br s, 4H); IR (KBr) 2950, 1650, 1630, 1595, 1505, 1250, 1220, 1020, 742 cm^{-1}.

***N*-(4-Pyridinylmethyl)-2-[(2-methoxyphenoxy)methyl]-β-oxo-1,3-thiazolidine-3-propionamide Hydrochloride (32g).** Under a nitrogen atmosphere, a stirred solution of 2-[(2-methoxyphenoxy)methyl]-β-oxo-1,3-thiazolidine-3-propionic acid (**27a**; 20 g, 64.2 mmol) in THF (150 mL) containing *N*-hydroxysuccinimide (9.5 g, 80.2 mmol) was cooled to 0–5 °C and 2-morpholinoethyl isocyanide (11.7 mL, 83.4 mmol) was added dropwise to the reaction mixture in about 30 min. After a further 3 h at 10 °C, 4-picolylamine (6.7 mL, 64.2 mol) was added dropwise in about 15 min to the resultant intermediate *N*-hydroxysuccinimido ester. One hour later at the same temperature, THF was mostly removed under vacuum and the residue was partitioned between demineralized water (150 mL) and EtOAc (200 mL). The organic layer was washed again with water (2 × 100 mL), dried (sodium sulfate), and concentrated to dryness to give a crude oil (28 g) which was purified by column chromatography using EtOAc as eluent. Collected fractions, containing the reaction product, afforded, after solvent removal, 25.6 g of a clear oil. The oil was dissolved in EtOAc (30 mL) under nitrogen, cooled to 10 °C, and treated with a solution of HCl in Et_2O (4.5 N, 14.3 mL, 64.3 mmol). Then the solution was slowly diluted with Et_2O (140 mL) and stirred at room temperature for about 2 h. The white resultant precipitates were filtered off under a nitrogen blanket, washed with Et_2O/EtOAc, 10:1, and dried to give 25 g (89%) of *N*-(4-pyridinylmethyl)-2-[(2-methoxyphenoxy)methyl]-β-oxo-1,3-thiazolidine-3-propionamide hydrochloride (**32g**) as a pale pink solid: mp hygroscopic 54–56 °C; TLC (eluent N) R_f 0.5; ^{1}H NMR (DMSO-d_6) δ 2.9–3.3 (m 2H), 3.3–4.3 (m, 6H), 3.75 (br s, 3H), 4.55, 4.6 (2 s, 3H), 5.5, 5.7 (2 m, 1H), 6.8–7.0 (m, 4H), 8.0 (d, 2H, J = 5 Hz), 8.85 (d, 2H, J = 5 Hz), 8.9–9.1 (m, NH); IR (KBr) 3207, 2986, 2525 (H^+), 1674, 1652, 1592, 1506, 1254, 1223, 1123, 1022, 783, 744 cm^{-1}.

(*S*)-(−)-2-[(2-Methoxyphenoxy)methyl]pyrrolidine (36a). To a cooled (−10 °C) solution of (*S*)-(−)-*N*-BOC-proline (**33a**) (40 g, 0.18 mol) and TEA (32.6 mL, 0.23 mol) in THF (220 mL) was added ethyl chloroformate (24.1 mL, 0.25 mol) dropwise in about 30 min, maintaining temperature below −6 °C. The resultant white precipitates were filtered off and washed with dry THF (440 mL). The filtered solution was cautiously dropped into a suspension of $NaBH_4$ in THF (140 mL) cooled at 6–8 °C. About 1 h later the resulting mixture was poured into aqueous NaH_2PO_4 (30%, 400 mL) and extracted with EtOAc (3 × 400 mL). Combined organic layers were washed with aqueous $NaHCO_3$ (5%), dried (sodium sulfate), and concentrated under vacuum. The residue was crystallized from hexane to yield 25.5 g (68%) of (*S*)-(−)-*N*-BOC-2-pyrrolidinemethanol (**34a**) as a white solid: mp 59–60 °C; TLC (eluent A) R_f 0.5; ^{1}H NMR ($CDCl_3$) δ 1.4 (s, 9H), 1.5–2.0 (m, 4H), 3.25 (br t, 2H), 3.5 (br t, 2H), 3.85 (m, 1H), 4.5 (m, OH); $[\alpha]^{20}_{\lambda} = -52°$ (589), −54° (578), −62° (546), −103° (436) (c = 2, EtOH).

