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Article

Synthesis of new 1,2-Benzothiazin-3-one Derivatives Designed as Dual Cyclooxygenase-2 and 5-Lipooxygenase Inhibitors[#]

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No âmbito de um programa de pesquisas que visa à síntese de novos fármacos antiinflamatórios não esteróides inibidores de enzimas da cascata do ácido araquidônico, descrevemos neste trabalho a síntese de duas novas séries de derivados 1,2-benzotiazin-3-ônicos α,β-insaturados (**3a-10a**) e (**3b-10b**), racionalmente planejados como possíveis inibidores duplos de cicloxigenase-2 (COX-2) e 5-lipoxigenase (5-LO). Os compostos-alvo (**3a-10a**) e (**3b-10b**) foram preparados com bons rendimentos globais, explorando como etapa chave da rota sintética empregada uma condensação de Knoevenagel-Doebner entre benzaldeídos substituídos (ex. 4-metoxi-benzaldeído) e o correspondente derivado 1,2-benzotiazin-3(4*H*)-ona 1,1-dióxido funcionalizado (**17a**) e (**17b**).

In the scope of a research program aiming at the synthesis of new nonsteroidal anti-inflammatory drugs (NSAIDs) acting on the enzymes of the arachidonic acid cascade, we describe in this paper the synthesis of two new series of functionalized α,β-unsaturated 1,2-benzothiazin-3-one derivatives (**3a-10a**) and (**3b-10b**), structurally designed as dual cyclooxigenase-2 and 5-lipooxygenase inhibitors by applying rational principles of molecular modification and hybridization. The target compounds (**3a-10a**) and (**3b-10b**) were prepared in good overall yields, exploring as the key step of the synthetic route a Knoevenagel-Doebner condensation between substituted benzaldehydes (*e.g.* 4-methoxy-benzaldehyde) and corresponding 1,2-benzothiazin-3(4*H*)-one 1,1-dioxide derivatives (**17a**) and (**17b**).

Keywords: *1,2-Benzothiazin-3-one 1,1-dioxide derivatives; diastereoselective Knoevenagel-Doebner condensation; dual COX-2/5-LO inhibitors; NSAID candidates*

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used in the treatment of rheumatoid arthritis and other inflammatory diseases[1].

The primary mechanism of action of most these agents involves the inhibition of the cyclooxygenase enzyme (COX) pathway[2], which is associated with the bioformation of prostaglandin H_2 (PGH_2) from cellular arachidonic acid (AA), the key step in the biosynthesis of prostaglandins (PG)[3].

A new isoform of COX, referred to as cyclooxigenase-2 (COX-2), has been recently described[4], which is involved in the production of pro-inflammatory prostaglandins[4]. The cyclooxygenase-1 (COX-1) is constitutively expressed in most tissues and in blood platelets; whereas the COX-2 is expressed only following cell activation for growth factors, lipopolysaccharide, and other cytokines, mitogens and endotoxins[5]. The structural comparison of COX-1 and COX-2 enzymes revealed 63% of identity and 77% of similarity at the amino acid sequence level[6]. Most studies have shown that recent new chemical entities, developed as NSAID

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candidates, which act as selective COX-2 inhibitors and presenting reduced side-effects, as the well-known irritant action on the stomach is the principle drawback of classical NSAIDs[7].

On the other hand, inhibition of 5-lipooxygenase (5-LO), the enzyme which catalyzes the biosynthesis of leukotrienes (LT) from AA, results in a decrease of these autacoids, which are involved in the physiopathological production of gastrointestinal ulceration and also promote inflammation due to chemotactic and chemokinetic effects[8]. Hence, the discovery of novel dual[9] and selective inhibitors of COX-2 and 5-LO has led to a new generation of NSAIDs with greater potency and reduced side-effect profile.

In the scope of a research program aiming at the synthesis and pharmacological evaluation of new lead-compounds, NSAID candidates, by exploring rational principles of molecular designing and hybridization[10], we described previously the development of new anti-inflammatory agents by modulating the COX[11], 5-LO[12], COX/5-LO[13] and selective COX-2[14] inhibition. Hereby, we describe in this paper the synthesis of two new series of functionalized 1,2-benzothiazin-3-one 1,1-dioxides (**3a-10a**) and (**3b-10b**), structurally planned as candidates for dual and selective inhibition of COX-2/5-LO enzymes.

These 1,2-benzothiazin-3-one compounds (**3a-10a**) and (**3b-10b**) were designed exploring the molecular hybridization of Meloxicam®[15] (**1**), a commercial NSAID of the oxicam class, described as a selective COX-2 agent and BF-389[16] (**2**), a substance containg a benzylidene moiety attached to a keto-heterocyclic nucleus, which also presents a selective COX-2 inhibitory action as well as 5-LO inhibition[9] due, at least in part, to the presence of 2,6-di-*tert*-butylphenol framework[17]. In fact, several derivatives possessing this structural unit have been described as dual CO/5-LO inhibitors[18]. In addition, the introduction of a di-*tert*-butylphenol unit produces a high lipophilic character in the compound, which could be useful for the desired activity. Both new series of target compounds, (**3a-10a**) and (**3b-10b**), possess an N-methy-aryl-sulfonamide moiety (A) and *(E)*-arylidene functionalized unit (B) (Chart 1), and present a *cis*-diaryl arrangement around the exo-cyclic double bond, as do several selective COX-2 inhibitors (*e.g.* **11** and **12**)[19] (Chart 1). The nature of the W substituent, present in the (*E*)-arylidene moiety of the *para*-monosubstituted derivatives (**3-8** and **10**), was defined in order to introduce in these series of compounds a variation in σ_p-Hammett values which could be used to investigate electronic effects of this structural sub-unit on the bioactivity. The choice of the oxygenated pattern present in the 1,2-benzothiazin-3-one unit of these new derivatives (**3a-10a**) and (**3b-10b**), was influenced by considering the 5-LO inhibitory activity of several compounds most likely mediated, at least in part, by an antioxidant or redox mechanism[20], and by naturally occurring diaryl-alkanoids, such as curcumin, displaying dual 5-LO and COX inhibition[21] due to the presence of a modified catechol unit capable of binding iron[22] present in the 5-LO. Additionally, the methylsulfone derivatives (**10a**) and (**10b**) were also planned as this functional group is present in some selective COX-2 agents (*e.g.* **11** and **12**)[19] and is considered to contribute to the enhancement of selectivity in COX-2 inhibition[19]. In short, these structural characteristics could introduce in compounds (**3a-10a**) and (**3b-10b**) an initial affinity-pattern for the target enzymes.

Results and Discussion

The synthesis of these new derivatives (**3-10**) was started by construction of the 1,2-benzothiazin-3-one 1,1-dioxide nucleus present in (**18**), which was identified as a common key intermediate to both series of derivatives (**3a-10a**) and (**3b-10b**), employing the synthetic sequence previously discovered in this laboratory by Fraga[11a] for the synthesis of new oxicam related compounds from natural safrole, using for this purpose the oxygenated phenylacetic acids (**13a,b**) as starting materials.

