New 5-Thiazolyl-carbohydrazon-n-allyl-thiazolines

Synthesis, characterization and antioxidant activity

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In an effort to obtain new NSAIDs, that act as COX-2 selective inhibitors with simultaneous iNOS inhibition properties and direct antioxidant activity, we designed a series of 8 new compounds bearing the 5-thiazolyl-carbohydrazon-N-allyl-thiazoline scaffold. The synthesized compounds were physicochemically characterized by: [1]H-NMR, MS and elemental analysis. An initial, in vitro, free radical scavenging assay (DPPH bleaching) test showed that most compounds are superior to standard antioxidants Trolox and BHT.

Keywords: thiazole, antioxidant, NSAIDs, iNOS, DPPH

Non-steroidal anti-inflammatory drugs (NSAIDs) are one of the most commonly used drugs [1]. However they are characterized by a number of undesirable effects: some are caused by their pharmacological mechanism of action (gastro-intestinal bleeding, ulcers, cardio-vascular disorders) [2,3] while other are idiosyncratic (hepato-toxicity).

The need for new and safer NSAIDs has led researchers to envision molecules that have a slightly different mechanism of action and/or have secondary or alternative biologic activities [4–6]. In regard of pharmacological mechanism modulation, an important approach was that of creating molecules that act as selective COX-2 inhibitors without being specific COX-2 inhibitors (selectivity degrees between meloxicam and coxibs) [7–10]. Also, obtaining NSAIDs that simultaneously inhibit COX and Inducible Nitric Oxide Synthase (iNOS) is thought to be highly effective as the 2 enzymes have many similarities in controlling inflammation and also stimulate each other's activity [11–13]. Another important strategy is to obtain molecule that also possess, as a secondary mechanism, direct antioxidant properties [14,15]. This is thought to decreases inflammation as it is well established that reactive oxygen species and reactive nitrogen species are both released in great amounts in the inflammatory processes [16,17]. Moreover, ROS and RNS promote inflammation by sustaining and re-activating both COX and iNOS [18–20].

Considering this state of facts, we decided to obtain a new molecular scaffold for NSAIDs. As shown in Figure 1, we combined molecular motifs form various molecules, some used as medicines while others just in development stages. In order to obtain COX-2 selectivity we based our model on meloxicam and lumiracoxib. The benzothiazine nucleus was replaced by a 4-methyl-2-phenylthiazole moiety, while the amide was converted to a more flexible carbohidrazone. The 2-aminothiazole residue was kept

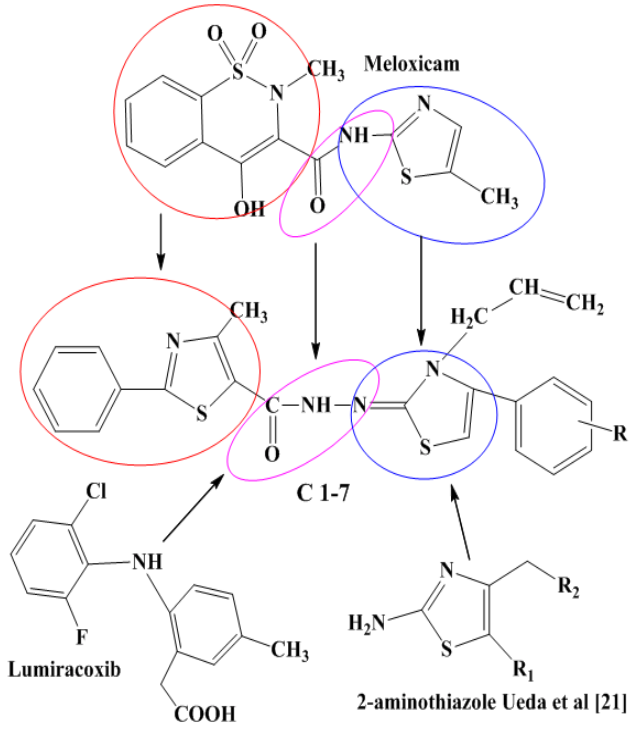

Fig. 1. The rational design of the new 5-thiazolyl-carbohydrazon-N-allyl- thiazolines as a potential NSAIDs scaffold.

and modified in order to resemble molecular scaffolds that inhibit iNOS [21,22] while an allyl residue was added in order to obtain direct antioxidant activity.

