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Novel thiazolyl, thiazolinyl and benzothiazolyl Schiff bases as possible lipoxygenase's inhibitors and anti-inflammatory agents☆

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Abstract

In continuation of our previous research, several new thiazolyl/thiazolinyl/benzothiazolyl Schiff bases have been designed, synthesized and identified. The referred compounds are reported to act as lipoxygenase inhibitors affecting inflammation and/or psoriasis. The compounds were screened for their reducing activity (with the stable free radical 1,1-diphenyl-2-picryl-hydrazyl, DPPH) and for inhibition of soybean lipoxygenase (LOX). Anti-inflammatory activity was examined in vivo using the carrageenin induced mice paw edema (32.6–75%). The results are discussed in terms of structural and physicochemical characteristics of the compounds. Compound **2d** possessed the highest inhibition 75%.
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Keywords: Lipoxygenase inhibitors; Anti inflammatory agents; Schiff bases

1. Introduction

Non steroidal anti-inflammatory drugs (NSAIDs) are the main therapeutic agents for the treatment of inflammatory diseases. The common mechanism of action of this broad class of drugs is believed to be inhibition of the enzyme cycloxygenase and consecutively inhibition of the conversion of arachidonic acid into prostaglandins [1]. Cyclooxygenase (CO) and 5-Lipoxygenase (5-LO) are enzymes which catalyze the rate-limiting steps in the biosynthesis of prostaglandins (PGs) and leukotrienes (LT) respectively, from arachidonic acid [2,3].

The biosynthetic cascade of arachidonic acid has been the object of intense research. Arachidonic acid liberated from phospholipids by various stimuli can be metabolized by the cyclooxygenase (COX) pathway to prostaglandins (PGs) and thromboxane A_2 or by lipoxygenase (LO) pathways to hydroperoxyeicosatetraenoic acids (HPETEs), hydroxyeicosatetranoic acids (HETEs) and leukotrienes (LTs). The major products of 5-LO leukotrienes (LTs) are a family of important biologically active mediators in a variety of conditions including asthma, psoriasis, ulcerative colitis and rheumatoid arthritis [2,3]. The recent recognition of the lipoxygenase products as mediators of inflammation had led to a better understanding of the pathogenesis of psoriasis and provides new targets for therapeutical interventions. For this reason it is believed that restricting LT synthesis by inhibition of 5-LO will have therapeutic utility for the treatment of a variety of inflammatory conditions (e.g. asthma, rheumatoid arthritis, psoriasis). Generally 5- and 12-LOs are attractive targets for the development of anti-psoriatic drugs [3]. Evidence for a correlation between anti-psoriatic activity of drugs of diverse structure and inhibition of lipoxygenases, came from assays using soybean LO [3].

Thiazolyl and benzothiazolyl groups are of importance in biological systems as anti-inflammatory, analgesic agents and inhibitors on lipoxygenase activities [4,5]. Vanilloids, capsaicin analogs as well as several phenols and catechols have been found [6] to possess anti-inflammatory and antioxidant activities. Topical application with the above-mentioned compounds was

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found to improve psoriatic skin lesions. Capsaicin analogs [7] in which the alkyl chain part of the molecule (amides of vanillylamine/homovanilic acid) is varied, have been reported to exert antinociceptive and anti-inflammatory effects.

The effective role of azomethine linkage in certain biological reactions [8] is well documented. Simple stable molecules containing the hydroxamic acid [9] functionality as well as methoxy –alkylthiazoles and 6-hydroxybenzothiazoles [10] were reported as LOs inhibitors. According to our previous findings (Table 1) [11], Schiff bases were found to be inhibitors of soybean lipoxygenase and potent anti-inflammatories.

As a part of a program to develop improved anti-inflammatory/anti-allergy agents, we tried: (a) to replace an H (R_1) by a Br atom (except of iodine); (b) to put a second bulky as well as highly lipophilic group at position 5 of the thiazolyl ring; (c) to have no substituent at position 6 ($R_3 = H$) of the benzothiazolyl ring, on the contrary to have a Cl atom at position 5, replacing the H; and (d) to replace the thiazolyl/benzothiazolyl ring moiety by a thiazolinyl ring in order to delineate the role of the nature of the ring on the biological activity.

