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Spirocyclic derivatives as antioxidants: a review†

Karen Acosta-Quiroga,‡[a] Cristian Rojas-Peña,‡[a] Luz Stella Nerio,[a] Margarita Gutiérrez*[b] and Efraín Polo-Cuadrado*[b]

In recent years, spiro compounds have attracted significant interest in medicinal chemistry due to their numerous biological activities attributed primarily to their versatility and structural similarity to important pharmacophore centers. Currently, the development of drugs with potential antioxidant activities is of great importance since numerous investigations have shown that oxidative stress is involved in the development and progression of numerous diseases such as cancer, senile cataracts, kidney failure, diabetes, high blood pressure, cirrhosis, and neurodegenerative diseases, among others. This article provides an overview of the synthesis and various antioxidant activities found in naturally occurring and synthetic spiro compounds. Among the antioxidant activities reviewed are DPPH, ABTS, FRAP, anti-LPO, superoxide, xanthine oxidase, peroxide, hydroxyl, and nitric oxide tests, among others. Molecules that presented best results for these tests were spiro compounds **G14**, **C12**, **D41**, **C18**, **C15**, **D5**, **D11**, **E1**, and **C14**. In general, most active compounds are characterized for having at least one oxygen atom; an important number of them (around 35%) are phenolic compounds, and in molecules where this functional group was absent, aryl ethers and nitrogen-containing functional groups such as amine and amides could be found. Recent advances in the antioxidant activity profiles of spiro compounds have shown that they have a significant position in discovering drugs with potential antioxidant activities.

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Introduction

Spiro compounds, molecules containing two rings with only one shared atom, are an essential class of synthetic or naturally occurring substances. Their good balance between conformational restriction and flexibility makes them free from absorption and permeability issues, characteristic of conformationally more flexible linear molecules, and more flexible compared to aromatic heterocycles, adapting to many biological targets attractive for new drug discovery projects.[1,2] Although spirocyclic systems are unusual scaffolds for bioactive molecules, recent progress on the isolation and characterization of new compounds from natural products and new synthetic routes to spiro building blocks have facilitated their incorporation into more molecules with pharmacological applications, such as antidiabetic, anticancer, anti-Alzheimer's, and in some cases, they have been successfully developed as commercial drugs.[2–8] It has also been found that an important number of spiro compounds act as antioxidants (AO), substances that may prevent damage caused by reactive oxygen species (ROS) and reactive nitrogen species (RNS). ROS and RNS are generated in living cells, either naturally or due to some biological dysfunction such as stress. These compounds have essential roles in cell signaling, but many of these compounds are harmful to cells and their significant components, including DNA, enzymes, cell membrane lipids, and proteins.[9] Thus, AOs are helpful as scavengers of free radicals, inhibiting oxidative degradation, such as protein oxidation, lipid oxidation, DNA oxidation, and glycoxidation, and processes associated with the development of neurodegenerative diseases, metabolic syndromes, atherosclerosis, infections, and cancer. In this way, the isolation and synthesis of molecules with AO properties for exogenous supplementation are promising ways of combating the undesirable effects of ROS and RNS-induced oxidative damage.

In order to characterize the AO properties of a compound or extracts, two parameters should be assessed: AO activity (rate constant of a reaction between an AO and an oxidant) and AO capacity (amount of a particular free radical captured by an AO sample). There is no universal method for measuring AO activity/capacity in a very accurate and quantitative way because these results are highly affected by the reactive species employed in the assay. The properties of the assay system can significantly influence the effectiveness of an AO, and hence, the results may vary with different methods.[10] Therefore, this property can be monitored by a wide variety of assays involving different mechanisms; *in vitro* methods can work through hydrogen atom transfer (HAT) or electron transfer (ET).[11] Most

[a]*Universidad de la Amazonia, Programa de Química, Cl. 17 Diagonal 17 con, Cra. 3F, Florencia 180001, Colombia*

[b]*Laboratorio Síntesis Orgánica y Actividad Biológica, Instituto de Química de Recursos Naturales, Universidad de Talca, Casilla 747, Talca 3460000, Chile. E-mail: mgutierrez@utalca.cl; epolo@utalca.cl*

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‡ These authors contributed equally to this work.