In the initial step of the planned synthetic route (Scheme 1), the phenylacetic acid derivatives (**13a**) and (**13b**) were converted into the corresponding methyl ester (**14a**) and (**14b**) by refluxing with MeOH containing a catalytic amount of concentrated sulfuric acid. Next, treatment of (**14a**) and (**14b**) with a mixture of concentrated sulfuric acid and acetic anhydride in ethyl acetate, followed by the

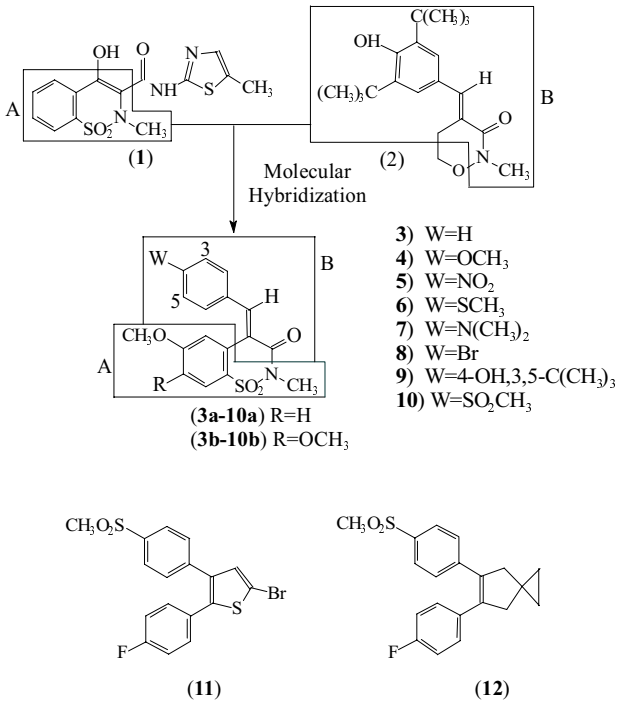


Chart 1.

addition of an ethanolic potassium acetate solution, furnished, as the only solid product, the corresponding potassium salt of the sulfonic acid derivatives (**15a**) and (**15b**), in 76% and 87% yield, respectively. The derivatives (**15a**) and (**15b**) were next treated with thionyl chloride in the presence of a catalytic amount of DMF, to furnish the unstable sulfonyl chloride intermediates, respectively in 86% and 92% yield. Immediately, these sulfonyl chloride derivatives were submitted to nucleophilic chloride atom displacement using a 40% aqueous methylamine solution, affording the nicely crystalline N-methylsulfonamide derivatives (**16a**) and (**16b**) in 91% and 85% yield, respectively. In the ^{1}H-NMR spectra of these derivatives we are able to detect a signal at δ 2.60 ppm, either as a singlet or a doublet due to the lability of **NH**, corresponding to N-methylsulfonamide hydrogens. Compounds (**16a**) and (**16b**) were subsequently hydrolyzed, by refluxing in an aqueous methanolic solution of KOH, furnishing the acid-sulfonamide derivatives (**17a**) and (**17b**) in 77% and 88% yield, respectively, which were submitted to the key cyclization step by refluxing in toluene under acidic conditions to afford the desired benzothiazin-3-one 1,1-dioxide derivatives (**18a**) and (**18b**) (Scheme 1), in 85% and 94% yield. These compounds exhibit in the ^{1}H-NMR spectra a typical singlet signal at δ 4.04 ppm attributed to the benzylic methylene hydrogens.

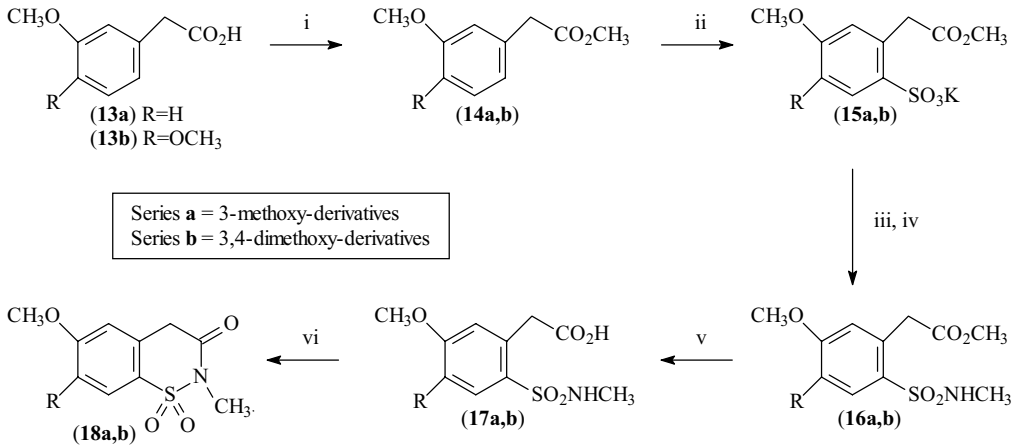
Finally, the desired new 1,2-benzothiazin-3-one derivatives (**3a-9a**) and (**3b-9b**) were prepared in good yield, as illustrated in Table 1, by condensation of (**18a**) or (**18b**) with the corresponding substituted benzaldehydes using classical Knoevenagel-Doebner conditions[23], *i.e.* pyridine and piperidine as bases. Under the experimental conditions employed, this process was highly diastereoselective, even specific in some cases. This became apparent from TLC experiments and NMR analytical data (Tables 2 and 3).

The preparation of the *para*-methyl-sulfone derivatives (**10a**) and (**10b**) was accomplished by selective S-oxidation of the corresponding methyl sulfide derivatives (**6a**) and (**6b**), using selenium dioxide in the presence of 30% aqueous hydrogen peroxide in MeOH at 0 °C[24], as shown in Table 4.

A careful analysis of the ^{1}H-NMR spectra of these new arylidene derivatives clearly indicated an unexpected high diastereoselectivity, producing the (*E*)-arylidene diastereomer as the major isomer for compounds (**4b**) and (**6-10a,b**), while one diastereomer was obtained in the case of compounds (**3a,b**), (**4a**) and (**5a,b**). The (*E*)-configuration of the major diastereomer was determined by ^{1}H-NMR spectroscopy, as follows. We are able to detect in the ^{1}H-NMR spectra of the (*E*)-(*Z*)-diastereomeric mixture (*e.g.* **4b**) a significant difference in the chemical shift of =C**H**- signals. For example, in the spectra of this compound (*e.g.* 78:22 ratio), the more downfield vinyl-**H** singlet signal (*ca.* 0.5 ppm; 7.87) was attributed to the (*E*)-isomer, whereas in the minor (*Z*)-isomer this hydrogen appears, also as a singlet, at δ 7.38. In addition, the diastereomeric ratio could be easily calculated by the difference of the relative integration of the C-6 methoxyl group occurring at 4.01 for the major (*E*)-isomer and at 4.06 for the minor (*Z*)-isomer.

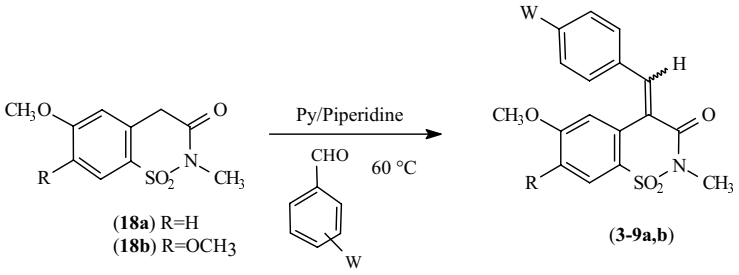
The determination of the relative configuration of the double bond in these compounds, could be confirmed by using NOEdif (nuclear Overhauser effect difference) technique in the ^{1}H-NMR which showed an important spatial interaction between H-5 and H-2' (NOE H-5 1.3%, H-2' 6.0%), indicative of the (*E*)-configuration for the major diastereomer[25]. The results of these experiments are described in Table 5.