In this paper, we have prepared some new substituted derivatives and we describe the synthesis, their antioxidant activity (as % interaction to DPPH), their activity against soybean lipoxygenase and their effect on the carrageenin induced mice paw edema [6].

2. Experimental

2.1. Chemistry

Melting points (uncorrected) were determined on a MEL-Temp II (Lab. Devices, Holliston, MA). UV (in absolute ethanol), IR (film neat or as Nujol mulls), ^{1}H NMR (in $CDCl_3$ for the bases, DMSO-d_6 for the salts, tetramethylsilane as internal standard). Spectra were recorded with Perkin–Elmer 597, a 554 double beam spectrophotometer (The Perkin–Elmer Corporation Ltd., Lane Beaconsfield, Bucks, England) and a Bruker Analytische Messtechnik GmbH, Rheinstetten, Germany). Chemical shifts were expressed in δ (ppm) values. MS spectra were determined on a VG-250 spectrometer (VG-Labs., Tritech, UK) with ionization energy maintained at 70 eV. All the compounds gave spectra consisted with the structures. Elemental analyses were obtained on an acceptable range ($\pm$0.4%) in a Perkin–Elmer 240B CHN analyzer (The Perkin–Elmer Corporation Ltd., Lane Beaconsfield, Bucks, UK). Thin layer chromatography (TLC) was performed on silica gel (60 F_{254}, Merck, Darmstadt, Germany). Acetylsalicylic acid was also purchased by Merck, Darmstadt, Germany.

All the chemicals used were of analytical grade and commercially available by Merck. Carrageenin K-type was commercially available.

$CDCl_3$, DMSO-d_6, tetramethylsilane, Nujol, nordihydroguaretic acid (NDGA) and 1,1-diphenyl-2-picrylhydrazyl free stable radical were purchased from the Aldrich Chemical Co., Milwaukee, WI. Soybean lipoxygenase, linoleic acid sodium salt and indomethacin came from Sigma Chemical Co., St. Louis, MO.

Table 1
Previous series of Schiff bases for the general structure: Z–N=CH–$C_6H_5R_1R_2OH$

Series of derivatives	R_1, R_2
a	H, H
b	H, OCH_3
c	OCH_3, OCH_3
d	I, OCH_3

Z = C_3H_2SN, 4-C_6H_5–C_3HSN, 6-OC_2H_5–C_7H_3SN, 6-F–C_7H_3SN, 6-CH_3–C_7H_3SN, 4-CH_3– C_3HSN.

2.2. Synthesis

2.2.1. General procedure A [8,11]

Substituted 2-amino-thiazoles (0.01 mol), vanillin or *p*-hydroxybenzaldehyde (0.01 mol), respectively, in ethanol (30 ml) and some drops of piperidine, were refluxed in a water bath for 3 h. After cooling the final products were precipitated, filtered and recrystallized from ethanol 95%.

2.2.2. General procedure B [11,12]

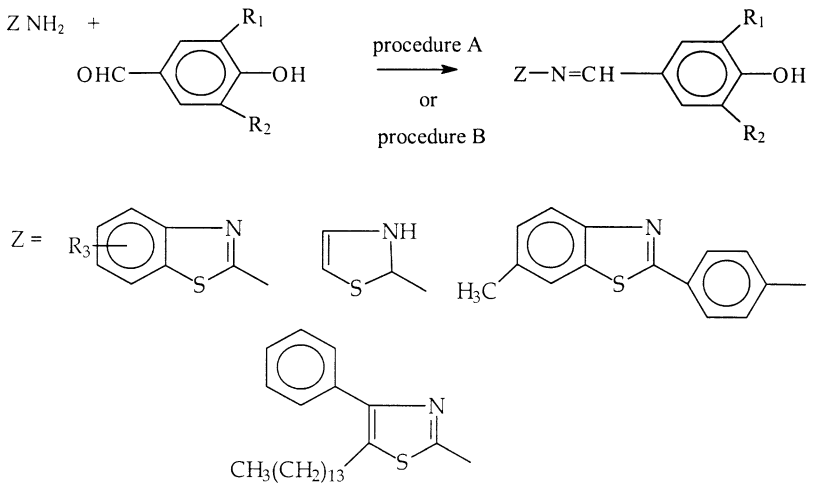
A mixture of 5-/ or not substituted-2-amino-benzothiazole (0.01 mol) and vanillin or 5-iodo- or 5-bromo-vanillin or *p*-hydroxy-benzaldehyde or syringic aldehyde (0.01 mol), respectively, in dry benzene, in the presence of a small amount of *p*-toluene-chloro-sulphonic acid was heated in a Dean–Stark apparatus. The solution was cooled and the final products were precipitated, filtered and recrystallized from ethanol 95%.