AO assays for spirocyclic compounds are based on ET reactions, including 2,2-diphenyl-1-picryl-hydrazyl-hydrate (DPPH) assay, Trolox Equivalent AO Capacity (TEAC) assay, ferric reducing AO power assay (FRAP) assay, cupric-reducing AO capacity (CUPRAC) assay, 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) assay, superoxide anion (SOA) radical scavenging assay and hydroxyl radical scavenging assay, these ET-based methods detect the ability of a potential AO to transfer one electron to reduce any compound, including metals, carbonyls, or radicals.[12] AO molecules can react either by multiple mechanisms or by a predominant mechanism, and the identification of these makes it possible to determine the possible uses for a molecule.[11]

In this review, the AO properties of spirocyclic compounds of natural and synthetic origin, assessed through "*in vitro*" and "*in vivo*" methods, are presented based on comparisons with substances used as positive controls in each case. For some compounds, to increase attention on their biological potential, information about other pharmacological properties associated with oxidative damage is presented. Articles used for this review were chosen through a search, up to December 2020, in the SciFinder and PubMed databases, using "spiro antioxidant" and "spiro antioxidative" as keywords. The ring combinations (where A = any atom) for molecules whose AO activity is described in this review are presented in Table 1.

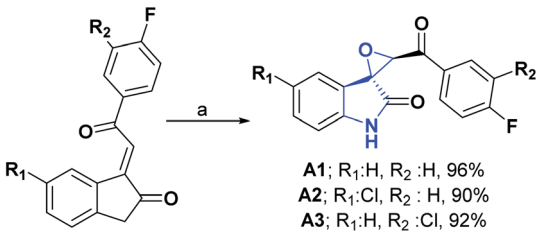
[2.4.0] Spirocyclic system (A)

[2.4.0] Spirocyclic system (A); compounds of synthetic origin

Heterocyclic spiropyran compounds are of great biological and medicinal interest; they have been reported as inhibitors of the growth of human colon adenocarcinoma and the HL-60 p

Table 1 The occurrence of various ring combinations in the spirocyclic compounds analysed in this review

Ring combinations						
	0	0	4	0	0	1
	0	0	0	0	0	0
	4	0	37	51	6	5
	0	0	51	14	1	0
	0	0	6	1	0	0
	1	0	5	0	0	0



Scheme 1 Structures, reagents and conditions for the synthesis of spiro heterocycles [2.4.0] **A1–A3**. (a) H_2O_2 (30%), NaOH, CTAB, H_2O, PTC, ultrasonic irradiation, (50% power, 1.0 A), rt, 12 min.

leukemia cell line and the production of the HIV-1 p-24 virus,[13,14] in addition to acting as strong vasopressin antagonists.[15]

In 2011, the synthesis of spiro [indole-3,2-oxirane]-30-benzoyl-2-(1*H*)-fluorinated compounds (**A1–A3**) was reported, and their AO activities were determined through nitric oxide (NO) and 2,2-diphenyl-1-picrylhydrazyl (DPPH) tests.

Compounds **A1–A3** had an inhibition percentage at 100 μM of 80.21, 90.12, 85.12%, respectively in the NO test, while for the DPPH test, inhibition percentages were obtained at 100 μM of 82.39, 91.32, and 86.32% correspondingly. In Scheme 1, the synthesis reported for compounds **A1–A3** is shown.[16]

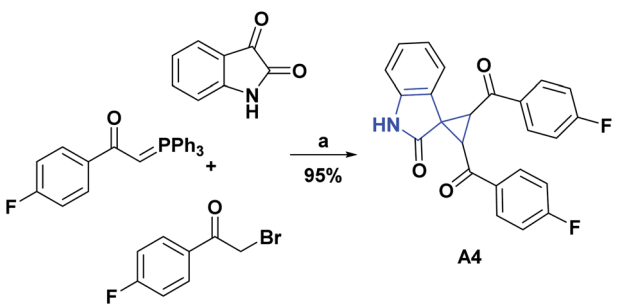
The synthesis and AO activity, using the DPPH test, of a new spirocyclopropanoxyindole [2.4.0] compound (**A4**) has been reported.[17] This compound showed moderately good activity, with an inhibition percentage at 1 mg mL^{-1} of 63.90%, compared to vitamin C as standard, with 82.30% inhibition at the same concentration. Scheme 2 shows the general procedure for the synthesis of compound **A4**.