Experimental part

Chemistry

All chemical reagents and solvents used in the synthesis, isolation and purification process were of analytical grade purity and were purchased from Alfa Aesar (Karlsruhe, Germany). Silica Gel thin layer chromatography sheets and

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UV visualization were used for initial purity assessment and ongoing reaction monitoring. The melting points are uncorrected and were obtained by using an Electrothermal 9100 melting point apparatus. The ^{1}H NMR spectra were recorded at room temperature on a Bruker Avance NMR spectrometer operating at 500 MHz. Chemical shift values were reported relative to tetramethylsilane (TMS) as internal standard. GC-MS analyses were performed with an Agilent gas chromatograph 6890 equipped with an apolar Macherey Nagel Permabond SE 52 capillary column. Elemental analyses were performed by an Elemental Analyser Systeme GmbH VarioEL. MS spectra were recorded on a LC-MSD-Trop-VL mass spectrophotometer.

*Synthesis of the ethyl 4-methyl-2-phenylthiazole-5-carboxylate (**1**)*

To a solution of thiobenzamide (13.7 g, 0.1 mol) in 40 mL ethanol an equimolar quantity of ethyl-2-chloro-aceto-acetate (16.45 g, 0.1 mol) was added and it was refluxed for 5 h. The reaction mixture was cooled to room temperature and neutralized with $NaHCO_3$. The solid obtained was filtered, washed with water and then with acetone and recrystallised from ethanol. m.p: 34 °C, Yield 75% [23–25].

Synthesis of the 4-methyl-2-phenylthiazole-5-carbohydrazide (**2**)

The solution obtained by dissolving 10 mM of the corresponding ester (1) in 4 mL ethanol was treated with 5 mL hydrazine hydrate and refluxed for 5h. The resulting mixture was allowed to cool overnight and then poured over ice water. The resulting solid was filtered and washed with water in order to yield the pure compound (2). m.p: 169 , Yield 80% [24].

*Synhesis of the N-allyl-2-(4-methyl-2-phenylthiazole-5-carbonyl)hydrazinecarbothioamide (**3**)*

An amount of 5 mM of 4-methyl-2-phenylthiazole-5-carbohydrazide (2) was dissolved in 20 mL absolute ethanol heated at 45° C, and then 5mM of allyl-isothiocyanate was added. The reaction mixture was refluxed for 3h and then allowed to cool down at room temperature. The resulting solid was filtered and recrystallised from ethanol. m.p: 185 °C, Yield 85% [24].

*General procedure for the synthesis of the N'-(3-allyl-4-arylthiazol-2(3H)-ylidene)-4-methyl-2-phenylthiazole-5-carbohydrazides (**4a-g**)*

An equimolar mixture of **3** and the corresponding α-bromoketone was solubilised in ethanol and then refluxed for 5 h. The reaction mixture was then evaporated under low pressure and the resulting solid was washed with a solution of $NaHCO_3$ 5%. The produce was then recrystallised from methanol.

Antioxidant activity assay -DPPH bleaching assay

The in vitro direct antioxidant activity was assessed by the stable DPPH radical method - which is a free radical scavenging assay. Initially, the DPPH (2,2-diphenyl-1-picrylhydrazyl) solution is colored in violet and has an absorbance maximum at 517 nm. When treated with radical scavenging substances the radicals are neutralized and absorbance intensity drops. The method aims at establishing the exact concentration of compound required to produce a reduction by half of the absorbance of the initial DPPH solution at 517 nm. Methanol DPPH (2,2-diphenyl-1-picrylhydrazyl) solutions (0.1g/L) were prepared and mixed with an equal amount of solution containing the new compounds, at various concentrations. Subsequently, they were incubated in a thermostatic bath for 30 min at 40 °C. In parallel, a control sample and standard antioxidant substances were also used: ascorbic acid (AA), butylated hydroxytoluene (BHT) and Trolox (6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid) a water-soluble analog of vitamin E. The DPPH scavenging ability was expressed as a percentage of absorbance reduction:

$$\text{DPPH scavenging ability \%} = (A_{control} - A_{sample}/A_{control}) \times 100$$

