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Article

Thiazolidin-4-ones from 3-(Aminomethyl)pyridine, Arenealdehydes and Mercaptoacetic Acid: Synthesis and Radical Scavenger Activity

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The efficient synthesis of fifteen novel thiazolidin-4-ones from reaction of 3-(aminomethyl) pyridine (3-picolylamine), arenealdenhydes and mercaptoacetic acid was described. The desired compounds were obtained in moderated to good yields by two methodologies: conventional heating and ultrasound irradiation. The thiazolidin-4-ones were fully identified and characterized by nuclear magnetic resonance (NMR), gas chromatography coupled to mass spectrometry (GC-MS) and high resolution mass spectrometry (HRMS) techniques. Four compounds showed radical scavenger activity in the 2,2'-azinobis-3-ethyl-benzothiazoline-6-sulfonic acid (ABTS) assay.

Keywords: thiazolidin-4-ones, picolylamine, sonochemistry, radical

Introduction

Thiazolidinones belongs to a class of heterocyclic compounds that showed important synthetic and biological properties.[1] In recent years, several methodologies were applied to the synthesis of thiazolidinones, for example: microwave irradiation,[2] solvent–free synthesis,[3] ionic liquid catalysis,[4] trypsin enzyme catalysis[5] and biocatalysis with *Saccharomyces cerevisae*.[6] Our research group also reported the efficient application of ultrasound irradiation to the synthesis of thiazolidin-4-ones.[7,8] There are some data showing the use of desiccant agents like as DCC (*N,N'*-Dicyclohexylcarbodiimide),[9] $ZnCl_2$,[10] molecular sieve[11] and DBSA (*p*-dodecylbenzenesulfonic acid).[12] In addition, the literature reports a wide broad spectrum of biological activities of thiazolidinones: anti-hepatitis C virus (HCV),[13] anti-human immunodeficiency virus (HIV),[14] antitumoral,[15] antifungal,[16,17] antibacterial,[18] anti-inflammatory[19] and antioxidant.[20]

It has been shown that oxidative stress induced by reactive species plays a central role in the onset and development of various diseases like atherosclerosis, carcinogenesis, diabetes mellitus, ageing and neurodegenerative disorders.[21-24] In this way, antioxidants therapy can be viewed as a relevant factor for the treatment and prevention of wide range of diseases that are believed to be caused or promoted by oxidative stress.[22,25] Importantly, the activity of endogenous antioxidants cannot be advisedly increased, so it would be reasonable to improve cell antioxidant capacity using exogenous compounds in order to minimize the damage caused by reactive species on vital constituents of living organisms as DNA, lipids and proteins.[21,23,26]

Based in that and in continuation of our research program, here we report the synthesis of 2-(aryl)-3-(pyridin-3-ylmethyl)-1,3-thiazolidin-4-ones. The synthesized heterocycles were also evaluated in α, α-diphenyl-β-picrylhydrazyl (DPPH) free radical scavenging method and 2,2'-azinobis-3-ethyl-benzothiazoline-6-sulfonic acid (ABTS), radical scavenger assays.

Results and Discussion

The desired compounds were synthesized by two methodologies: conventional heating and ultrasound irradiation. First of all, the conventional methodology was studied using two strategies: (*i*) multicomponent reaction; and (*ii*) one-pot reaction. The multicomponent reaction of 3-picolylamine **1**, corresponding arenealdehyde **2a-o** and mercaptoacetic acid **3** in reflux of toluene for 4 h afforded the thiazolidin-4-ones **4a-o** in good yields after purification (Scheme 1). Similar reaction time and yields were found for one-pot reactions. In this condition, the

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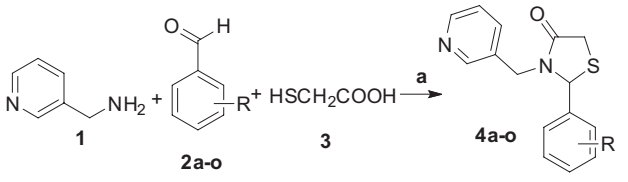
intermediate imine was formed *in situ* by reaction of 3-picolylamine **1** with arenealdehyde **2** in refluxing toluene for 1 h, after this time, the mercaptoacetic acid **3** was added and the mixture was refluxed for 3 h. The progress of all reactions were performed by thin layer chromatography (TLC) using a mixture of hexane:ethyl acetate 3:1 and/or gas chromatography (GC) to observe the complete consummation of arenealdehydes and the formation of thiazolidin-4-ones. It is important to note that these thiazolidin-4-ones **4a-o** from 3-picolylamine were obtained in shorter reaction times than thiazolidin-4-ones from similar 2-picolyamine (16 h).[8] Experimental section shows the yields and selected physical properties of thiazolidin-4-ones **4a-o** synthesized by conventional heating.