The results of the observed diastereoselectivity in the condensation process were rationalized as follows. It is well known that two mechanisms can be operating in the



Scheme 1. i) MeOH, H_2SO_4, 60 °C, 4 h, a = 90%, b = 83%; ii) $(CH_3CO)_2O$, $CH_3CO_2CH_2CH_3$, H_2SO_4, CH_3CO_2K, rt, 3.5 h, a = 76%, b = 87%; iii) $SOCl_2$, DMF (cat), 60 °C, 3.5 h, a = 86%, b = 92%; iv) 40% aq. NH_2CH_3, $CHCl_3$, 0 °C, 3 h, a = 91%, b = 85%; v) KOH, MeOH/H_2O, reflux, 4 h, a = 77%, b = 88%; vi) TsOH, $PhCH_3$, reflux, 18 h, a = 85%, b = 94%.

Table 1. Preparation of 1,2-benzothiazin-3-one 1,1-dioxide derivatives (3a-9a) and (3b-9b) using Knoevenagel-Doebner conditions[23].



Compound	R	W	Time (h)	Yield (%)	mp (°C)	E:Z ratio[1,2]
3a	H	H	2	71	141-144	100:0
3b	OCH_3	H	2	75	220-223	100:0
4a	H	4'-OCH_3	3	88	152-155	100:0
4b	OCH_3	4'-OCH_3	4	81	177-180	78:22
5a	H	4'-NO_2	1	87	234-236	100:0
5b	OCH_3	4'-NO_2	1.5	94	239-241	100:0
6a	H	4'-SCH_3	1.5	94	133-136	88:12
6b	OCH_3	4'-SCH_3	1.5	90	216-218	93:7
7a	H	4'-$N(CH_3)_2$	2	83	164-166	93:7
7b	OCH_3	4'-$N(CH_3)_2$	2.5	77	215-218	87:13
8a	H	4'-Br	3	80	189-191	89:11
8b	OCH_3	4'-Br	3	75	217-219	85:15
9a	H	3',5'-di*t*Bu, 4'-OH	3	90	148-150	93:7
9b	OCH_3	3',5'-di*t*Bu, 4'-OH	3	76	157-159	89:11

1) Determined by relative integration of the 6-methoxyl proton signal on the ^{1}H-NMR spectrum ($CDCl_3$, 200 MHz).
2) The relative configuration of the major diastereomer was determined by NOEdif experiment, when the alkenyl proton signal is irradiated[25].

Knoevenagel-Doebner condensation[23], one of them, E_{1cb} and the other the E_2 mechanism. In this case, the observed diastereoselectivy can be explained by the E_{1cb} mechanism with intramolecular tautomeric catalysis (Scheme 2), due to the possibility of selective dehydration of the enol intermediate (**II**), with intramolecular hydrogen transfer, driving the preferential (*E*)-diastereomer formation.

Conclusions

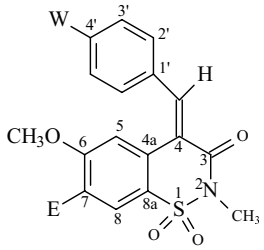
The synthetic route described herein to synthesize the new title compounds, (*E*)-N-methyl-6-methoxy- and (*E*)-N-methyl-6,7-dimethoxy-1,2 - benzothiazin - 3-one-4-benzylidene 1,1-dioxide derivatives (**3-10**), presented a very good overall yield, employing the classical Knoevenagel-Doebner condensation as the key step in the construction of the arylidene moiety. A very high level of diastereoselectivity was attained in the preparation of these compounds. These compounds will be submitted to biological assays in order to investigate the planned dual inhibitory activity of COX-2 and 5-LO enzymes.

Experimental

Melting points were determined with a Thomas-Hoover apparatus and are uncorrected. Proton magnetic resonance (^{1}H-NMR), unless otherwise stated, was performed in deuterated chloroform containing *ca.* 1% tetramethylsilane as an internal standard using Varian Gemini 200 and Brucker AC 200A spectrometers at 200 MHz. Splitting patterns are as follows: s, singlet; d, doublet; dd, doubled doublet; t, triplet; q, quartet; m, multiplet; br, broad. Carbon magnetic resonance (^{13}C-NMR) was determined on the same spectrometers described above at 50 MHz, using deuterated chloroform as internal standard. Infrared (IR) spectra were obtained with Nicolet-205, Nicolet-550 Magna and Perkin-Elmer-257 spectrophotometers using potassium bromide pellets. The mass spectra (MS) were obtained by electron impact with a GC/VG Micromass 12 spectrometer.

The progress of all reactions was monitored by TLC which was performed on 2.0 x 6.0 cm aluminum sheets precoated with silica gel 60 (HF-254, Merck) to a thickness of 0.25 mm. The developed chromatograms were

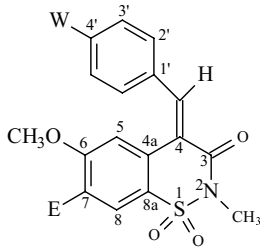
Table 2. ^{1}H-NMR data of benzothiazinone derivatives (3a-8a) and (3b-8b) [δ-ppm, 200 MHz, $CDCl_3$].



(3a-8a)
(3b-8b)

Compound	R	W	=C-H	Ar'-H_2,	Ar'-H_3,	C8-H	C5-H	C7-H	N-CH_3	O-CH_3
3a	H	H	8.00 (s)	7.45 (m)	7.35 (m)	7.90 (d, J = 9.00 Hz)	6.82 (d, J = 2.00 Hz)	6.93 (dd, J = 9.00 e 2.00 Hz)	3.35 (s)	3.51 (s)
3b	OCH_3	H	7.95 (s)		7.30 (m)		6.70 (s)	---	3.30 (s)	3.45 (s)
4a	H	OCH_3	7.90 (s)	7.45 (d, J = 8.90 Hz)	6.85 (d, J = 8.80 Hz)	6.96 (dd, J = 4.50 and 2.40 Hz)	7.02 (d, J = 2.40 Hz)	6.92 (dd, J = 4.20 and 2.40 Hz)	3.34 (s)	3.62 (s)
4b	OCH_3	OCH_3	7.87 (s)	7.45 (d, J = 8.40 Hz)	6.85 (d, J = 8.80 Hz)	7.38 (s)	6.92 (s)	---	3.35 (s)	3.55 (s)
5a	H	NO_2	7.89 (s)	7.55 (d, J = 8.50 Hz)	8.15 (d, J = 8.50 Hz)	7.89 (d, J = 8.50 Hz)	6.63 (d, J = 2.00 Hz)	6.95 (dd, J = 8.50 and 2.00 Hz)	3.33 (s)	3.58 (s)
5b	OCH_3	NO_2	7.90 (s)	7.60 (d, J = 8.80 Hz)	8.20 (d, J = 8.80 Hz)	6.60 (s)	7.40 (s)	---	3.40 (s)	3.48 (s)
6a	H	SCH_3	7.90 (s)	7.39 (d, J = 8.40 Hz)		7.15 (d, J = 8.55 Hz)	7.88 (d, J = 5.19 Hz)	6.93 (m)	3.35 (s)	3.65 (s)
6b	OCH_3	SCH_3	7.26 (s)	7.24 (d, J = 8.50 Hz)	7.62 (d, J = 8.32 Hz)	7.36 (s)	7.03 (s)	----	3.40 (s)	4.02 (s)
7a	H	$N(CH_3)_2$	7.88 (s)	7.45 (d, J = 8.70 Hz)	6.55 (d, J = 8.90 Hz)	7.82 (s)	7.25 (d, J = 2.50 Hz)	6.9 (dd, J = 9.00 and 2.50 Hz)	3.31 (s)	3.65 (s)
7b	OCH_3	$N(CH_3)_2$	7.85 (s)	7.45 (d, J = 8.80 Hz)	6.60 (d, J = 8.80 Hz)	7.20 (s)	7.40 (s)	---	3.35 (s)	3.60 (s)
8a	H	Br	7.32 (s)	7.53 (s)	7.86 (d, J = 8.6 Hz)	7.13 (d, J = 2.34 Hz)	7.0 (dd, J = 8.60 and 2.34 Hz)		3.35 (s)	3.95 (s)
8b	OCH_3	Br	7.85 (s)	7.31 (d, J = 8.30 Hz)	7.49 (d, J = 8.55 Hz)	7.40 (s)	6.71 (s)	---	3.38 (s)	4.0 (s)