The plotted curve resulting from numerous concentrations levels was used to calculate IC_{50}. All experiments were performed in triplicates with standard deviations less than 5% [15,26–28].

Results and discussions

Chemistry

The synthesis route consisted of 4 reaction steps, as shown in figure 2. Initially a Hantzsch condensation between thiobenzamide and ethyl-2-chloro-aceto-acetate yielded a phenyl-thiazole ester **1.** This ester was then

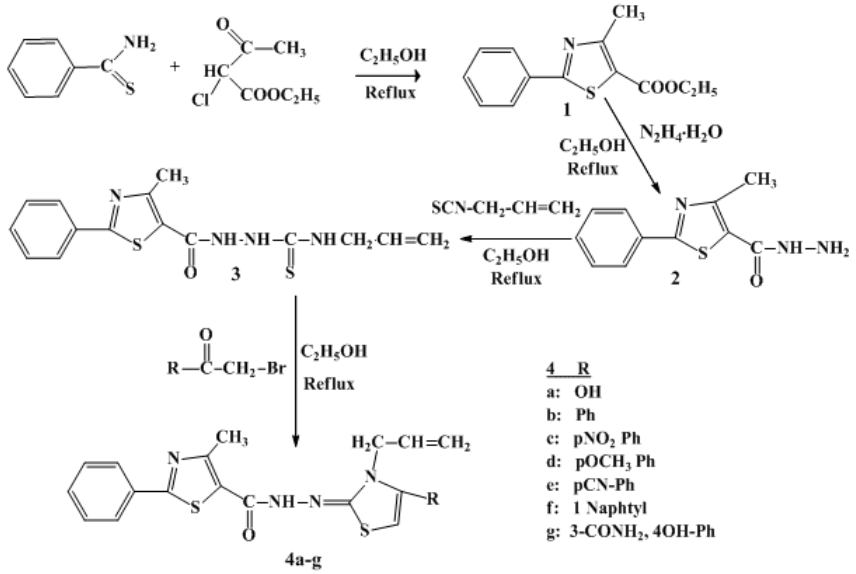

Fig. 2. General synthesis procedure and structures for the new 5-thiazolyl-carbohydrazon-N-allyl-thiazolines

transformed to the corresponding carbohydrazide **2** onto which an adition of allyl-isothiocyanate took place in order to obtain the key intermediate **3**. Condensation of **3** with various alpha-bromoketones yielded an array of 5-thiazolyl-carbohydrazon-N-allyl-thiazolines end products **4a-g**.

The results obtained from the spectral data and elemental analysis confirmed the initially proposed structures.

N'-(3-allyl-4-oxothiazolidin-2-ylidene)-4-methyl-2-phenylthiazole-5-carbohydrazide ***(4a)***

Light yellow powder. Yield 85%. m.p. 173 °C. ^{1}H NMR (DMSO-d6, 500 MHz, ppm): δ 11.45 (s, 1H, CONH-N=), 8.44 (s, 1H, thiazol-ylidene C5-H), 8.08 (dd, 2H, Ph), 7.52 (m, 3H, Ph), 5.83 (m, 1H, Tz-CH_2-C**H**=CH_2), 5.27 (d, 1H, C=CH_2) 5.92 (d, 1H, C=CH_2), 4.63 (s, 2H, Tz-C**H$_2$**-CH=CH_2), 4.30 (s, 1H, C5 oxothiazolidin-2-ylidene), 3.89 (s, 1H, C5 oxothiazolidin-2-ylidene), 2.75 (s, 3H, CH_3). Anal. calcd. (%) for $C_{17}H_{16}N_4O_2S_2$ (372.07): C, 54.82; H, 4.33; N, 15.04; S, 17.22. Found: C, 54.80; H, 3.65; N, 9.08; S, 20.75. MS (EI, 70eV): m/z 373.7 (M+1).