The general method [11,12] employed to prepare the final compounds is shown in Scheme 1 (Tables 2–4).

2.3. Biological evaluation

2.3.1. In vitro assays

2.3.1.1. Interaction of the tested compounds with 1,1-diphenyl-2-picryl-hydrazyl (DPPH) stable free radical. Typical compounds synthesized above in 10^{-4} M ethanolic solution, were added to an equal molar ethanolic solution of DPPH (10^{-4} M). The mixture was kept at room temperature. After 20 min the absorbance at 517 nm was measured and the percent reduction according to Refs. [11,13] was estimated.



Scheme 1. Reaction series of the synthesized compounds.

Ethanol was of analytical grade, iron content less than 10^{-5}% (as a standard nordihydroguaretic acid 94%).

2.3.1.2. Soybean lipoxygenase inhibition [11]. The conversion of sodium linoleate to 13-hydroxy-peroxylinoleic acid at 234 nm, was recorded. As a reference compound nordihydroguaretic acid was used (83%). The tested compounds, dissolved in 60% aqueous ethanol (final concentrations 0.1 mM) with sodium linoleate (0.1 mM), 0.15 ml of enzyme solution (1/10 w/v in saline) were evaluated in room temperature. The conversion of sodium linoleate in pH 9.00 by Tris, to 13-hydroxy-peroxy-linoleic acid with appropriate standard, in each case, at 234 nm was compared.

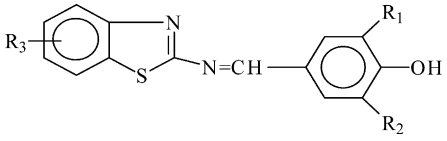
2.3.2. In vivo assay

2.3.2.1. Animals. AKR or A mice (20–30 g, groups of six, 2–3 months old), both sexes were used. Females pregnant excluded. The animals, bred in our laboratory, were housed under standard conditions and received a diet of commercial food pellets and water ad libitum. Four hours before carrageenin treatment, food was withdrawn from all animals with water freely available.

2.3.2.2. Inhibition of the carrageenin-induced edema [11]. Edema was induced in the right hind paw of AKR or A mice (20–30 g, 2– 3 months old) by the intradermal injection of 0.05 ml 2% w/v carrageenin in water. These studies were in accordance with recognized guidelines on animal experimentation (guidelines for the care and use of laboratory animals published by the Greek Government 160/1991, based on EU regulations 86/609).

All the tested compounds 0.5 mmol/kg body weight (with the exception of compound **7**, 0.25 mmol/kg body weight), were suspended in water, with few drops of Tween 80 and ground in a mortar before use and were

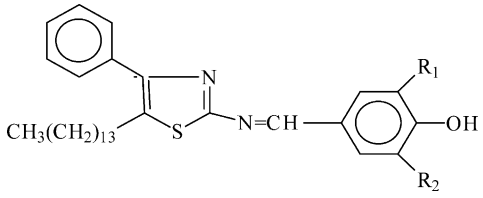
Table 2
Characterization data of the synthesized Schiff bases



N	R_1	R_2	R_3	Yield (%)	M.p. (°C)	R_f	M^+ (m/z) (%)	MF [a]
1a	H	H	H	38	205–7	0.737	254 (65)	$C_{14}H_{10}N_2OS$
1b	H	OCH_3	H	40	166–8	0.836	284 (100)	$C_{15}H_{12}N_2O_2S$
1c	OCH_3	OCH_3	H	48	196–9	0.644	314 (18)	$C_{16}H_{14}N_2O_3S$
2d	I	OCH_3	H	42	136–8	0.730	410 (12)	$C_{15}H_{11}N_2O_2SI$
2e	Br	OCH_3	H	39	152–4	0.539	364 (22)	$C_{15}H_{11}N_2O_2SBr$
2f	H	OCH_3	5-Cl	40	169–72	0.705	[b]	$C_{15}H_{11}N_2O_2SCl$

[a] Elemental analyses for molecular formulas MF.
[b] = no results for a molecular ion peak; eluent system benzene/ethanol = 9/1.