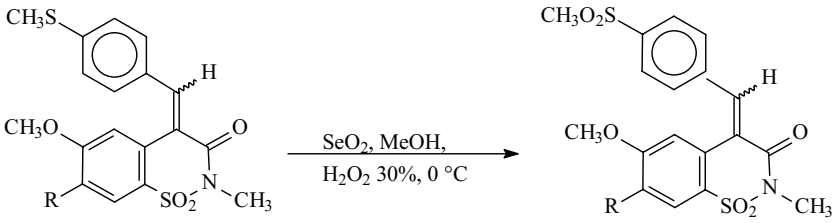
Table 3. ^{13}C-NMR data of benzothiazinone derivatives (3a-8a) and (3b-8b) [δ-ppm, 50 MHz, $CDCl_3$].



(**3a-8a**)
(**3b-8b**)

Compound	R	W	C=O	C-4	C-4a	C-5	C-6	C-7	C-8	C-8a	=C-H	C-1'	C-2'	C-3'	C-4'
3a	H	H	165.85	127.42	128.02	113.98	162.15	114.82	129.74	133.58	143.08	132.94	129.74	128.68	125.08
3b	OCH_3	H	165.81	124.11	126.94	105.19	151.63	149.03	111.67	128.02	141.55	133.93	129.66	129.66	128.57
4a	H	OCH_3	166.04	125.55	127.89	113.68	162.12	114.33	124.79	133.38	142.82	---	132.00	114.03	161.16
4b	OCH_3	OCH_3	166.07	124.50	124.50	105.18	160.94	148..86	111.22	127.90	141.32	125.86	131.94	113.89	151.64
5a	H	NO_2	162.73	128.98	---	114.74	139.34	115.20	125.75	---	140.55	132.16	124.03	130.55	131.28
5b	OCH_3	NO_2	165.34	122.89	128.65	111.43	151.97	149.82	105.72	130.28	137.68	140.58	123.77	130.55	147.81
6a	H	SCH_3	165.86	126.14	129.45	113.91	162.14	114.35	125.12	133.04	142.34	127.90	125.41	130.36	142.14
6b	OCH_3	SCH_3	164.32	128.40	126.06	108.25	153.07	148.92	104.96	126.79	142.03	130.03	125.17	130.73	141.77
7a	H	$N(CH_3)_2$	166.57	121.28	127.92	111.38	162.30	113.42	114.15	134.57	144.20	125.09	120.48	132.80	151.94
7b	OCH_3	$N(CH_3)_2$	167.20	121.38	126.55	111.90	152.50	152.36	105.98	128.44	143.34	121.77	---	133.29	149.35
8a	H	Br	---	124.31	127.17	111.64	163.53	113.18	124.73	128.17	142.15	132.56	131.45	131.45	136.43
8b	OCH_3	Br	165.72	123.73	128.24	111.40	149.30	151.79	105.41	127.59	139.81	123.99	131.41	131.97	132.75

Table 4. Preparation, diastereomer ratio and melting point of the new methylsulfone benzothiazinone derivatives (10a) and (10b)[24].



(**6a**) R=H
(**6b**) R=OCH_3

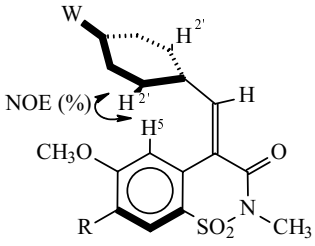
(**10a**) R=H
(**10b**) R=OCH_3

Compound	R	Time (h)	Yield (%)	mp (°C)	E:Z ratio[1,2]
10a	H	1	98	191-192	83:17
10b	OCH_3	1	95	222-223	88:12

1) Determined by relative integration of the 6-methoxyl proton signal on the pmr spectrum ($CDCl_3$, 200 MHz).
2) The relative configuration of the major diastereomer was determined by NOEdif experiment, when the alkenyl proton signal is irradiated[25].

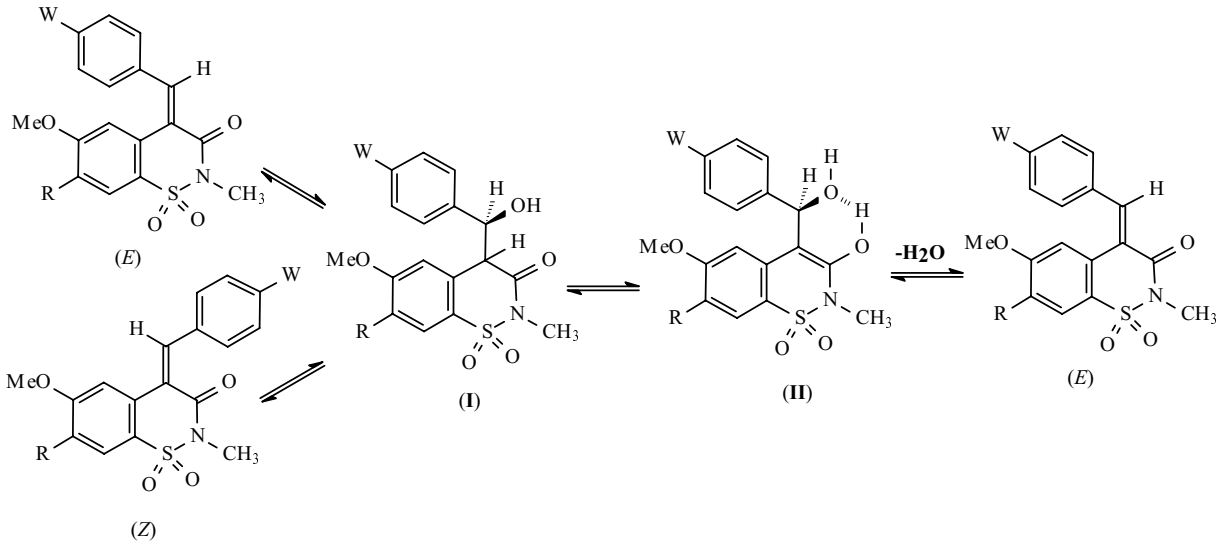
viewed under ultraviolet light. For column chromatography Merck silica gel (70-230 mesh) was used. Solvents used in the reactions were generally redistilled prior to use and stored over 3-4 A molecular sieves. Reactions were generally stirred under a dry nitrogen atmosphere. The usual work-up means that the organic extracts prior to concentration, under reduced pressure, were treated with a saturated aqueous sodium chloride solution, referred to as brine, dried over anhydrous sodium sulfate and filtered.

Table 5. Nuclear Overhauser Effect Difference (NOEdif) experiment, with representative benzothiazinone derivative (4b) at ^{1}H-NMR ($CDCl_3$, 200 MHz)[25].