N'-(3-allyl-4-phenylthiazol-2(3H)-ylidene)-4-methyl-2-phenylthiazole-5-carbohydrazide ***(4b)***

Off-white powder. Yield 80%. m.p. 229 °C. ^{1}H NMR (DMSO-d6, 500 MHz, ppm): δ 11.5 (s, 1H, CONH-N=), 8.49 (s, 1H, thiazol-ylidene C5-H), 7.40-8.1 (m, 10H, Ph), 5.80 (m, 1H, Tz-CH_2-**CH**=CH_2), 5.26 (d, 1H, C=CH_2), 5.97 (d, 1H, C=CH_2), 4.63 (s, 2H, Tz-C**H$_2$**-CH=CH_2), 2.75 (s, 3H, CH_3). Anal. calcd. (%) for $C_{23}H_{20}N_4OS_2$ (432.11): C, 63.86; H, 4.66; N, 3.70; S, 14.83. Found: C, 63.77; H, 4.60; N, 12.99; S, 14.90. MS (EI, 70eV): m/z 433.7 (M+1).

N'-(3-allyl-4-(4-nitrophenyl)thiazol-2(3H)-ylidene)-4-methyl-2-phenylthiazole-5-carbohydrazide ***(4c)***

Yellow powder. Yield 75%. m.p. 238 °C. ^{1}H NMR (DMSO-d6, 500 MHz, ppm): δ 11.45 (s, 1H, CONH-N=), 8.46 (s, 1H, thiazol-ylidene C5-H), 8.32 (dd, 2H, Ph-NO2), 8.25 (dd, 2H, Ph-NO2), 8 (dd, 2H, Ph), 7.55 (m, 3H, Ph), 5.80 (m, 1H, Tz-CH_2-**CH**=CH_2), 5.23 (d, 1H, C=CH_2) 5.96 (d, 1H, C=CH_2), 4.64 (s, 2H, Tz-C**H$_2$**-CH=CH_2), 2.77 (s, 3H, CH_3). Anal. calcd. (%) for $C_{23}H_{19}N_5O_3S_2$ (477.09): C, 57.85; H, 4.01; N, 14.66; S, 13.43. Found: C, 57.60; H, 4.15; N, 14.75; S, 13.35. MS (EI, 70eV): m/z 478.4 (M+).

N'-(3-allyl-4-(4-methoxyphenyl)thiazol-2(3H)-ylidene)-4-methyl-2-phenylthiazole-5-carbohydrazide ***(4d)***

Off-white powder. Yield 70%. m.p. 226-228 °C. ^{1}H NMR (DMSO-d6, 500 MHz, ppm): δ 11.4 (s, 1H, CONH-N=), 8.47 (s, 1H, thiazol-ylidene C5-H), 8.04 (dd, 2H, Ph), 7.75 (dd, 2H, Ph-OCH_3), , 7.55 (m, 3H, Ph), 7.0 (dd, 2H, Ph-OCH3), 5.82 (m, 1H, Tz-CH_2-C**H**=CH_2), 5.25 (d, 1H, Tz-CH_2-CH=C**H$_2$**) 5.98 (d, 1H, Tz-CH_2-CH=C**H$_2$**), 4.60 (s, 2H, Tz-C**H$_2$**-CH=CH_2), 3.75 (s, 3H, -OCH_3), 2.78 (s, 3H, CH_3). Anal. calcd. (%) for $C_{24}H_{22}N_4O_2S_2$ (462.12): C, 62.31; H, 4.79; N, 12.11; S, 13.86. Found: C, 62.20; H, 4.85; N, 12.01; S, 13.70. MS (EI, 70eV): m/z 463.8 (M+).