[2.7.0] Spirocyclic system (B)

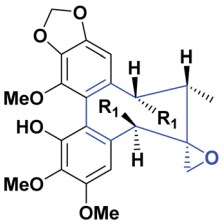
[2.7.0] Spirocyclic system (B); compounds of natural origin

Various substances obtained from nature are considered rich sources of AO. They are accountable for minimizing the cell damage that may lead to heart diseases, cancer, Alzheimer's, and other diseases. The only spirocyclic combinations of three and eight-membered rings are represented in natural products. The spiro-compound **B1**: Kadsuphilol C, was isolated from the leaves and stems of *Kadsura philippinensis.*

This compound was screened for radical scavenging activity through DPPH assay, compared with well-known AO, vitamin C,

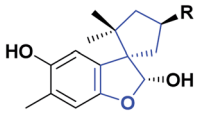


Scheme 2 Structures, reagents and conditions for the synthesis of spiro heterocycle [2.4.0] **A4**. (a) Et_3N, H_2O, ultrasonic irradiation, 60 W, rt, 20 min.



B1; R_1: OAng
Kadsuphilol C
Kadsura philippinensis

Fig. 1 Structure of the spiro heterocycle [2.7.0] compound **B1**.



C1; R: OH
C2; R: (=O)
Hericiu coralloides

Fig. 2 Structures of spiro heterocycles [4.4.0] compounds **C1–C2**.

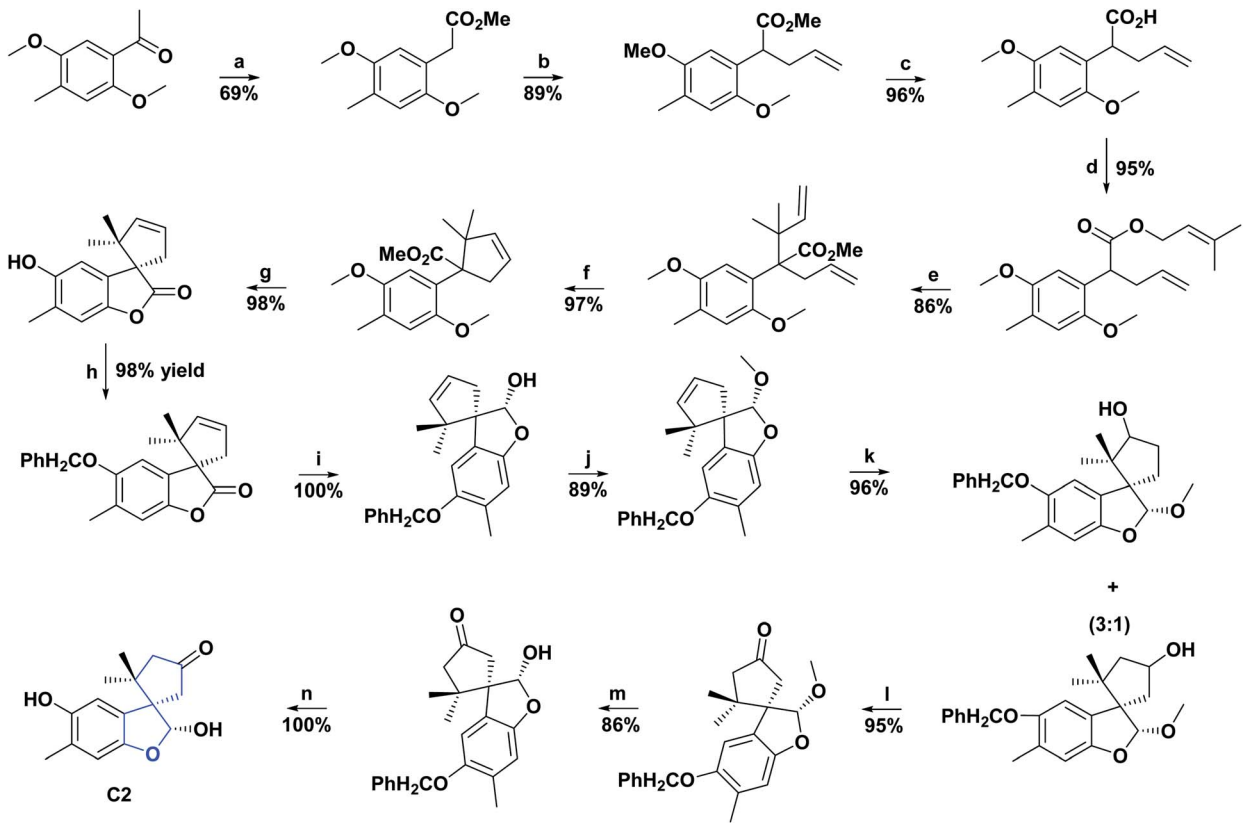
and vitamin E. **B1** exhibited more potent activity than vitamins C and E at several concentrations (6.25, 12.50, 25.00, 50, and 100 μM). The data were 47.40% and 51.40% for **B1**, compared with 19.20% and 36.70% for vitamin C, 1.30% and 12.90% for vitamin E at 6.25 and 50 μM, respectively (see Fig. 1).[18]