(**4b**) R=OCH_3 ; W=OCH_3

	NOE (%)		
Irradiation	H-5	=C-H	H-2'
H-5	---	---	6
=C-H	0.8	---	14
H-2'	1.3	7.6	---



Scheme 2.

Methyl 3-methoxyphenylacetate[11a] (14a)

To a solution of 5 g (30.1 mmol) of acid derivative (13a) and 60 mL of absolute methanol were added dropwise 3.5 mL of concentrated sulfuric acid. The reaction mixture was refluxed for 4 h, poured into an ice water mixture and extracted with methylene chloride (3 x 40 mL). The organic extracts were washed with a 5% aqueous sodium bicarbonate solution (*ca.* 50 mL), dried and evaporated to give 5.6 g (90%) of compound 14a as brown oil; ^{1}H-NMR (200 MHz): δ 3.60 (s, 2H, Ar-C$\underline{H}_2CO_2CH_3$), 3.70 (s, 3H, Ar-$CH_2CO_2C\underline{H}_3$), 3.80 (s, 3H, Ar-O$C\underline{H}_3$), 6.83 (m, 3H, Ar-$\underline{H}_{2,4,6}$), 7.24 (m, 1H, Ar-$\underline{H}_3$) ppm; ^{13}C-NMR (50 MHz) δ: 41.05 (Ar$C\underline{H}_2$-), 51.85 (COO$\underline{C}H_3$,), 55.0 (ArO$\underline{C}H_3$), 112.46 (C_5), 114.75 (C_6), 121.42 (C_4), 129.37 (C_2), 135.22 (C_1), 159.55 (C_3), 171.70 ($\underline{C}$=O) ppm; IR (neat) cm^{-1}: 1740 (ν C=O), 1591 (ν C=C), 1151 (ν C-O).

Methyl 3,4-dimethoxyphenylacetate (14b)[26]

The derivative (14b) was prepared in 83% yield, employing the same procedure described above for compound (14a), as an yellow oil; ^{1}H-NMR (200 MHz): δ 3.60 (s, 2H, Ar-C$\underline{H}_2CO_2CH_3$), 3.73 (s, 3H, Ar-$CH_2CO_2C\underline{H}_3$), 3.90 (s, 3H, Ar-*m*-O$C\underline{H}_3$), 3.91 (s, 3H, Ar-*p*-O$C\underline{H}_3$), 6.85 (s, 3H, Ar-$\underline{H}_{2,5,6}$) ppm; ^{13}C-NMR (50 MHz) δ: 40.50 (Ar$C\underline{H}_2$-), 51.80 (COO$\underline{C}H_3$), 55.66 (Ar-*p*-O$\underline{C}H_3$), 55.68 (Ar-*m*-O$\underline{C}H_3$), 111.06 (C_6), 112.24 (C_5), 121.20 (C_2), 126.25 (C_1), 147.98 (C_3), 148.75 (C_4), 172.04 (C=O) ppm; IR (neat) cm^{-1}: 1737 (ν C=O), 1593 (ν C=C), 1155 (ν C-O).

Potassium 4-methoxy-2-carbomethoxymethylbenzenesulfonate[11a] (15a)

To a solution of 2 g (11.1 mmol) of ester derivative (14a) and 3.1 mL (33.8 mmol) of acetic anhydride in 16.5 mL of ethyl acetate was added, dropwise at 0 °C, a solution of 0.6 mL (12.0 mmol) of concentrated sulfuric acid in 4.4 mL of cold ethyl acetate. The reaction mixture was stirred at room temperature over 3 h, after which a solution of 1.2 g (12.0 mmol) of potassium acetate in 95% ethanol was added and the mixture was stirred additionally for 30 min at room temperature. The potassium salt 15a (1.52 g, 76%) was isolated by filtration as a white solid, mp 226 °C; ^{1}H-NMR (D_2O, 200 MHz): δ 3.62 (s, 3H, Ar-$CH_2CO_2C\underline{H}_3$), 3.80 (s, 3H, Ar-$OC\underline{H}_3$), 4.1 (s, 2H, Ar-$C\underline{H}_2CO_2CH_3$), 6.92 (m, 1H, Ar-H_3), 6.97 (d, 1H, J = 2.66 Hz, Ar-H_6), 7.80 (dd, 1H, J = 8.24 Hz and J = 0.82 Hz, Ar-H_5) ppm; IR (KBr) cm^{-1}: 1733 (ν C=O), 1608 and 1576 (ν C=C), 1224 and 1202 (ν C-O), 1164 and 1092 (ν SO_3).

Potassium 4,5-dimetoxy-2-carbomethoxymethylbenzenesulfonate (15b)

The derivative (15b) was prepared in 87% yield, employing the same procedure described above for compound (15a), as a white solid, mp 237 °C; IR (KBr) cm^{-1}: 1713 (ν C=O), 1604 and 1576 (ν C=C), 1286 and 1202 (ν C-O), 1171 and 1077 (ν SO_3).

4-Methoxy-2-carbomethoxymethylbenzene-N-methylsulfonamide[11a] (16a)

A solution of 2.76 mL (37.8 mmol) of thionyl chloride and 0.05 mL of dry dimethylformamide was added to 2 g (6.7 mmol) of potassium salt (15a). The reaction mixture, was stirred at 60 °C for 3.5 h, poured into an ice water mixture and extracted with methylene chloride (3 x 40 mL). The organic extract was dried and evaporated to give 1.7 g (85%) of the corresponding sulfonyl chloride as an unstable yellow solid, mp 73 °C. This sulfonyl chloride derivative was next dissolved in 17 mL of chloroform and then 1.5 mL (19.3 mmol) of an aqueous solution (40%) of methylamine was added. The reaction mixture was stirred for 3 h at 0 °C and then 17 mL of chloroform was added. The organic layer was separated, washed with a solution of 5% aqueous HCl solution (*ca.* 17 mL), water (*ca.* 17 mL) and then submitted to the usual workup, furnishing 1.55g (91%) of an orange solid, mp 77 °C; ^{1}H-NMR (200 MHz): δ 2.60 (s, 3H, -$SO_2NHC\underline{H}_3$), 3.75 (s, 3H, Ar-$CH_2CO_2C\underline{H}_3$), 3.88 (s, 3H, Ar-$OC\underline{H}_3$), 4.18 (s, 2H, Ar-$C\underline{H}_2CO_2CH_3$), 5.27 (s, 1H, -$SO_2N\underline{H}CH_3$), 6.88 (dd, 1H, J = 7.87 Hz and J = 2.4 Hz, Ar-H_5), 6.93 (d, 1H, J = 2.4 Hz, Ar-H_3), 7.93 (d, 1H, J = 8.48 Hz, Ar-H_6) ppm; ^{13}C-NMR (50 MHz) δ: 29.25 ($NHC\underline{H}_3$), 39.04 (Ar-$\underline{C}H_2$-), 52.29 ($COO\underline{C}H_3$), 55.42 (Ar-$O\underline{C}H_3$), 111.89 (C_3), 118.97 (C_5), 128.75 (C_2), 132.44 (C_6), 134.35 (C_1), 162.46 (C_4), 171.70 (C=O) ppm; IR (KBr) cm^{-1}: 3279 (ν N-H), 1733 (ν C=O), 1597 (C=C), 1331 and 1153 (ν SO_2), 1256 and 1207 (ν C-O).