A solution of *p*-toluenesulfonyl chloride (28.4 g, 0.15 mol) in CH_2Cl_2 (140 mL) was added in about 20 min to an ice-cooled solution of compound **34a** (25 g, 0.124 mol) and pyridine (72.1 mL, 0.89 mol) in CH_2Cl_2 (125 mL). Then the reaction mixture was stirred overnight at room temperature. The mixture was poured onto water (1 L) and extracted wtih CH_2Cl_2 (2 × 150 mL). Combined extracts were dried (sodium sulfate) and concentrated under vacuum to yield 45 g of (*S*)-(−)-*N*-BOC-2-pyrrolidinemethanol *p*-toluenesulfonate as a pale yellow oil: $[\alpha]^{20}_{\lambda} = -45.7°$ (589) (c = 1.9, EtOH).

A solution of the above-mentioned *p*-toluenesulfonate (30 g, 84 mmol) in DMSO (70 mL) was dropped at 25 °C into a solution of sodium guaiacolate, previously prepared by adding, under a nitrogen atmosphere, guaiacol (12.5 g, 0.101 mol) to a suspension of NaH (80%, 3.28 g, 0.113 mol) in DMSO (150 mL). The reaction mixture was stirred overnight and heated

at 80 °C. After cooling it was diluted with water (400 mL) and extracted with EtOAc (3 × 300 mL). Combined extracts were washed with 1 N NaOH (150 mL) and aqueous NaH_2PO_4 (10%, 100 mL), dried (sodium sulfate), and concentrated in vacuo to yield a crude oil (14 g) which was purified by column chromatography (silica gel, EtOAc 20% in hexane as eluent). Fractions containing mostly the reaction product were concentrated to dryness, and the resultant oil was crystallized from hexane, affording 12.2 g (47%) of (*S*)-(−)-2-[(2-methoxyphenoxy)methyl]-*N*-BOC-pyrrolidine (**35a**) as a white solid: mp 65−67 °C; TLC (eluent EtOAc/hexane, 2:8) R_f 0.5; ^{1}H NMR ($CDCl_3$) δ 1.5 (s, 9H), 1.6−2.3 (m, 4H), 3.2−3.5 (m, 2H), 3.8 (s, 3H), 3.8−4.3 (m, 3H), 6.8−7.0 (br s, 4H); $[\alpha]^{20}_{\lambda} = -67°$ (589) (*c* = 2, EtOH).

To an ice-cooled solution of compound **35a** (12 g, 38.9 mmol) in CH_2Cl_2 (60 mL) was added CF_3COOH (58 mL, 510 mmol) dropwise in about 40 min. After about 1 h at 25 °C, the reaction mixture was poured in NaOH (3 N, 248.5 mL) and the pH adjusted to 8.5 by adding NaOH (1 N). The aqueous layer was extracted with CH_2Cl_2 (3 × 300 mL), washed with aqueous $NaHCO_3$ (5%) and brine, dried (sodium sulfate), and concentrated under vacuum to yield 7.3 g (90%) of (*S*)-(−)-2-[(2-methoxyphenoxy)methyl]pyrrolidine (**36a**) as a colorless oil: TLC (eluent D) R_f 0.5; ^{1}H NMR ($CDCl_3$) δ 1.5−2 (m, 4H), 2.6 (br s, NH), 2.9 (br t, 2H), 3.45 (t, 1H, J = 6 Hz), 3.75 (s, 3H), 3.85 (d, 2H, J = 6 Hz), 6.85 (br s, 4H); $[\alpha]^{20}_{\lambda} = -10°$ (589) (*c* = 2, EtOH).