R = **2a** = **4a** = 2-NO_2 **2f** = **4f** = 4-F **2k** = **4k** = 4-OCH_3
2b = **4b** = 3-NO_2 **2g** = **4g** = 2-Cl **2l** = **4l** = 4-CH_3
2c = **4c** = 4-NO_2 **2h** = **4h** = 4-Cl **2m** = **4m** = 2-OH
2d = **4d** = 2-F **2i** = **4i** = 2-OCH_3 **2n** = **4n** = 3-OH
2e = **4e** = 3-F **2j** = **4j** = 3-OCH_3 **2o** = **4o** = 4-OH

Scheme 1. Reaction conditions: (a) toluene, reflux, 4 h (yields 59-97%).

To gain more scope to this work, the synthesis of six thiazolidin-4-ones were also carried out using the sonochemistry methodology (Scheme 2). Previous works published by us showed that the reaction time and the multicomponent or the one-pot procedure is important to find the best results.[7,8] To the formation of 2-aryl-3-(pyridin-3-ylmethyl)thiazolidin-4-ones **4c, 4f, 4h, 4k, 4l** and **4o**, the one-pot reactions were carried out without intermediate isolation. So, a mixture of 3-picolylamine **1** and corresponding arenealdehyde (**2c, 2f, 2h, 2k, 2l** and **2o**) in toluene was sonicated for 5 min. After this time, the mercaptoacetic acid **3** was added and the mixture was sonicated for more 5 min to the complete consumption of the imine. The products were obtained in moderate to good yields (30-78%) without any further purification. As we already observed in previous work,[8] some reactions carried out in ultrasound afforded lower yields than reactions in conventional heating (Table 1). Despite the yields, the short reaction time is the great advantage of the sonochemistry methodology.

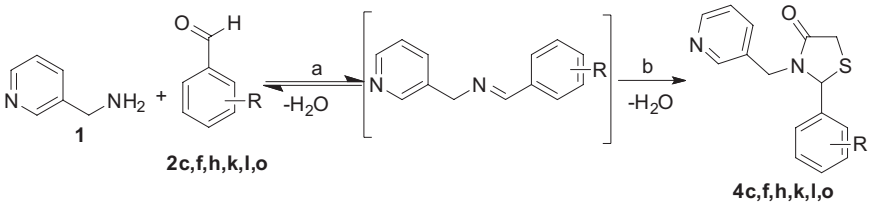
Table 1. Comparative yields for the synthesis of thiazolidin-4-ones (**4c**,**f**,**h**,**k**,**l** and **o**)

Compound	R	Yields / %[a]	
		Ultrasound	Conventional heating
4c	4-NO_2	78	75
4f	4-F	57	94
4h	4-Cl	72	97
4k	4-OCH_3	64	97
4l	4-CH_3	67	80
4o	4-OH	30	74

[a]Yields of isolated compounds.

The thiazolidin-4-ones **4a-o** were fully identified and characterized by mass spectrometry and ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectroscopy. Five thiazolidinones [**4c** (R = 4-NO_2), **4d** (R = 2-F), **4g** (R = 2-Cl), **4k** (R = 4-OCH_3) and **4o** (R = 4-OH)] were also characterized by high resolution mass spectrometry (HRMS). The mainly signals of ^{1}H NMR spectra are the H2 and H5 hydrogen's of the thiazolidinone ring. The H2 is shown at 5.37-6.02 ppm as a singlet or a doublet signal (coupling with the diastereotopic methylene hydrogen H5a, ^4J 1.2-1.7 Hz). The H5a is assigned as a doublet or a double-doublet at 3.80-3.95 ppm (^2J 15.4-16.0 Hz and ^4J 0.8-1.9 Hz) and the H5b appear as a doublet at 3.68-3.81 ppm (^2J 15.2-16.0 Hz). The also diastereotopic methylene hydrogens of pyridin-3-ylmethyl group also appear as two doublets at 4.97-5.16 ppm for CH_2a (^2J 14.8-15.2 Hz) and at 3.68-3.78 ppm for CH_2b (^2J 14.8-16.0 Hz). In the ^{13}C NMR spectra, the mainly signals are the carbonyl group (C4, 171.2-172.5 ppm), the C2 (57.8-62.9 ppm), the methylene C5 (31.5-32.9 ppm) and the methylenic carbon of pyrydin-3-ylmethyl goup (43.6-44.7 ppm). Plus, the aromatic signals of the arenealdehyde and pyridil moieties confirm the structure of desired products.

Several synthetic organic compounds have been studied as antioxidant agents by its scavenger free radicals



Scheme 2. Reaction conditions**:** (a) toluene, ultrasound irradiation, 5 min; (b) $HSCH_2COOH$ **3**, ultrasound irradiation, 5 min (yields 30-78%).

activities. In this context, the antioxidant properties of thiazoles and thiazolidinones were extensively reviewed recently.[27] Two important tests used as screening to antioxidant activities are the 2,2-diphenyl-1-picrylhydrazyl (DPPH) and the 2,2'-azinobis-(3-ethyl-benzthiazoline-6-sulphonate) cation ($ABTS^+$) radical scavenger assays. These procedures are extensively used and need lower times than other methods.[28] DPPH is a stable free radical which has an unpaired valence electron at one atom of nitrogen with a characteristic absorbance. Compounds reacts with DPPH and convert it to the stable 1,1-diphenyl-pieryl hydrazine causing a decrease in DPPH absorbance. The ABTS radical scavenging test is also a rapid and efficient method, based on the ability of the hydrogen donating antioxidants to scavenge the long-life radical cation ABTS.