4,5-Dimethoxy-2-carbomethoxymethylbenzene-N-methylsulfonamide (16b)

The derivative (16b) was prepared in 85% yield, employing the same procedure described above for compound (16a), as an orange solid; mp 132 °C, ^{1}H-NMR (200 MHz): δ 2.60 (d, 3H, -$SO_2NHC\underline{H}_3$, J = 5.22 Hz), 3.75 (s, 3H, Ar-$CH_2CO_2C\underline{H}_3$), 3.95 (s, 6H, Ar-$OC\underline{H}_3$) 4.15 (s, 2H, Ar-$C\underline{H}_2CO_2CH_3$), 5.35 (q, 1H, J = 5.22 Hz, $SO_2N\underline{H}CH_3$), 6.80 (s, 1H, Ar-H_3), 7.50 (s, 1H, Ar-H_6) ppm; ^{13}C-NMR (50 MHz) δ: 29.34 ($NHC\underline{H}_3$), 38.47 (Ar$\underline{C}H_2$-), 52.32 ($COO\underline{C}H_3$), 56.02 and 56.15 (Ar-$O\underline{C}H_3$), 112.90 (C_3), 115.14 (C_6), 125.66 (C_2), 128.72 (C_1), 147.48 (C_4), 151.74 (C_5), 172.67 (C=O) ppm; IR (KBr) cm^{-1}: 3270 (ν N-H), 1733 (ν C=O), 1603 and 1578 (ν C=C), 1306 and 1144 (ν SO_2), 1227 and 1208 (ν C-O).

2-(N-Methylsulfamoyl)-5-methoxyphenylacetic acid[11a] (17a)

The methyl ester (16a) (2 g, 7.3 mmol) was refluxed in 240 mL of aqueous methanolic solution (1:1) containing 4.6 g (82.4 mmol) of potassium hydroxide for 4 h. Neutralization of the reaction mixture with hydrochloric acid followed by extraction with ethyl acetate (5 x 40 mL) furnished after usual workup 1.54 g (77%) of (17a), as a light yellow solid, mp 130 °C; ^{1}H-NMR (200 MHz): δ 2.50 (s, 3H, -$SO_2NHC\underline{H}_3$), 3.85 (s, 3H, Ar-$OC\underline{H}_3$), 4.05 (s, 2H, Ar-$C\underline{H}_2CO_2CH_3$), 5.00 (br, 2H, -$SO_2N\underline{H}CH_3$ and -$COO\underline{H}$), 6.97 (m, 2H, Ar-$H_{4,6}$), 7.85 (dd, 1H, J = 9.4 Hz and J = 1,74 Hz, Ar-H_3) ppm; IR (KBr) cm^{-1}: 3335 (ν N-H), 3000 (ν O-H), 1703 (ν C=O), 1601 (C=C), 1321 and 1158 (ν SO_2), 1247 (C-O).

2-(N-Methylsulfamoyl)-4,5-dimethoxyphenylacetic acid (17b)

The derivative (17b) was prepared in 88% yield, employing the same procedure described above for compound (17a), as a yellow solid; mp 176 °C; ^{1}H-NMR (200 MHz): ν 2.53 (s, 3H, -$SO_2NHC\underline{H}_3$), 3.90 (s, 6H, Ar-$OC\underline{H}_3$), 4.05 (s, 2H, Ar-$C\underline{H}_2CO_2CH_3$), 4.90 (br, 2H, $SO_2N\underline{H}CH_3$ and $COO\underline{H}$), 7.05 (s, 1H, Ar-H_2), 7.45 (s, 1H, Ar-H_5) ppm; IR (KBr) cm^{-1}: 3329 (ν N-H), 1706 (ν C=O), 1604 (ν C=C), 1324 and 1176 (ν SO_2), 1272 (ν C-O).

2-Methyl-6-methoxy-1,2-benzothiazin-3-one 1,1-dioxide[11a] (18a)

A solution of compound (17a) (0.6 g, 2.32 mmol) and p-toluenesulfonic acid (0.063 g, 0.37 mmol) in 105 mL of toluene was refluxed using a Dean-Stark trap for 18 h. The

solvent was next evaporated and the resulting solid recrystallized from ethanol:water to give (18a) (0.48 g, 80%), as a beige solid, mp 133-134 °C; ^{1}H-NMR (200 MHz): ν 3.35 (s, 3H, -$SO_2NC\underline{H}_3$), 3.90 (s, 3H, Ar-$OC\underline{H}_3$), 4.08 (s, 2H, Ar-$C\underline{H}_2CO$-), 6.85 (d, 1H, J = 2.29 Hz, Ar-H_5), 6.95 (dd, 1H, J = 8.70 Hz and J = 2.38 Hz, Ar-H_7), 7.30 (d, 1H, J = 8.70 Hz, Ar-H_8) ppm; ^{13}C-NMR (50 MHz) δ: 26.66 (-$N\underline{C}H_3$), 39.41 (Ar-$\underline{C}H_2CO$-), 55.67 (Ar-$O\underline{C}H_3$), 112.60 (C_5), 114.17 (C_7), 124.97 (C_8), 127.41 (C_{4a}), 133.20 (C_{8a}), 163.22 (C_6), 167.97 (C=O); IR (KBr) cm^{-1}: 1705 (ν C=O), 1598 (ν C=C), 1335 and 1158 (ν SO_2), 1271 (ν C-O).

2-Methyl-6,7-dimethoxy-1,2-benzothiazin-3-one 1,1-dioxide (18b)

The derivative (18b) was prepared in 94% yield, employing the same procedure described above for compound (18a), as a beige solid; mp 182-183 °C; ^{1}H-NMR (200 MHz): δ 3.35 (s, 3H, -$SO_2NC\underline{H}_3$), 3.95 (s, 6H, Ar-$OC\underline{H}_3$), 4.02 (s, 2H, Ar-$C\underline{H}_2CO$-), 6.80 (s, 1H, Ar-H_5), 7.40 (s, 1H, Ar-H_8) ppm; ^{13}C-NMR (50 MHz) ν: 26.65 (-$NH\underline{C}H_3$), 38.73 (Ar-$\underline{C}H_2CO$-), 56.27 and 56.32 (Ar-$O\underline{C}H_3$), 105.59 (C_5), 110.80 (C_8), 124.33 (C_{4a}), 126.95 (C_{8a}), 148,32 (C_6), 152.82 (C_7), 168.23 (C=O) ppm; IR (KBr) cm^{-1}: 1705 (ν C=O), 1603 and 1582 (ν C=C), 1328 and 1158 (ν SO_2), 1275 (ν C-O).

General procedure for the reaction of methoxybenzothiazinones (18a) and (18b) with benzaldehydes[23]

To a solution of 1 mmol of benzothiazin-3-one derivative (18a) or (18b) in pyridine (3 mmol) containing a catalytic amount of piperidine was added 1.2 mmol of the respective benzaldehyde derivative. The reaction mixture was heated at 60 °C, until the TLC analysis indicated total consumption of methylene-active compound (see Table 1). Then, *ca.* 5 mL of water were added and the resulting precipitate filtered out, washed with 5% aqueous copper sulfate solution, 5% aqueous Girard'P® solution (*ca.* 10 mL) then the precipitate was filtered out and air dried. Recrystallization from ethanol:water gave the analytically pure compound.

2-Methyl-6-methoxy-1,2-benzothiazin-3-one-4-benzylidene 1,1-dioxide (3a)

The derivative (3a) was obtained in 71% yield, by condensation of (18a) with benzaldehyde, as a beige solid, mp 141-144 °C; for NMR data see Tables 2 and 3; IR (KBr) cm^{-1}: 1691 (ν C=O), 1595 (ν C=C), 1338 and 1151 (ν SO_2), 1271 (ν C-O); MS (m/z): 359 (M^+, 100%), 223 (10%), 152 (20%), 76 (13%).