Table 3
Characterization data of the synthesized Schiff bases



N	R_1	R_2	Yield (%)	M.p. (°C)	R_f	M^+ (m/z) (%)	MF [a]
3a	H	H	37	129–30	0.78	476 (15)	$C_{30}H_{40}N_2OS$
3b	H	OCH_3	41	91–2	0.84	506 (98)	$C_{31}H_{42}N_2O_2S$
3c	OCH_3	OCH_3	45	[b]	0.68	536 (25)	$C_{32}H_{44}N_2O_3S$

[a] Elemental analyses for molecular formulas MF.
[b] Decomposes upon heating; eluent system benzene/ethanol = 9/1.

given intraperitoneally (i.p) at the same time as the carrageenin. The animals were euthanized 3.5 h after carrageenin injection. The experiment was repeated twice for each compound (two groups of six animals). The difference between the weight of the injected and uninjected paws was calculated for each animal. The change in paw weight was compared with that in control animals (injected with water) and expressed as a percent inhibition of the edema (CPE % values Table 4). Indomethacin in 0.11 mmol/kg (44%) was administered as a standard comparative drug ($P < 0.01$ compared with control values).

2.4. Statistical analysis

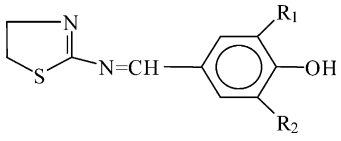
In vivo results are means ± SEM standard error of the mean less than 10%. Each in vitro experiment was performed at least in triplicate and the standard deviation in absorbance values was less than ±10%. The results were evaluated using Student's t-test.

3. Results and discussion

3.1. Chemistry

The general method employed to prepare the final compound is shown in Scheme 1. Overall the reactions proceeded smoothly in good yields. In the synthesis of the derivatives of benzothiazolyl series, problems were overcome by heating the reactants in a Dean–Stark apparatus, using p-toluene-chloro-sulphonic acid as a catalyst. It is assumed that the harsher conditions are required to overcome steric hindrance of these bulky groups. Under these experimental conditions we succeeded in resulting higher yields of the benzothiazolyl Schiff bases. The structures of the synthesized compounds and their physicochemical properties are shown in Tables 2–4. All intermediates and final products gave satisfactory analytical and spectroscopic data in full accord with their assigned structures [8,11]. IR spectra showed a sharp band at 3460 cm^{-1} (free OH) and a sharp band in the region 1625–1640 cm^{-1} (N=CH). In the ^1H NMR spectra thiazol-2-yl-amino derivatives

Table 4
Characterization data of the synthesized Schiff bases



N	R_1	R_2	Yield (%)	M.p. (°C)	R_f	M^+ (m/z) (%)	MF [a]
4b	H	OCH_3	31	75–8	0.37	235 (47)	$C_{11}H_{12}N_2O_2S$
4c	OCH_3	OCH_3	85	Oil	0.29	266 (13)	$C_{12}H_{14}N_2O_3S$

Eluent system benzene/ethanol = 7/3.
[a] Elemental analyses for molecular formulas MF.

showed peaks in the region of δ 6.91–7.40 (m, H azomethine and 3H aromatic) whereas, benzothiazol-2-yl-amino showed peaks in the region of δ 7.3–8.1, m (aromatic protons), δ 9.3 (H azomethine), δ 3.97 (methoxy, s, 3H); δ 8.84 (hydroxy, s, 1H).). In the MS the existence of daughter ions is assigned by suggested fragmentation patterns which are in agreement with the findings from pertinent studies of simpler compounds [8,11]. All substances gave stable molecular ions. Other characteristic fragments observed, were formed by the loss of CO–, CN–, HCN radicals. The $[M^+ - OH]$ peaks have also been observed (Tables 2–4).