In this preliminary study, we applied the DPPH and ABTS radical scavenger assays to investigate the antioxidant properties of thiazolidinones **4**. The values of EC_{50} (the amount of compound that decreases the initial DPPH concentration by 50%) and TEAC (trolox equivalent antioxidant capacity) were determined as shown in Table 2. Compounds are considered inactive if the EC_{50} is higher than 200 μM for DPPH and if the TEAC is lower than 0.5 for ABTS.

Table 2. Radical scavenger activities of thiazolidin-4-ones **4a-o**

Compound	R	$DPPH^{\bullet}$ EC_{50} / μM[a]	$ABTS^{\bullet+}$ TEAC[b]
4a	2-NO_2	none	none
4b	3-NO_2	none	none
4c	4-NO_2	none	none
4d	2-F	none	none
4e	3-F	none	none
4f	4-F	none	0.59
4g	2-Cl	none	0.95
4h	4-Cl	none	none
4i	2-OCH_3	none	none
4j	3-OCH_3	none	7.14
4k	4-OCH_3	none	0.93
4l	4-CH_3	none	7.07
4m	2-OH	none	2.92
4n	3-OH	none	0.79
4o	4-OH	none	1.57

[a]EC_{50} means the amount of antioxidant necessary to decrease the initial DPPH concentration by 50%; [b]TEAC means the trolox equivalent antioxidant capacity; none: ineffective due EC_{50} higher than 200 μM for DPPH or TEAC lower than 0.5 for ABTS.

Generally, phenolic hydroxyl group is associated to antioxidant activities due to hydrogen donation and stabilization of the free radical by resonance.[28,29] However, the literature reports that compounds with no phenolic hydroxyl group have also antioxidant properties,[30] including thiazolidin-4-ones.[31] Saundane *et al*.[32] suggest that the hydrogen at the 2-position of 2-aryl-thiazolidin-4-ones ring might be a position to form a radical due a possible stabilization by resonance with the aryl group. According to this, we study the potential radical scavenger property of 3-(pyridin-2-ylmethyl)-thiazolidin-4-ones **5**,[33] 3-(pyrimidin-2-il)thiazolidin-4-ones **6**[11] and now of 3-(pyridin-3-ylmethyl)-thiazolidin-4-ones **4** (Figure 1). In comparison of these three series, the new thiazolidin-4-ones **4** and previous published thiazolidin-4-ones **5** have similar structure that differs only at position of nitrogen on pyridine ring; and thiazolidinones **6** present a pyrimidine ring and the absence of a methylene bridge.

The Table 2 shows clearly that the thiazolidin-4-ones **4a-o** have different results in the preliminary DPPH and ABTS tests. In DPPH assay, all thiazolidin-4-ones **4a-o** showed EC_{50} higher than 200 μM. However, in the ABTS assay, the thiazolidin-4-ones **4j** and **4l** showed the best radical scavenger activities, even better than compounds that contain a phenolic hydroxyl group (**4m** and **4o**). In general, the scavenger activities of thiazolidinones **4** were quite similar to those found for thiazolidinones **5**,[33] however lower than those found for thiazolidinones **6**.[11] These results showed that the bioisoster change of pyridin-2-ylmethyl (compounds **5**) to pyridin-3-ylmethyl moiety (compounds **4**) did not affect the scavenger ability. It also suggests that the absence of a methylenic group and/or the presence of a pyrimidine ring attached to the nitrogen of thiazolidinone ring is important to the stabilization of a free radical.

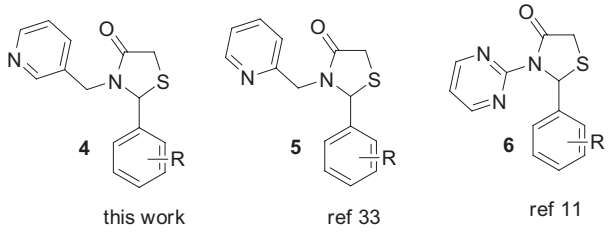


Figure 1. General structures of 2-aryl-thiazolidin-4-ones studied by our research group.

Conclusions

In conclusion, fifteen novel 2-aryl-3-(pyridin-3-ylmethyl)thiazolidin-4-ones were easily synthesized in good yields by conventional methodology. Six of them were also obtained by ultrasound irradiation in good yields and short reaction time. All compounds were fully identified and characterized by ^1H, ^{13}C-NMR and by mass spectroscopy (see supplementary information). In addition, four thiazolidinones showed moderate radical scavenger

activity in the ABTS assay. These results will guide us for further modifications to find better scavenger activities.