N'-(3-allyl-4-(4-cyanophenyl)thiazol-2(3H)-ylidene)-4-methyl-2-phenylthiazole-5-carbohydrazide ***(4e)***

White powder. Yield 75%. m.p. 242 °C. ^{1}H NMR (DMSO-d6, 500 MHz, ppm): δ 11.5 (s, 1H, CONH-N=), 8.46 (s, 1H, thiazol-ylidene C5-H), 8.41 (dd, 2H, Ph-CN), 8.03 (dd, 2H, Ph), 7.70 (dd, 2H, Ph-CN), 7.57 (m, 3H, Ph), 5.82 (m,1H, Tz-CH_2-C**H**=CH_2), 5.25 (d, 1H, Tz-CH_2-CH=C**H$_2$**), 4.94 (d, 1H, Tz-CH_2-CH=C**H$_2$**), 4.63 (s, 2H, Tz-C**H$_2$**-CH=CH_2), 2.73 (s, 3H, CH_3). Anal. calcd. (%) for $C_{24}H_{19}N_5OS_2$ (457.10): C, 63.00; H, 4.19; N, 15.31; S, 14.02. Found: C, 63.20; H, 4.10; N, 15.39; S, 14.57. MS (EI, 70eV): m/z 458.4 (M+).

N'-(3-allyl-4-(naphthalen-1-yl)thiazol-2(3H)-ylidene)-4-methyl-2-phenylthiazole-5-carbohydrazide **(4f)**

Dark-yellow powder.Yield 70%. m.p. 182-184 °C. ^{1}H NMR (DMSO-d6, 500 MHz, ppm): δ 11.50 (s, 1H, CONH-N=), 8.45 (s, 1H, thiazol-ylidene C5-H), 8.15 (d,1H, naphthyl), 8.01 (dd, 2H, Ph), 7.85-7.90 (m, 2H, Naph), 7.65 (m, 3H, Ph), 7.56-7.50 (m, 4H, naphthyl) 5.81 (m, 1H, Tz-CH_2-**CH**=CH_2), 5.25 (d, 1H, Tz-CH_2-CH=C**H$_2$**), 4.93 (d, 1H, Tz-CH_2-CH=C**H$_2$**), 4.65 (s, 2H, Tz-C**H$_2$**-CH=CH_2), 2.74 (s, 3H, CH_3). Anal. calcd. (%) for $C_{27}H_{22}N_4OS_2$ (482.12): C, 67.19; H, 4.59; N, 11.61; S, 13.29. Found: C, 66.85; H, 4.49; N, 11.51; S, 13.45. MS (EI, 70eV): m/z 483.5 (M+).

5-(3-Allyl-2-(2-(4-methyl-2-phenylthiazole-5-carbonyl)hydrazono)-2,3-dihydrothiazol-4-yl)-2-hydroxybenzamide **(4g)**

Light-brown powder. Yield 75%. m.p. 248 °C. ^{1}H NMR (DMSO-d6, 500 MHz, ppm): δ 13.2 (s, 1H, Ar-OH), 11.53 (s, 1H, CONH-N=), 8.48 (s, 1H, thiazol-ylidene C5-H), 8.1 (s, 1H, C-NH_2), 8.07 (s, 2H, C-NH_2), 8.00 (dd, 2H, Ph), 7.57 (m, 4H, Ph si Ph-R), 7.08 (s, 1H, Ph-R), 7.04 (d, 1H, Ph-R), 5.82 (m,1H, Tz-CH_2-C**H**=CH_2), 5.25 (d, 1H, C=C**H$_2$**) 4.94 (d, 1H, C=C**H$_2$**), 4.63 (s, 2H, Tz-C**H$_2$**-CH=CH_2), 2.73 (s, 3H, CH_3). Anal. calcd. (%) for $C_{24}H_{21}N_5O_3S_2$ (491.11): C, 58.64; H, 4.31; N, 14.25; S, 13.05. Found: C, 58.55; H, 4.25; N, 14.15; S, 13.35. MS (EI, 70eV): m/z 492.6 (M+).