Ethyl (*S*)-(−)-2-[(2-Methoxyphenoxy)methyl]-β-oxopyrrolidine-3-proplonate (37a). To a biphasic solution of compound **36a** (8 g, 38.5 mmol) in EtOAc and aqueous $KHCO_3$ (14%) (1/1, 64 mL) cooled to 0 °C was added ethyl malonyl chloride (5.1 mL, 40.4 mmol) dropwise. After about 30 min the organic layer was separated and the aqueous one extracted with EtOAc (2 × 20 mL). Combined organic extracts were washed with 5% $NaHCO_3$ and 20% NaH_2PO_4, dried (sodium sulfate), and concentrated under vacuum. The residue was purified by chromatography (silica gel, 50% EtOAc in hexane) to yield 9.5 g (77%) of ethyl (*S*)-(−)-2-[(methoxyphenoxy)-methyl]-β-oxopyrrolidine-3-propionate (**37a**) as a colorless oil: TLC (eluent A) R_f 0.4; ^{1}H NMR ($CDCl_3$) δ 1.2−1.4 (t, 3H), 2.8−3.2 (m, 4H), 3.3−3.6 (m, 4H), 3.6−4.3 (m, 4H), 3.85 (s, 3H), 4.3−4.6 (m, 1H), 6.7−7.0 (m, 3H), 7.1 (m, 1H); $[\alpha]^{20}_{\lambda}$ = −64° (589), −66° (578), −75.9° (546) (*c* = 2.7, EtOH); IR (KBr) 2970, 1740, 1650, 1597, 1510, 1429, 1250, 1225, 1030, 750 cm^{-1}.

(*S*)-(−)-2-[(2-Methoxyphenoxy)methyl]-3-[2-(acetylthio)acetyl]pyrrolidine (39a). Following the same procedure described for the preparation of compound **18a** but using (*S*)-(−)-2-[(2-methoxyphenoxy)methyl]pyrrolidine (**36a**) as starting material, (*S*)-(−)-2-[(2-methoxyphenoxy)methyl]-3-[2-(acetylthio)acetyl]pyrrolidine (**39a**) was obtained with a global yield (two steps) of 55% after crystallization from Et_2O: mp 53−55 °C; TLC (eluent A) R_f 0.3; ^{1}H NMR ($CDCl_3$) δ 2.7−2.2 (m, 4H), 2.3 (br s, 3H), 3.3−3.7 (m, 4H), 3.8 (br s, 3H), 3.8−4.2 (m, 4H), 4.2−4.6 (m, 1H), 6.85−7.1 (br s, 4H); $[\alpha]^{20}_{\lambda} = -60°$ (589), −64° (578), −74° (546) (*c* = 2, EtOH); IR (KBr) 2929, 1682, 1623, 1510, 1255, 1223, 1127, 1024, 736 cm^{-1}.

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References

(1) Eddy, N. B.; Friebel, H.; Hahn, K. J.; Halbach, H. Codeine and its Alternates for Pain and Cough Relief. *Bull. W. H. O.* **1969**, *40*, 721−730.

(2) Miller, D. Antitussives. *Burger's Medicinal Chemistry*; Wiley Interscience: New York, 1981; Part III, Cap. 53, pp 759−785.

(3) (a) Craviso, G. L.; Musacchio, J. M. High-Affinity Dextromethorphan Binding Sites in Guinea Pig Brain I. Initial Characterization. *Mol. Pharmacol.* **1983**, *23*, 619−628. (b) Craviso, G. L.; Musacchio, J. M. High-Affinity Dextromethorphan Binding Sites in Guinea Pig Brain II. Competition Experiments. *Mol. Pharmacol.* **1983**, *23*, 629−640. (c) Musacchio, J. M.; Klein, M.; Santiago, L. J. Allosteric Modulation of Dextromethorphan Binding Sites. *Neuropharmacology* **1987**, *26*, 997−1001. (d) Tortella, F. C.; Pellicano, M.; Bowery, N. G. Dextromethorphan and neuromodulation: old drug coughs up new activities. *Trends Pharmacol. Sci.* **1989**, *10*, 501−506.

(4) (a) Kasé, Y.; Kito, G.; Miyata, T.; Uno, T.; Takahama, K.; Ida, H. Antitussive Activity and other Related Pharmacological Properties of d-3-Methyl-N-methylmorphinan (AT-17). *Arzneim.-Forsch.* **1976**, *26*, 353−360. (b) Kasé, Y.; Kito, G.; Miyata, T.; Takahama, K.; Uno, T.; Ida, H. On the Sites of Antitussive Action of d-3-Methyl-N-methylmorphinan (AT-17). *Arzneim.-Forsch.* **1976**, *26*, 361−366.