Experimental

Unless otherwise indicated, all common reagents and solvents were used as obtained from commercial suppliers without further purification. The sonochemistry reactions were carried out with a microtip probe (3 mm) connected to a 500 Watt Sonics Vibra-cell ultrasonic processor operating at 20 kHz at 24% of the maximum power output. The progress of reactions and the purity of compounds were monitored by thin layer chromatography (TLC) with hexane:ethyl acetate 9:1, using silica gel 60 F253 aluminum sheets; visualization by ultraviolet light 254 nm and by a Shimadzu Gas Chromatograph GC-2010, HP-1 column (cross linked methyl siloxane, 30 m × 0.32 mm × 0.25 μm): Column head pressure, 14 psi, program: T_0 = 60 °C; t_0 = 2.0 min; rate 10.0 °C min^{-1}; T_f = 280 °C; t_f = 13.0 min; Inj. = 250 °C; Det. = 280 °C. Melting points were determined using open capillaries on a Fisatom model 430 apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Oxford AS-400 spectrometer or on a Bruker Ac-200F spectrometer in $CDCl_3$ containing TMS as in internal standard. Chemical shifts δ in ppm with respect to TMS and coupling constants $J_{H\text{-}H}$ (^{1}H) and $J_{C\text{-}F}$ (^{13}C) in Hz. The mass spectra were obtained on a Shimadzu GCMS-QP2010SE with a split-splitless injector and equipped with a RDX-SMS capillary column (30 m × 0.25 mm × 0.25 μm); helium was used as the carrier gas (56 Kpa). High resolution mass spectrum were obtained on a LTQ Orbitrap Discovery mass spectrometer (Thermo Fisher Scientific). This hybrid system meets the LTQ XL linear ion trap mass spectrometer and an Orbitrap mass analyzer. The experiments were performed via direct infusion of sample (flow: 10 μL min^{-1}) in the positive-ion mode using electrospray ionization. Elemental composition calculations for comparison were executed using the specific tool included in the QualBrowser module of Xcalibur (Thermo Fisher Scientific, release 2.0.7) software.

Conventional heating synthesis of thiazolidin-4-ones **4a-o**

A mixture of 3-picolylamine **1** (1 mmol), corresponding arenaldehyde **2a-o** (1 mmol) and mercaptoacetic acid **3** (3 mmol) in toluene (30 mL) was heated at 110 °C with a Dean-Stark apparatus for 4 h. The organic layer was washed with saturated solution of $NaHCO_3$ (3 × 20 mL), dried with $MgSO_4$ and concentrated to give the thiazolidin-4-ones. When necessary, the crude products were washed with a hot solution of hexane:ethyl acetate (9:1).

Ultrasonics synthesis of thiazolidin-4-ones (**4c, 4f, 4h, 4k, 4l** and **4o**)

In a 25 mL vessel was added a mixture of 3-picolylamine **1** (1 mmol) and the arenaldehyde **2c**, **2f**, **2h**, **2k**, **2l** or **2o** (1 mmol) in toluene (10 mL). The mixture was sonicated by an ultrasonic probe with a frequency of 20 kHz for 5 min. After this time, the mercaptoacetic acid **3** (3 mmol) was immediately added and the reaction was sonicated for more 5 min. The solution was washed with saturated solution of $NaHCO_3$ (3 × 10 mL), dried with $MgSO_4$ and concentrated to give the pure products without any further purification.

2-(2-nitrophenyl)-3-(pyridin-3-ylmethyl)-1,3-thiazolidin-4-ones (**4a**)

Yield: 94%; mp 53-56 °C yellow; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.70 (d, 1H, *J* 16.0, H-5b), 3.80 (dd, 1H, *J* 16.0, 1.6, H-5a), 3.82 (d, 1H, *J* 15.2, CH_2b), 5.16 (d, 1H, ^2J 15.2, CH_2a), 6.02 (d, 1H, *J* 1.6, H-2), 7.30-7.24 (m, 1H, Ar-H), 7.35 (dd, 1H, *J* 7.8, 1.2, Ar-H), 7.58-7.50 (m, 2H, Ar-H), 7.70 (dt, 1H, *J* 7.4, 0.8, Ar-H), 8.12 (dd, 1H, *J* 8.2, 1.6, Ar-H), 8.35 (d, 1H, *J* 1.6, Ar-H), 8.55 (dd, 1H, *J* 4.7, 1.9, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.5 (C-5), 44.7 (CH_2), 58.0 (C-2), 123.9, 124.5, 125.9, 126.4, 129.6, 130.1, 134.5, 135.6, 136.0, 149.0, 149.3, 172.5 (C-4); GC-MS *m/z* (%) 285 (M^+-30, 49), 209 (10), 92 (100), 65 (40).