Mass spectrometry results contain a molecular peak for each of the calculated molecular masses. The

Compound	IC $_{50\%}$ µg/mL	IC $_{50\%}$ µM	Std. Dev. ± (%)	Equation	R^2
4a	-	-	-	-	-
4b	12.758	29.52	4.1	y=3.6446x+3.5021	0.9968
4c	11.31	23.71	3.8	y=4.1287x+3.3148	0.9901
4d	17.91	38.76	4	y=2.987x-3.4761	0.9985
4e	11.19	24.48	3.9	y=4.5432x-0.8364	0.9969
4f	14.06	29.16	2.5	y=3.5144x+0.5984	0.9976
4g	23.08	46.99	3.6	y=2.005x+3.7281	0.9910
AA	7.43	42.18	3.25	y=6.767x+0.2915	0.9995
BHT	16.39	74.38	3.55	y=2.031x+ 16.719	0.9993
TROLOX	11.99	47.90	2.7	y=3.125x+12.53	0.996

Determination not possible, reaction products interfere with UV determination

Table 1
THE ANTIOXIDANT EFFECT OF THE NEW 5-THIAZOLYL-CARBOHYDRAZON-N-ALLYL-THIAZOLINES

elemental analysis performed revealed that all compounds have the elemental composition estimated from their proposed formula, within a variation of under 0.5%.

^{1}H NMR confirmed the molecular structures initially proposed. As such, all the spectra showed a singlet signal, with 1H intensity, around δ 11.4-11.55, corresponding to the proton in carbohydrazide (-CONH-N=). The presence of the N-allyl group was confirmed by: a multiplet signal of 1H intensity at δ 5.80-5.85 (Tz-CH_2-C**H**=CH_2), the doublet of doublets between δ 5.25-4.95 (Tz-CH_2-CH=C**H$_2$**), and a singlet signal with 2H intensity at δ 4.60-4.65 (Tz-C**H$_2$**-CH=CH_2). Another common characteristic is the presence of the singlet 3H signal, corresponding to the methyl group, at δ 2.7-2.8.

Antioxidant activity assay

The results for the free radical scavenging activity of the new compounds are summarized in table 1. IC_{50} values are presented both in mass and also μM concentrations in order to better evaluate the activity. By comparing with the results obtained for the standard antioxidant it is obvious that all compounds have good antioxidant activity. From the point of view of μM concentrations, all compounds are superior the standards Trolox and BHT, and most are also superior to ascorbic acid.

The most active were **4c** and **4e** that showed an activity equal to that of the standard Trolox but far superior to the standard BHT, at the same mass concentrations. When comparing results expressed in μM concentrations, these compounds have twice the activity of ascorbic acid and Trolox, and about 3 times the activity of BHT.

Compounds **4b** and **4f** have an antioxidant effect of intermediate potency between BHT and Trolox, at the same mass concentrations. When considering μM concentrations the compounds are active at half the concentrations of BHT.

Compounds **4d** and **4g** are active at μM concentrations similar to ascorbic acid and Trolox.

Conclusions

In an effort to develop new NSAIDs we synthesized 8 new compounds with a 5-thiazolyl-carbohydrazon-N-allyl-thiazoline scaffold. All new compounds were characterized by ^{1}H-NMR, MS and elemental analyses, with results firmly proving that the proposed structures are correct. Furthermore, initial activity assessment was performed by measuring *in vitro* antioxidant potential via the DPPH bleaching assay. All compounds have good free radical scavenging activity while most have results far superior to that of the standard antioxidant substances used. Further studies will be performed in order to confirm the antioxidant potential by other methods and also investigate the *in vivo* anti-inflammatory and antioxidant activity as well as their mechanism of action (COX and/or iNOS inhibition).

Acknowledgements: This research was carried out with the partial financial support of the European Social Fund through the project: POSDRU 107/1.5/S/78702.

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Manuscript received: 7.11.2018