(5) Hahn, K. J.; Friebel, H. Wirkungen hustenhemmender Pharmaka im zentralen Anteil der Hustenreflexbahn. (Effects of antitussive agents on the coughing center and in other parts of the central structures of the cough reflex.) *Med. Pharmacol. Exp.* **1966**, *14*, 87−97.

(6) Grösswald, R. 1-Phenyl-1-(o-chlorophenyl)-3-dimethylamino-propanol-(1), ein neuer hustenhemmender Stoff. (1-Phenyl-1-(o-chlorophenyl)-3-dimethylamino-propanol-(1), a new antitussive agent.) *Arzneim.-Forsch.* **1958**, *8*, 550−553.

(7) (a) Canti, G.; Franco, P.; Micolin, A. Study on the pharmacological activity of 1-[2-(p-chloro-α-phenylbenzyloxy)ethylpiperidine (cloperastine). *Boll. Chim. Farm.* **1983**, *122*, 384−92. (b) Oldini, C.; Vecchi, E. Double-blind investigation of the antitussive effectiveness of cloperastine. *Curr. Ther. Res. Clin. Exp.* **1987**, *42*, 99−105.

(8) Rispat, G.; Burgi, H.; Cosnier, D.; Duchêne-Marullaz, P.; Streichenberger, G. General Pharmacological Properties of a New Non-opiate Antitussive: Zipeprol (3024 CERM). *Arzneim.-Forsch.* **1976**, *26*, 523−530. (b) Constantin, M.; Pognat, J. F. Zipeprol Metabolism in Man and in the Animal. *Arzneim.-Forsch.* **1978**, *28*, 64−72.

(9) (a) Noel, P. R. B. Dropropizine (UCB 1967), an Antitussive: Oral Toxicity Study in Pure-bred Dogs. *Arzneim.-Forsch.* **1969**, *19*, 1246−1249. (b) Cartwright, K.; Paterson, J. L. Human volunteer studies of the antitussive activity of dropropizine. *J. Pharm. Pharmacol.* **1971**, *23* (Suppl.), 247S. (c) Nosalova, G.; Korpas, J.; Strapkova, A. Experimental evaluation of a new Czechoslovak antitussive drug dropropizine (Ditustat). *Farmakoter. Zpr.* **1983**, *29*, 303−317.

(10) (a) Giani, R.; Marinone, E.; Melillo, G.; Borsa, M.; Tonon, G. C. Synthesis and Pharmacological Screening of New Phenylpiperazinepropane Derivatives and Their Enantiomers. *Arzneim.-Forsch.* **1988**, *38*, 1139−114. (b) Malandrino, S.; Melillo, G.; Bestetti, A.; Borsa, M.; Giuliani, P.; Tonon, G. C. Antitussive Properties of Levodropropizine. *Arzneim.-Forsch.* **1988**, *38*, 1141−1143. (c) Bosi, R.; Braga, P. C.; Centanni, S.; Legnani, D.; Moavero, N. E.; Allegra, L. Antitussive Activity and Respiratory System Effects of Levodropropizine in Man. *Arzneim.-Forsch.* **1988**, *38*, 1159−1166.

(11) Silvestrini, B.; Pozzatti, C. Antitussive Activity and Other Pharmacological Properties of Six Oxadiazoles. *Arch. Int. Pharmacodyn. Ther.* **1960**, *129*, 249−263. (b) Silvestrini, B.; Pozzatti, C. Pharmacological Properties of 3-Phenyl-5β-Diethylaminoethyl-1,2,4-Oxadiazole. *Br. J. Pharmacol. Chemother.* **1961**, *16*, 209−217.