2-(3-nitrophenyl)-3-(pyridin-3-ylmethyl)-1,3-thiazolidin-4-ones (**4b**)

Yield 94%; mp 85-88 °C pale yellow; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.81 (dd, 1H, *J* 15.6, 0.8, H-5b), 3.82 (d, 1H, *J* 15.2, CH_2b), 3.96 (ddd, 1H, *J* 15.6, 1.9, 0.8, H-5a), 5.01 (d, 1H, *J* 14.8, CH_2a), 5.51 (d, 1H, *J* 1.6, H-2), 7.28 (2dd, 1H, *J* 7.8, 0.8, Ar-H), 7.59-7.53 (m, 3H, Ar-H), 8.12-8.11 (m, 1H, Ar-H), 8.26-8.22 (m, 2H, Ar-H), 8.54 (dd, 1H, *J* 5.1, 1.9, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.6 (C-5), 44.2 (CH_2), 62.1 (C-2), 122.2, 123.9, 124.3, 130.3, 130.8, 133.1, 136.2, 141.2, 149.1, 149.3, 171.3 (C-4); GC-MS *m/z* (%) 315 (M^+, 18), 148 (60), 119 (28), 92 (100), 65 (36).

2-(4-nitrophenyl)-3-(pyridin-3-ylmethyl)-1,3-thiazolidin-4-ones (**4c**)

Yield 75%; pale brown oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.74 (d, 1H, *J* 15.0, CH_2b), 3.79 (d, 1H, *J* 15.4, H-5b), 3.93 (dd, 1H, *J* 15.2, 1.3, H-5a), 5.08 (d, 1H, *J* 15.0, CH_2a), 5.49 (d, 1H, *J* 1.5, H-2), 7.29 (2dd, 1H, *J* 7.8, 0.7, Ar-H),

7.43 (d, 2H, *J* 8.7, Ar-H), 7.53 (dt, 1H, *J* 7.8, 1.8, Ar-H), 8.25 (d, 2H, *J* 8.7, Ar-H), 8.29 (d, 1H, *J* 2.1, Ar-H), 8.55 (dd, 1H, *J* 4.8, 1.6, Ar-H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 32.5 (C-5), 44.2 (CH_2), 61.7 (C-2), 123.8, 124.5 (2 C), 127.9 (2 C), 130.7, 136.2, 146.0, 148.3, 149.2, 149.4, 171.3 (C-4); GC-MS *m/z* (%) 315 (M^+, 11), 148 (71), 119 (29), 92 (100), 65 (38); HRMS (ESI) *m/z* calcd: $C_{15}H_{13}SN_3O_3$ + H, 316.0750; found: 316.0742 (M + H).

2-(2-fluorophenyl)-3-(pyridin-3-ylmethyl)-1,3-thiazolidin-4-ones (**4d**)

Yield 87%; mp 61-64 °C pale yellow; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.74 (d, 1H, *J* 15.6, H-5b), 3.80 (d, 1H, *J* 15.2, CH_2b), 3.92 (d, 1H, *J* 15.6, H-5a), 4.99 (d, 1H, *J* 14.8, CH_2a), 5.70 (s, 1H, H-2), 7.07 (2d, 1H, *J* 10.0, 8.6, Ar-H), 7.14 (t, 1H, *J* 7.4, Ar-H), 7.29-7.22 (m, 2H, Ar-H), 7.38-7.33 (m, 1H, Ar-H), 7.53 (d, 1H, *J* 7.8, Ar-H), 8.30 (d, 1H, *J* 1.5, Ar-H), 8.50 (d, 1H, *J* 4.7, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.5 (C-5), 44.1 (CH_2), 56.7 (d, $^5J_{C\text{-}F}$ 3.7, C-2), 116.2 (d, $^2J_{C\text{-}F}$ 20.6), 123.7, 124.8, 126.0 (d, $^2J_{C\text{-}F}$ 11.0), 128.2 (d, $^4J_{C\text{-}F}$ 3.7), 130.9 (d, $^3J_{C\text{-}F}$ 8.8), 131.1, 136.2, 149.1, 149.3, 160.4 (d, $^1J_{C\text{-}F}$ 249.9), 171.4 (C-4); GC-MS *m/z* (%) 288 (M^+, 40), 213 (34), 148 (56), 92 (100), 65 (37); HRMS (ESI) *m/z* calcd: $C_{15}H_{13}FSN_2O$ + H, 289.0805; found: 289.0798 (M + H).

2-(3-fluorophenyl)-3-(pyridin-3-ylmethyl)-1,3-thiazolidin-4-ones (**4e**)