3.2. Biological studies

The biological activity of the compounds was measured against isolated enzyme (soybean lipoxygenase). It has been previously reported [11], that Schiff bases inhibited the soybean LOX activity and demonstrated good anti-inflammatory activity. Our newly compounds tested were not found to highly inhibit soybean LO (20.6–29%, Table 5) under the reported experimental conditions (0.1 mM). It is important to be noticed that during our experimental procedure, the solutions of compounds **3b**, **3c**, **4b** and **4c** became cloudy and the determination was not possible to be performed. For the thiazolyl series the existence of both a phenyl group and a $CH_3(CH_2)_{13}-$ chain has a negative effect on the overall stereochemistry of the molecule and through it on the biological effect.

Lipophilicity is an important physicochemical parameter for the kinetics of biologically active compounds.

Table 5
Biological results

No	LO (%)	Clog *P*	CPE (%)	DPPH (%)
1a	29	3.614	36*	12.3
1b	No	3.473	54	26.9
1c	No	3.220	49.5	No
2d	20.6	4.324	75	27.7
2e	No	2.33	63	22.2
2f	No	3.54	44	Nr
3a	No	10.665	64.2	7.3
3b	Nr	10.524	47.6	Nr
3c	Nr	10.271	58.5	Nr
4b	Nr	1.405	52.3	Nr
4c	Nr	1.152	38.7	Nr
5 [a]	24	2.420	47.3	77.9
6 [a]	Nr	2.61	23.9	Nr
7 [a]	37.3	2.80	24.3	29.7

No tested compound was found to be inactive under the reported experimental conditions and in comparison to the controls under the same experimental conditions; Nr, no results were found under the reported experimental conditions.

[a] Reported in Ref. [11] compounds are derivatives of $Z = 6\text{-}CH_3-C_7H_3SN$, and of **a**, **b**, **c** series.

* $P < 0.05$; all the others are statistically significant as $P < 0.01$.

Antioxidants of hydrophilic or hydrophobic character are both needed to act as radical scavengers in the aqueous phase or as chain-breaking antioxidants in biological membranes. In our case no relationship between LO inhibition and lipophilicity was found. There are many structurally unrelated compounds that have been prepared with the goal of developing LO inhibitors or have been discovered as such. The most of the LO inhibitors are antioxidants or free radical scavengers [3], since lipoxygenation occurs via a carbon centered radical. Moreover, many LO inhibitors also inhibit lipid peroxidation [3]. Some studies suggest a relationship [3] between LO inhibition and the ability of the inhibitors to reduce Fe^{3+} at the active site to the catalytically inactive Fe^{2+}.

Lipoxygenases contain a non-heme iron per molecule in the enzyme active site as high -spin Fe^{2+} in the native state, and high-spin Fe^{3+} in the activated state. Iron is also present in human 5-LO and is essential for enzyme activity[3]. Several LO-inhibitors are excellent ligands for Fe^{3+}. It has been demonstrated that their mechanism of action is presumably related to its coordination with a catalytically crucial Fe^{3+}-ion. In our case, it could not be able to synthesize an iron chelate, using the examined compounds as a ligand. Thus, we concluded that they might not produce LO inhibition as iron chelators [3].

The reducing abilities were determined by their interaction with the stable DPPH radical. This interaction indicates if the compounds have the ability to scavenge free radicals. All the tested compounds were found to interact slightly from 12.3 to 29.7%, whereas compound **3a** was almost inactive and compound **1c** did not show any result. Compounds **2f**, **3b**, **3c**, **4b** and **4c** possessed dissolution problems and it could not be possible to be tested under the same experimental conditions.

Taking into consideration that Schiff bases can act as anti-inflammatory agents [11], the compounds prepared were tested for such an activity. The mice carrageenin-induced paw edema assay was employed as a model for acute inflammation and indomethacin was included as a reference drug. The model represents reliable the responses of clinically observed inflammatory diseases and predicts the anti-inflammatory ability of the NSAIDs. During the second phase, it detects compounds that are anti-inflammatory as a result of inhibition of prostaglandin amplification [14,15]. The in vivo data are summarized in Table 5.