2-Methyl-6,7-dimethoxy-1,2-benzothiazin-3-one-4-benzylidene 1,1-dioxide (3b)

The derivative (3b) was obtained in 75% yield, by condensation of (18b) with benzaldehyde, as a beige solid, mp 220-223 °C; for NMR data see Tables 2 and 3; IR (KBr) cm^{-1}: 1681 (ν C=O), 1595 (ν C=C), 1339 and 1177 (ν SO_2), 1278 (ν C-O); MS (m/z): 328 (M^+, 100%), 264 (17%), 165 (30%), 77 (13%).

2-Methyl-6-methoxy-1,2-benzothiazin-3-one-4-(4'-methoxybenzylidene) 1,1-dioxide (4a)

The derivative (4a) was obtained in 88% yield, by condensation of (18a) with 4-methoxybenzaldehyde, as a yellow solid, mp 152-155 °C; for NMR data see Tables 2 and 3; IR (KBr) cm^{-1}: 1685 (ν C=O), 1598 (ν C=C), 1339 and 1174 (ν SO_2), 1255 (ν C-O); MS (m/z): 359 (M^+, 100%), 294 (8%), 152 (15%), 121 (13%).

2-Methyl-6,7-dimethoxy-1,2-benzothiazin-3-one-4-(4'-methoxybenzylidene) 1,1-dioxide (4b)

The derivative (4b) was obtained in 81% yield, by condensation of (18b) with 4-methoxybenzaldehyde, as a yellow solid, mp 177-180 °C; for NMR data see Tables 2 and 3; IR (KBr) cm^{-1}: 1682 (ν C=O), 1593 (ν C=C), 1336, 1174 and 1151 (ν SO_2), 1268 (ν C-O); MS (m/z): 389 (M^+, 100%), 374 (8%), 139 (7%), 91 (4%).

2-Methyl-6-methoxy-1,2-benzothiazin-3-one-4-(4'-nitrobenzylidene) 1,1-dioxide (5a)

The derivative (5a) was obtained in 87% yield, by condensation of (18a) with 4-nitrobenzaldehyde, as a yellow solid, mp 234-236 °C; for NMR data see Tables 2 and 3; IR (KBr) cm^{-1}: 1685 (ν C=O), 1592 (ν C=C), 1523 and 1293 (ν N=O), 1344 and 1178 (ν SO_2), 1272 (ν C-O); MS (m/z): 374 (M^+, 100%), 163 (30%), 152 (13%), 63 (10%).

2-Methyl-6,7-dimethoxy-1,2-benzothiazin-3-one-4-(4'-nitrobenzylidene) 1,1-dioxide (5b).

The derivative (5b) was obtained in 94% yield, by condensation of (18b) with 4-nitrobenzaldehyde, as a yellow solid, mp 239-241 °C; for NMR data see Tables 2 and 3; IR (KBr) cm^{-1}: 1694 (ν C=O), 1596 (ν C=C), 1504 (ν N=O), 1345 and 1151 (ν SO_2), 1276 (ν C-O); MS (m/z): 404 (M^+, 100%), 271 ($M^{+\cdot}$ -133, 14%), 150 ($M^{+\cdot}$ -254, 44%), 77 ($M^{+\cdot}$ -327, 9%).

2-Methyl-6-methoxy-1,2-benzothiazin-3-one-4-(4'-methylthiobenzylidene) 1,1-dioxide (6a)

The derivative (6a) was obtained in 94% yield, by condensation of (18a) with 4-methylthiobenzaldehyde, as a yellow solid, mp 133-136 °C; for NMR data see Tables 2 and 3; IR (KBr) cm^{-1}: 1686 (ν C=O), 1589 (ν C=C), 1344

and 1175 (ν SO_2), 1274 (ν C-O), 643 (ν S-C); MS (m/z): 375 (M^+, 100%), 195 (9%), 151 (10%), 63 (5%).

2-Methyl-6,7-dimethoxy-1,2-benzothiazin-3-one-4-(4'-methylthio-benzylidene) 1,1-dioxide (6b)

The derivative (6b) was obtained in 90% yield, by condensation of (18b) with 4-methylthiobenzaldehyde, as a yellow solid, mp 216-218 °C; for NMR data see Tables 2 and 3; IR (KBr) cm^{-1}: 1679 (ν C=O), 1602 and 1590 (ν C=C), 1339 and 1155 (ν SO_2), 1283 (ν C-O), 643 (ν S-C); MS (m/z): 405 (M^+, 100%), 390 (5%), 150 (9%), 137 (7%).

2-Methyl-6-methoxy-1,2-benzothiazin-3-one-4-(4'-dimethylaminebenzylidene) 1,1-dioxide (7a)

The derivative (7a) was obtained in 83% yield, by condensation of (18a) with 4-dimethylaminobenzaldehyde, as an orange solid, mp 164-166 °C; for NMR data see Tables 2 and 3; IR (KBr) cm^{-1}: 1678 (ν C=O), 1582 (ν C=C), 1331 and 1170 (ν SO_2), 1273 (ν C-O); MS (m/z): 372 (M^+, 100%), 148 (53%), 77 (11%).

2-Methyl-6,7-dimethoxy-1,2-benzothiazin-3-one-4-(4'-dimethylaminebenzylidene) 1,1-dioxide (7b)

The derivative (7b) was obtained in 77% yield, by condensation of (18b) with benzaldehyde, as an orange solid, mp 215-218 °C; for NMR data see Tables 2 and 3; IR (KBr) cm^{-1}: 1671 (ν C=O), 1610 and 1568 (ν C=C), 1327 and 1166 (SO_2), 1266 (ν C-O); MS (m/z): 402 (M^+, 13%), 262 (140), 148 (75%), 77 (18%).

2-Methyl-6-methoxy-1,2-benzothiazin-3-one-4-(4'-bromobenzylidene) 1,1-dioxide (8a)

The derivative (8a) was obtained in 80% yield, by condensation of (18a) with 4-bromobenzaldehyde, as a beige solid, mp 189-191 °C; for NMR data see Tables 2 and 3; IR (KBr) cm^{-1}: 1686 (ν C=O), 1593 and 1578 (ν C=C), 1343 and 1176 (ν SO_2), 1282 (ν C-O); MS (m/z): 409 (M^+, 100%), 164 (32%), 63 (10%).

2-Methyl-6,7-dimethoxy-1,2-benzothiazin-3-one-4-(4'-bromobenzylidene) 1,1-dioxide (8b)

The derivative (8b) was obtained in 75% yield, by condensation of (18b) with 4-bromobenzaldehyde, as a beige solid, mp 217-219 °C; for NMR data see Tables 2 and 3; IR (KBr) cm^{-1}: 1690 (ν C=O), 1597 (ν C=C), 1337 and 1152 (ν SO_2), 1272 (ν C-O); MS (m/z): 439 (M^+, 9%), 366 (73), 209 (100%), 89 (78%).