Yield 80%; mp 84-87 °C pale yellow; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.73 (d, 1H, *J* 14.8, CH_2b), 3.76 (d, 1H, *J* 15.6, H-5b), 3.90 (d, 1H, *J* 16.0, H-5a), 5.04 (d, 1H, *J* 14.8, CH_2a), 5.38 (s, 1H, H-2), 6.98 (d, 1H, *J* 8.6, Ar-H), 7.08 (d, 1H, *J* 8.2, Ar-H), 7.02 (d, 1H, *J* 8.2, Ar-H), 7.29-7.26 (m, 1H, Ar-H), 7.37 (2d, 1H, *J* 8.2, 7.8, Ar-H), 7.53 (d, 1H, *J* 7.8, Ar-H), 8.30 (s, 1H, Ar-H), 8.55 (d, 1H, *J* 4.7, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.6 (C-5), 43.9 (CH_2), 62.2 (d, $^5J_{C\text{-}F}$ 1.4, C-2), 114.0 (d, $^2J_{C\text{-}F}$ 22.1), 116.5 (d, $^2J_{C\text{-}F}$ 21.3), 122.7 (d, $^4J_{C\text{-}F}$ 3.0), 123.8, 130.8 (d, $^3J_{C\text{-}F}$ 8.1), 131.0, 136,3, 141.3, 149.3, 149.4, 163.1 (d, $^1J_{C\text{-}F}$ 248.4), 171.3 (C-4); GC-MS *m/z* (%) 288 (M^+, 24), 213 (32), 148 (65), 92 (100), 65 (35).

2-(4-fluorophenyl)-3-(pyridin-3-ylmethyl)-1,3-thiazolidin-4-ones (**4f**)

Yield 94%; pale brown oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.70 (d, 1H, *J* 15.0, CH_2b), 3.76 (d, 1H, *J* 14.9, H-5b), 3.90 (d, 1H, *J* 15.6, 1.3, H-5a), 5.00 (d, 1H, *J* 14.9, CH_2a), 5.40 (s, 1H, H-2), 7.11-7.03 (m, 2H, Ar-H), 7.29-7.21 (m, 3H, Ar-H), 7.51 (dt, 1H, *J* 7.8, 1.7, Ar-H), 8.28 (d, 1H, *J* 2.0, Ar-H), 8.54 (dd, 1H, *J* 4.8, 1.7, Ar-H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 32.7 (C-5), 43.8 (CH_2), 62.3 (C-2), 116.1 (d, $^2J_{C\text{-}F}$ 21.9), 123.7, 129.2 (d, $^3J_{C\text{-}F}$ 8.4), 131.1, 134.1 (d, $^4J_{C\text{-}F}$ 3.2), 136.2, 149.2, 149.4, 160.9 (d, $^1J_{C\text{-}F}$ 248.9), 171.2 (C-4); GC-MS *m/z* (%) 288 (M^+, 24), 213 (63), 148 (67), 92 (100), 65 (38).

2-(2-chlorophenyl)-3-(pyridin-3-ylmethyl)-1,3-thiazolidin-4-ones (**4g**)

Yield 84%; mp 64-67 °C pale yellow; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.72 (d, 1H, *J* 15.2, H-5b), 3.75 (d, 1H, *J* 15.3, CH_2b), 3.85 (dd, 1H, *J* 16.0, 1.3, H-5a), 5.08 (d, 1H, *J* 14.9, CH_2a), 5.88 (d, 1H, *J* 1.2, H-2), 7.43-7.20 (m, 5H, Ar-H), 7.55 (dt, 1H, *J* 7.8, 1.8, Ar-H), 8.35 (d, 1H, *J* 1.8, Ar-H), 8.54 (dd, 1H, *J* 4.7, 1.4, Ar-H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 32.3 (C-5), 44.4 (CH_2), 59.3 (C-2), 123.7, 127.5, 127.7, 130.1, 130.5, 130.9, 133.0, 136.1, 136.2, 149.3, 149.5, 171.8 (C-4); GC-MS *m/z* (%) 304 (M^+, 26), 148 (39), 92 (100), 65 (35); HRMS (ESI) *m/z* calcd: $C_{15}H_{13}ClSN_2O$ + H, 305.0510; found: 305.0502 (M + H).

2-(4-chlorophenyl)-3-(pyridin-3-ylmethyl)-1,3-thiazolidin-4-ones (**4h**)

Yield 97%; yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.68 (d, 1H, *J* 15.0, H-5b), 3.75 (d, 1H, *J* 15.0, CH_2b), 3.91 (dd, 1H, *J* 15.8, 1.2, H-5a), 5.03 (d, 1H, *J* 14.9, CH_2a), 5.37 (d, 1H, *J* 1.2, H-2), 7.49-7.17 (m, 6H, Ar-H), 8.28 (d, 1H, *J* 2.0, Ar-H), 8.56 (dd, 1H, *J* 4.8, 1.7, Ar-H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 32.7 (C-5), 43.8 (CH_2), 62.2 (C-2), 123.8, 127.6, 128.6 (2C), 129.4 (2C), 131.0, 136.3, 137.0, 149.3, 149.4, 171.3 (C-4); GC-MS *m/z* (%) 304 (M^+, 18), 229 (41), 148 (66), 92 (100), 65 (39).