(12) (a) Gandolfi, C. A.; Spinelli, S.; Tofanetti, O.; Russo, R.; Tognella, S. Antitussive and mucus regulating 2-substituted Thiazolidines. EP 169581 (26.07.85). (b) Di Domenico, R.; Castoldi, D.; Spinelli, S.; Tofanetti, O.; Tognella, S.; Gandolfi, C. A. 2-Sulphinyl acetyl 1,3-thiazolidines, their preparation and pharmaceutical compositions. EP 287042 (16.09.92). (c) Gandolfi, C. A.; Di Domenico, R.; Spinelli, S.; Lumachi, B.; Gallico, L.; Tognella, S. β-carbonyl carboxyamides of 1,3-thiazolidines. EP 333080 (13.10.93).

(13) Charlier, R.; Prost, M.; Binon, F.; Deltour, G. Etude Pharmacologique d'un antitussif, le fumarate acide de Phenethyl-1-(propyne-2-yl)-4-propionoxy-4-piperidine. (Pharmacological Studies on the Antitussive, Phenethyl-1-(propyne-2-yl)-4-propionoxy-4-piperidine fumarate.) *Arch. Int. Pharmacodyn.* **1961**, *84*, 306−327.

(14) Cavanagh, R. L.; Gylis, J. A.; Bierwagen, M. E. Antitussive properties of butorphanol. *Arch. Int. Pharmacodyn.* **1976**, *220*, 258−268.

(15) (a) Kasé, Y.; Yuizono, T.; Muto, M. Piperidino groups in antitussive Activity. *J. Med. Chem.* **1963**, *6*, 118−122. (b) Kano, H.; Adachi, I.; Kido, R.; Hirose, K. Isoxazoles. Synthesis and Pharmacological Properties of 5-Aminoalkyl- and 3-Aminoalkyl-isoxazoles and Related Derivatives. *J. Med. Chem.* **1967**, *10*, 411−418. (c) Miyano, S.; Abe, A.; Kasé, Y.; Yuizono, T.; Tachibana, K.; Miyata, T.; Kito, G. Synthesis and Pharmacological Evaluation of Some Pyridylmethyl Substituted Ethylenediamines. *J. Med. Chem.* **1970**, *13*, 704−708. (d) Rips, R.; Boschi, G.; Derappe, C.; Crucifix, M.; Albert, O. Etude pharmacochimique de benzhydramides. (Pharmaco-chemical studies on benzhydramides.) *Eur. J. Med. Chem.* **1976**, *11*, 25−28.

(16) (a) Lumachi, D.; Tofanetti, O. Internal report BBR 1501, Boehringer Mannheim Italia, 17.12.1986. (b) Maffei Ficino, R.; Carini, M. Metabolic investigation of BBR 1501. Unpublished results, 1986.

(17) De Angeli, L. Moguisteine. *Drugs Future* **1991**, *16*, 618−619.

(18) Kasua, Y.; Watanabe, M.; Miyasaka, K.; Ishii, Y. Potentiation of antitussive effect of Codeine by some 1-dimethoxyphenyl-3-3-alkylaminobutanols in guinea pigs. *Arzneim.-Forsch.* **1977**, *27*, 1450−1455.