Compound **2d** possessed the highest inhibition 75% whereas compounds **1b**, **1c**, **2e**, **3a**, **3c**, **4b**, produced approximately 56.1% edema reduction. Compounds **1a**, **2f**, **3b**, **4c**, exhibited mild activity. From the point of the magnitude of the administered dose, compound **2f** should be more effective, since the carrageenin-induced paw edema inhibition, produced by 0.25 mmol/kg body weight, was 52.3%. Concerning the structures of the

tested compounds the anti-inflammatory efficacy decreases by the presence of a second methoxy group at position R_1. The replacement of an H (R_1) by an I or a Br atom increases the inhibition. The increase in the hydrophobic contribution of group R_1 (I > Br), as p values, affects positively the inhibition of carrageenin induced mice paw edema ($\pi = 1.12$ for iodine and $\pi = 0.86$ for Bromine, compounds **2d** 75% > **2e** 63%). The replacement of a 5-H by a 5-Cl in R_3 (C5), decreases the anti-inflammatory ability. In general, in all the series (thiazolyl/thiazolinyl/benzothiazolyl) the presence of a second methoxy group at position 5 ($R_1 = R_2 = OCH_3$) of the aldehydic moiety, decreases the efficacy.

Concerning the structure of the Z ring, the order of increasing activity in the series of compounds was **3b** (47.6%) < **4b** (52.3%) < **1b** (54 5%) and **4c** (38.7%) < **1c** (49.5%) < **3c** (58.5%). In general, in both series (thiazolyl/ benzothiazolyl), between the derivatives with $R_1 = R_2 = H$, more potent is the one of the thiazolyl ring, e.g. **1a** (36%) < **3a** (64%).

For the series of derivatives of benzothiazolyl-bases, the order of increasing activity in this series of compounds was **1a** (36%) < **1c** (49.5%) < **1b** (54%). The replacement of 6-CH_3 by a 6-H highly influences the anti-inflammatory activity (**5**, **6** and **7**). Compounds **1a**, **1b** and **1c** were found to be less potent than the corresponding 6-ethoxy derivatives (values CPE % are taken from literature) [11].

Regression analysis was performed [16] to find out whether any correlation exists between the percentage inhibition of carrageenin mice paw edema (CPE %) and several physicochemical parameters (lipophilicity, steric and electronic variables). However, the anti-inflammatory effect in correlation with lipophilicity—theoretically calculated (clog P) and $I\text{-}_1$ (an indicator variable assigning 1 for the presence of one $R_2 = OCH_3$ group) gave the following equation:

$$\text{Log CPE \%} = 0.023\text{clog } P + 0.159\text{I-}_1 + 1.555$$

$n = 9$, $r = 0.864$, $r^2 = 0.747$, $s = 0.059$, $F_{2,8} = 11.619$, $a = 0.01$.

The above correlation is statistically significant with a high F value but low correlation coefficient r. Both the intercept and the slope are contributing to the equation in a significant manner. Two compounds were omitted, **2f** and **3b**. Compound **2f** was the only one with asubstituent on the benzothiazolyl moiety, whereas compound **3b** was the less active within the series of the $CH_3(CH_2)_{13}$-substituted thiazolyl derivatives.The equation has a low correlative power but it could describe the reduction of the carrageenin induced raw edema from a qualitative point of view. This indicates that the basic nucleus of Schiff bases and the substituents on the phenyl, thiazolyl, thiazolinyl, or benzothiazolyl rings are contributing to the anti-inflammatory activity to an appreciable extent. Since inflammation is a complex phenomenon involving interrelationship between humoral and cellular reactions no much evidence on QSAR studies on NSAIDs is found.

4. Conclusion

The present study has shown that certain Schiff bases designed after previous findings, structurally related to vanilloids, possess high anti-inflammatory activity. Only two compounds **1a** and **2d** are inhibiting in vitro soybean LO. Compound **2d** exerts significant 75% anti-inflammatory and not a high LO inhibitory activity. The present results did not correlate LO inhibiting and carrageenin edema properties. These are preliminary results and further investigation is in progress to delineate the anti-inflammatory action of the modified derivatives.

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