2-(2-methoxyphenyl)-3-(pyridin-3-ylmethyl)-1,3-thiazolidin-4-ones (**4i**)

Yield 94%; yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.68 (d, 1H, *J* 15.4, H-5b), 3.78 (d, 1H, *J* 15.2, CH_2b), 3.79 (s, 3H, OCH_3), 3.85 (d, 1H, *J* 15.4, H-5a), 5.01 (d, 1H, *J* 14.9, CH_2a), 5.77 (d, 1H, *J* 1.6, H-2), 6.89 (d, 1H, *J* 8.2, Ar-H), 6.99 (d, 1H, *J* 6.8, Ar-H), 7.14 (dd, 1H, *J* 7.6, 1.7, Ar-H), 7.33-7.23 (m, 2H, Ar-H), 7.54 (dt, 1H, *J* 7.8, 1.8, Ar-H), 8.30 (d, 1H, *J* 1.9, Ar-H), 8.52 (dd, 1H, *J* 4.7, 1.5, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.7 (C-5), 44.0 (CH_2), 55.4 (OCH_3), 57.8 (C-2), 111.0, 120.8, 123.5, 126.5, 127.1, 130.2, 131.4, 136.1, 149.0, 149.5, 156.9, 171.9 (C-4); GC-MS *m/z* (%) 300 (M^+, 10), 225 (49), 208 (99), 92 (100), 65 (35).

2-(3-methoxyphenyl)-3-(pyridin-3-ylmethyl)-1,3-thiazolidin-4-ones (**4j**)

Yield 88%; yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$ δ 3.79 (s, 3H, OCH_3), 3.94-3.70 (m, 4H, H-5 and CH_2), 5.02 (d, 1H, *J* 14.9, CH_2a), 5.37 (d, 1H, *J* 1.2, H-2), 6.84-6,75 (m, 2H, Ar-H), 6.90 (ddd, 1H, *J* 8.3, 2.5, 0.90, Ar-H), 7.30 (m, 2H, Ar-H), 7.54 (dt, 1H, *J* 7.8, 1.8, Ar-H), 8.30 (d, 1H, *J* 2.0, Ar-H), 8.54 (dd, 1H, *J* 4.7, 1.5, Ar-H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 32.7 (C-5), 43.9 (CH_2), 55.3 (OCH_3), 62.9 (C-2), 112.5, 114.9, 119.3, 123.7, 130.2, 131.3, 136.4, 140.0, 149.0, 149.4, 160.2, 171.4 (C-4); GC-MS *m/z* (%) 300 (M^+, 28), 225 (49), 92 (100), 65 (36).

2-(4-methoxyphenyl)-3-(pyridin-3-ylmethyl)-1,3-thiazolidin-4-ones (**4k**)

Yield 97%; mp 67-70 °C pale yellow; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.68 (d, 1H, *J* 14.8, CH_2b), 3.76 (d, 1H, *J* 15.6, H-5b), 3.83 (s, 3H, OCH_3), 3.87 (dd, 1H, *J* 15.6, 1.9, H-5a), 4.99 (d, 1H, *J* 14.8, CH_2a), 5.37 (s, H-2), 6.90 (d, 2H, *J* 8.9, Ar-H), 7.18 (d, 2H, *J* 8.6, Ar-H), 7.29-7.24 (m, 1H, Ar-H), 7.51 (d, 1H, *J* 7.8, Ar-H), 8.27 (d, 1H, *J* 1.9, Ar-H), 8.53 (dd, 1H, *J* 4.7, 1.6, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.9 (C-5), 43.6 (CH_2), 55.3 (OCH_3), 62.6 (C-2), 114.4 (2 C), 123.6, 128.7, 129.9, 131.2, 136.2, 149.2, 149.6 (2 C), 160.3, 171.2 (C-4); GC-MS *m/z* (%) 300 (M^+, 44), 225 (100), 92 (61), 65 (26); HRMS (ESI) *m/z* calcd: $C_{16}H_{16}SN_2O_2$ + H, 301.1005; found: 301.0997 (M + H).

2-(4-methylphenyl)-3-(pyridin-3-ylmethyl)-1,3-thiazolidin-4-ones (**4l**)

Yield 80%; yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.37 (s, 3H, CH_3), 3.68 (d, 1H, *J* 14.9, CH_2b), 3.74 (dd, 1H, *J* 15.6, 0.7, H-5b), 3.90 (dd, 1H, *J* 15.6, 1.3, H-5a), 4.99 (d, 1H, *J* 14.9, CH_2a), 5.37 (d, 1H, *J* 1.4, H-2), 7.28-7.10 (m, 5H, Ar-H), 7.52 (dt, 1H, *J* 7.8, 1.9, Ar-H), 8.28 (d, 1H, *J* 2.0, Ar-H), 8.53 (dd, 1H, *J* 4.8, 1.6, Ar-H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.1 (CH_3), 32.8 (C-5), 43.7 (CH_2), 62.8 (C-2), 123.7, 127.2 (2 C), 129.8 (2 C), 131.3, 135.3, 136.3, 139.5, 149.1, 149.5, 171.3 (C-4); GC-MS *m/z* (%) 284 (M^+, 86), 209 (98), 92 (100), 65 (50).