(19) Forsberg, K.; Karlsson, J. A. Cough induced by stimulation of capsaicin-sensitive sensory neurons in conscious guinea pigs. *Acta Physiol. Scand.* **1986**, *128*, 319–320.
(20) (a) Gallico, L.; Borghi, A.; Dalla Rosa, C.; Lumachi, B.; Tofanetti, O.; Tognella, S. BBR 2173, a new non narcotic antitussive agent. *Pharm. Res. Commun.* **1988**, *20*, 171. (b) Gallico, L.; Borghi, A.; Della Rosa, C.; Oggioni, N.; Lumachi, B.; Tofanetti, O.; Tognella, S. Moguisteine: a new drug effective in experimental cough and hyperreactivity. *Am. Rev. Respir. Dis.* **1990**, *141*, A654.
(21) Gallico, L.; Borghi, A.; Dalla Rosa, C.; Ceserani, R.; Tognella, S. Effect of dexametasone and moguisteine on allergen induced early bronchocostriction and late-phase airway leucocyte recruitment in sensitised guinea pigs. *Br. J. Pharmacol.* **1992**, *106*, 75P.
(22) Montaguti, P.; Cavalletti, E. Preclinical toxicological evaluation of moguisteine. *Pharmacology and Toxicology EUROTOX 1993 Abstract volume*; Hellman, B., Lund, B. O., Deucker, L., Eds.; Published by the Nordic Pharmacological Society; Distributed by MUNKSGAARD: Copenhagen, 1993; Vol. 73 (Suppl. II), 74 (P4/03).
(23) (a) Bernareggi, A.; Carlesi, R. M.; Castoldi, D.; Casciarri, I.; Ceserani, R.; Silva, A.; Tognella, S. Moguisteine pharmacokinetics in animals and in man. *Eur. J. Drug Metab. Pharmacokinet.* **1993**, *18*, 163. (b) Ratti, D.; Bernareggi, A.; Carlesi, R. M.; Ceserani, R.; Silva, A.; Tognella, S. Moguisteine pharmacokinetics in adults and in elderly. *Eur. J. Drug Metab. Pharmacokinet.* **1993**, *18*, 171.
(24) (a) Sestini, P.; Refini, R. M.; Pieroni, M. G.; Ferretti, B.; Carlesi, R. M.; Assereto, R.; Bianco, S. Protective effect of the new antitussive drug moguisteine on citric acid-induced cough. *Eur. Respir. J.* **1990**, *3*, 160. (b) Moscato, G.; Della Bianca, A.; Carlesi, R. M.; Assereto, R.; Bertoletti, R. Preliminary clinical experiences with moguisteine in acetylcholine induced cough. *Eur. Respir. J.* **1990**, *3*, 93. (c) Morrone, L.; Pizza, A.; Martinelli, A.; Merlo, G.; Maiorano, V.; Chianese, R. Pilot study on efficacy and safety of a new antitussive drug, moguisteine: a double blind placebo controlled trial. *Adv. Ther.* **1993**, *10*, 67–73. (d) Del Donno, M.; Aversa, C.; Corsico, R.; Foresi, A.; Grassi, V.; Mastropasqua, B.; Scoditti, S.; Olivieri, D. Efficacy and safety of moguisteine in comparison with dextromethorphan in patient with persistent cough. *Eur. Respir. J.* **1993**, *6*, 324. (e) Adams, R.; Hosie, J.; James, I.; Kong, T.; Smith, I.; Wade, A. Antitussive activity and tolerability of moguisteine in patients with acute cough: a randomised, double–blind, placebo–controlled study. *Adv. Ther.* **1993**, *10*, 263–271.
(25) Cochran, W. G.; Snedecor, G. W. *Statistical methods*; Iowa State University Press: Aimes, IA, 1967; pp 159–160.
(26) Ashton, W. D. In *The logit transformation*; Stuart, A., Ed.; Charles Griffin & Co. LTD: London, 1972.
(27) (a) Brown, H. C.; MacFarlin, R. F. The Reaction of Lithium Aluminum Hydride with Alcohols. Lithium tri-*t*-butoxy-aluminohydride as a New Selective Reducing Agent. *J. Am. Chem. Soc.* **1958**, *80*, 5372. (b) Brown, H. C.; Shoaf, C. J. Selective Reductions. III. Further Studies of the Reaction of Alcohols with Aluminum Hydride as a Route to the Lithium Alkoxyaluminohydrides. *Ibid.* **1964**, *86*, 1079.
(28) Commercial grade (Fluka) or prepared from monoethylmalonic acid monopotassium salt (*Organic Synthesis*; Wiley, New York, 1963; Collect. Vol. IV, 417) in toluene (3 mL/g of reagent) with thionyl chloride (1.5 mol equiv cooled in 1 h at 10 °C). After about 24 h at room temperature, the solution can be used directly in the acylation step, after removing the excess of thionyl chloride, or ethyl malonyl chloride can be purified by distillation (60 °C, 3 mbar).
(29) If toluene is used as solvent, at the end of the reaction, it is removed in vacuo and the crude product is crystallized from methyl *tert*-butyl ether and recrystallized from the mixture EtOH/water.
(30) Ethyl 2,2-dimethylmalonyl chloride was prepared from diethyl 2,2-dimethylmalonate following the indication reported in ref 28 concerning the synthesis of ethyl malonyl chloride.

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