2-Methyl-6-methoxy-1,2-benzothiazin-3-one-4-(3',5'-ditertbutyl-4'-hydroxybenzylidene) 1,1-dioxide (9a)

The derivative (9a) was obtained in 90% yield, by condensation of (18a) with 4-hydroxy-3,5-di-tertbutylbenzaldehyde, as a yellow solid, mp 148-150 °C; ^{1}H-NMR (200 MHz): Δ 1.33 (s, 18H, Ar'-C($C\underline{H}_3$)$_3$), 3.32 (s, 3H, $SO_2NC\underline{H}_3$), 3.63 (s, 3H, Ar-$OC\underline{H}_3$), 5.52 (s, 1H, Ar'-O<u>H</u>), 6.92 (dd, 1H, J = 8.63 Hz and J = 2.32 Hz, Ar-H_7), 7.04 (d, 1H, J = 2.32 Hz, Ar-H_5), 7.33 (s, 2H, Ar'-$H_{2'}$), 7.86 (s and d, 2H, Ar'-$H_{8'}$ and =C<u>H</u>, respectively, J = 8.62 Hz) ppm; ^{13}C-NMR (50MHz): δ 26.85 (N-$\underline{C}H_3$), 30.10 (Ar'-C($\underline{C}H_3$)$_3$), 34.32 (Ar'-$\underline{C}(CH_3)_3$), 55.49 (Ar-$O\underline{C}H_3$), 114.03 (C_5), 114.12 (C_7), 124.24 ($C_{3'}$ and C_{4a}), 125.16 (C_8), 128.24 ($C_{2'}$), 134.09 ($C_{1'}$), 136.34 (C_{8a}), 144.35 (=<u>C</u>-H), 156.23 ($C_{4'}$), 162.18 (C_6), 166.44 (C=O) ppm; IR (KBr) cm^{-1}: 3570 (ν O-H), 1684 (ν C=O), 1591 (ν C=C), 1339 and 1176 (ν SO_2), 1268 (ν C-O); MS (m/z): 457 (M^+, 100%), 442 (15%), 147 (17%), 57 (24%).

2-Methyl-6,7-dimethoxy-1,2-benzothiazin-3-one-4-(3',5'-ditertbutyl-4'-hydroxy benzylidene) 1,1-dioxide (9b)

The derivative (9b) was obtained in 76% yield, by condensation of (18b) with 4-hydroxy-3,5-ditertbutylbenzaldehyde, as a yellow solid, mp 157-159 °C, ^{1}H-NMR (200 MHz): δ 1.34 (s, 18H, Ar'-C($C\underline{H}_3$)$_3$), 3.31 (s, 3H, $SO_2NC\underline{H}_3$), 3.52 (s, 3H, C_6-$OC\underline{H}_3$), 3.94 (s, 3H, C_7-$OC\underline{H}_3$), 5.48 (s, 1H, Ar'-O<u>H</u>), 6.89 (s, 1H, Ar-H_8), 7.24 (d, 3H, J = 4.00 Hz, Ar-$H_{2'}$ and Ar-H_5), 7.83 (s, 1H, =C-<u>H</u>) ppm; ^{13}C-NMR (50MHz): δ 27.48 (N-$\underline{C}H_3$), 30.78 (Ar'-C($\underline{C}H_3$)$_3$), 34.95 (Ar'-$\underline{C}(CH_3)_3$), 56.52 (C_6-$O\underline{C}H_3$), 57.13 (C_7-$O\underline{C}H_3$), 106.05 (C_8), 112.14 (C_5), 124.73 (Ar-<u>C</u>=C-H), 125.55 (C_{8a}), 126.04 (C_{4a}), 128.56 ($C_{2'}$), 137.03 ($C_{1'}$), 143.67 (=<u>C</u>-H), 149.47 ($C_{4'}$), 152.83 (C_7), 156.53 (C_6), 167.11 (C=O) ppm; IR (KBr) cm^{-1}: 1688 (ν C=O), 1602 (ν C=C), 1343 and 1150 (ν SO_2), 1271 (ν C-O); MS (m/z): 487 (M^+, 100%), 472 (15%), 147 (7%), 57 (15%).

2-Methyl-6-methoxy-1,2-benzothiazin-3-one-4-(4'-methylsulfonebenzylidene) 1,1-dioxide (10a)

To a solution of 0.15 g (0.37 mmol) of the methylsulfide derivative (**6a**) in 0.3 mL of absolute methanol was added 0.041 g (0.37 mmol) of selenium dioxide and 0.05 mL (0.5 mmol) of the 30% aqueous hydrogen peroxide. The reaction mixture was stirred at 0 °C for 1 h. Then, 10 mL of chloroform was added and the resulting organic layer was washed with water and submitted to the usual work-up to give 0.158 g (98%) of the methylsulfone derivative (**10a**) as a yellow solid, mp 191-192 °C ; ^{1}H-NMR (200 MHz): δ 3.10 (s, 3H, Ar'-$SO_2C\underline{H}_3$), 3.40 (s, 3H, $SO_2NC\underline{H}_3$), 3.60 (s, 3H, Ar-$OC\underline{H}_3$), 6.75 (d, 1H, J = 2.5 Hz, Ar-H_5), 6.98 (dd, 1H, J = 8.79 Hz and J = 2.48 Hz, Ar-H_7), 7.62 (m, 3H, Ar'-$H_{2'}$ and Ar-H_8), 7.92 (s, 1H, =C<u>H</u>), 7.95 (s, 2H, Ar'-$H_{3'}$) ppm; ^{13}C-NMR (50MHz): δ 26.86 (N$\underline{C}H_3$), 44.13 (Ar'-$SO_2\underline{C}H_3$), 55.43 (Ar-$O\underline{C}H_3$), 114.26 (C_5), 114.27 (C_5), 123.80 ($C_{3'}$), 125.33 (C_8), 128.02 (C_4), 129.09 (C_{4a}), 130.42 ($C_{2'}$), 132.13 (C_{8a}), 136.31 ($C_{1'}$), 140.69 (=<u>C</u>H), 147.26 ($C_{4'}$), 162.20 (C_6), 165.44 (C=O) ppm; IR (KBr)

cm^{-1}: 1689 (ν C=O), 1595 (ν C=C), 1344 and 1178 (ν SO_2), 1280 (ν C-O).

2-Methyl-6,7-dimethoxy-1,2-benzothiazin-3-one-4-(4'-methylsulfonebenzylidene) 1,1-dioxide (10b)

The derivative (10b) was prepared in 95% yield, employing the same procedure described above for compound (10a), as a yellow solid; mp 222-223 °C; ^{1}H-NMR (200 MHz): δ 3.10 (s, 3H, Ar'-$SO_2C\underline{H}_3$), 3.38 (s, 3H, $SO_2NC\underline{H}_3$), 4.00 (s, 6H, Ar-$OC\underline{H}_3$), 7.10 (s, 1H, Ar-H_5), 7.40 (s, 1H, Ar-H_8), 7.67 (d, 2H, J = 8.43 Hz, Ar'-$H_{2'}$), 7.76 (d, 2H, J = 8.40 Hz, Ar'-$H_{3'}$), 7.95 (s, 1H, =C$\underline{H}$) ppm; ^{13}C-NMR (50MHz): δ 26.95 (N$\underline{C}H_3$), 44.10 (Ar'-$SO_2\underline{C}H_3$), 55.87 and 56.55 (Ar-O$\underline{C}H_3$), 105.79 (C_8), 111.75 (C_5), 123.57 ($C_{3'}$), 127.18 (C_{8a}), 128.66 (C_{4a}), 130.37 (C_4), 130.49 ($C_{2'}$), 138.08 ($C_{4'}$), 140.29 (=$\underline{C}$H), 151.86 (C_7), 153.11 (C_6), 163.86 (C=O); IR (KBr) cm^{-1}: 1680 (ν C=O), 1600 (ν C=C), 1342 and 1154 (ν SO_2), 1286 (ν C-O).

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