2-(2-hydroxyphenyl)-3-(pyridin-3-ylmethyl)-1,3-thiazolidin-4-ones (**4m**)

Yield 59%; mp 168-171 °C pale yellow; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.73 (d, 1H, *J* 15.6, H-5b), 3.91 (d, 1H, *J* 14.8, CH_2b), 3.97 (dd, 1H, *J* 15.6, 1.9, H-5a), 4.93 (d, 1H, *J* 14.5, CH_2a), 6.02 (s, 1H, H-2), 6.83-6.89 (m, 2H, Ar-H), 7.13-7.17 (m, 1H, Ar-H), 7.26-7.29 (m, 1H, Ar-H), 7.36 (2d, 1H, *J* 8.2, 7.8, Ar-H), 7.82 (d, 1H, *J* 7.8, Ar-H), 8.47 (d, 1H, *J* 1.6, Ar-H), 8.52 (dd, 1H, *J* 4.7, 1.6, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.3 (C-5), 43.8 (CH_2), 57.1 (C-2), 115.8, 120.0, 124.4, 124.5, 128.7, 130.3, 132.6, 138.3, 147.7, 148.8, 155.7, 171.8 (C-4); GC-MS *m/z* (%) 286 (M^+, 32), 211 (100), 92 (100), 65 (52).

2-(3-hydroxyphenyl)-3-(pyridin-3-ylmethyl)-1,3-thiazolidin-4-ones (**4n**)

Yield 90%; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.73 (d, 1H, *J* 15.6, H-5b), 3.85 (dd, 1H, *J* 15.6, 1.9, H-5a), 3.90 (d, 1H, *J* 14.8, CH_2b), 4.89 (d, 1H, *J* 15.2, CH_2a), 5.36 (s, 1H, H-2), 6.76-6.72 (m, 2H, Ar-H), 6.85 (dd, 1H, *J* 7.8, 1.9, Ar-H), 7.19 (t, 1H, *J* 7.8, Ar-H), 7.33-7.28 (m, 1H, Ar-H), 7.61 (d, 1H, *J* 7.8, Ar-H), 8.26 (d, 1H, *J* 1.5, Ar-H), 8.50 (dd, 1H, *J* 4.7, 1.2, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.7 (C-5), 44.0 (CH_2), 63.2 (C-2), 114.1, 116.9, 118.3, 124.2, 130.3, 132.0, 137.4, 139.7, 148.1, 148.5, 157.9, 171.7 (C-4); GC-MS *m/z* (%) 286 (M^+, 69), 211 (44), 92 (100), 65 (46).

2-(4-hydroxyphenyl)-3-(pyridin-3-ylmethyl)-1,3-thiazolidin-4-ones (**4o**)

Yield 74%; mp 139-142 °C cream-coloured; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72 (d, 1H, *J* 14.8, CH_2b), 3.74 (d, 1H, *J* 15.6, H-5b), 3.85 (d, 1H, *J* 15.6, H-5a), 4.93 (d, 1H, *J* 15.2, CH_2a), 5.37 (s, 1H, H-2), 6.84 (d, 2H, *J* 8.6, Ar-H), 7.09 (d, 2H, *J* 8.6, Ar-H), 7.27 and 7.26 (2d, 1H, *J* 7.8, 7.8, Ar-H), 7.51-7.48 (m, 1H, Ar-H), 8.29 (d, 1H, *J* 1.6, Ar-H), 8.52 (dd, 1H, *J* 4.5, 1.4, Ar-H), 9.38 (br, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.2 (C-5), 42.9 (CH_2), 62.2 (C-2), 115.3 (2 C), 122.9, 127.5, 128.2 (2 C), 130.7, 135.5, 148.3, 148.8, 157.8, 170.4 (C-4); GC-MS *m/z* (%) 286 (M^+, 66), 211 (100), 92 (94), 65 (52); HRMS (ESI) *m/z* calcd: $C_{15}H_{14}SN_2O_2$ + H, 287.0849; found: 287.0843 (M + H).

DPPH assay

The 2,2-diphenyl-1-picryl-hydrazyl (DPPH) free radical-scavenging assay was performed in accordance with the procedure reported by Brand-Williams *et al.*[34] with some modifications. Different concentrations of compounds were mixed with a solution containing the DPPH radical. The mixture was incubated for 30 min at 30 °C, and the absorbance was measured at 517 nm. The antiradical activity was defined as the amount of antioxidant necessary to decrease the initial DPPH concentration by 50% (EC_{50}).

ABTS assay

The ABTS radical-scavenging activity was evaluated as described by Re *et al*.[35] with some modifications. ABTS radical cation ($ABTS^{\bullet+}$) was produced by reacting ABTS stock solution with potassium persulfate. Different concentrations of compounds were mixed with $ABTS^{\bullet+}$, and the final mixture was left to stand at 30 °C; the absorbance was measured at 734 nm. Trolox was used as standard reference. The percentage of radical scavenging was calculated as TEAC.

Supplementary Information

Supplementary Information (^1H and ^{13}C NMR, mass and HRMS spectrum) is available free of charge at http://jbcs.sbq.org.br.

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