[4.4.0] Spirocyclic system (C)

[4.4.0] Spirocyclic system (C); compounds of natural origin

Hericium coralloide is a basidiomycete mushroom that belongs to the Hericiaceae family; it has a strong resemblance to white coral, is edible, used as a traditional medicine in Korea and China and distributed in Europe, North America, and Asia. The most famous representative species of the Hericiaceae family is *H. erinaceus*, which is used in alternative medicine, and is processed into food supplements.[19] Numerous investigations have reported various activities in *H. erinaceus*, such as cytotoxic, neuroprotective, and antibacterial activities.[20,21]

In contrast, there are only a few reports regarding the activities of *H. coralloide*. Studies have demonstrated that *H. coralloides* produce inducers of neurotrophic factors and brain-derived nerve growth factors known as corallocins A–C. Furthermore, *H. coralloides* ethyl acetate extract has been reported to have high AO activity "*in vitro*" with IC_{50} of 0.93, 1.84, 1.59, and 0.60 mg mL^{-1} against DPPH, hydroxyl radicals (HOR), ABTS and superoxide anion (SOA), respectively. Two spirobenzofurans (**C1** and **C2**) were isolated from the culture broth



Scheme 3 Reagents and conditions for the synthesis of compound **C2**. (a) I_2 (2 equiv.), $HC(OMe)_3$, rt, 6 h; reflux, 6 h; (b) LDA, THF; $CH_2{=}CHCH_2Br$, −70 °C → rt, 7 h; (c) 10% NaOH, MeOH–H_2O (1 : 1), reflux, 7 h; (d) DCC, DMAP (catalytic), $Me_2C{=}CHCH_2OH$, DCM, rt, 5 h; (e) (1) LDA, THF; TMSCl, Et_3N, −70 °C, 30 min; rt, 6 h; reflux, 3 h; (2) dil. HCl, 40 min; (3) CH_2N_2, Et_2O, 0 °C, 30 min; (f) $Cl_2Ru(PCy_3)_2{=}CHPh$ (5 mol%), DCM, rt, 5 h; (g) BBr_3, DCM, −70 °C, 1.5 h; (h) K_2CO_3, $PhCH_2Br$, acetone, rt, 6 h; (i) DIBAL-H, THF, rt → 70 °C, 1.5 h; (j) MeOH, $HC(OMe)_3$, PPTS, reflux, 40 min; (k) (1) $NaBH_4$, $BF_3{\cdot}Et_2O$, THF, 0 °C → rt, 1 h; (2) 30% aq H_2O_2, 3 N aq NaOH, 0 °C → rt, 7 h; (l) PCC, silica gel, DCM, rt, 1 h; (m) AcOH–H_2O (2 : 1), CF_3COOH (catalytic), reflux, 14 h; (n) 10% Pd/C, H_2, EtOH, 1 atm, 1.5 h.

of *H. coralloides*[22] and their AO capacities were assessed using ABTS and DPPH scanning test methods.

These compounds presented AO activity in a dose-dependent manner. Both compounds showed potent AO activity in the ABTS radical scavenging assay with IC_{50} values of 66.00 and 29.60 μM, respectively, and significant AO activity with IC_{50} of 121.00 and 90.80 μM, correspondingly in the DPPH radical scavenging test. **C1** and **C2** were compared with the positive controls Trolox and butylated hydroxyanisole, presented in the ABTS test IC_{50} values of 25.20 and 18.50 μM and for the DPPH assay 55.70 and 78.30 μM, respectively (see Fig. 2). The total synthesis of compound **C2** was described in 2005, and the general procedure is shown in Scheme 3.[23]

The genus *Yucca* (Agavaceae) comprises several species characterized by the presence of steroidal saponins; one of the best-known species is *Yucca schidigerao*,[24,25] also called *Yucca*, found mainly in the southwestern United States and Mexico. Studies carried out on the phenolic extract of yucca roots have found that it has potent AO activity and great antiplatelet activity.[25,26]

Cassava bark studies have reported that "*in vitro*" tests of phenolic compounds exert an AO effect on different reactive oxygen species (ROS), produced in resting blood platelets and blood platelets activated by thrombin.

From the methanolic extract of the *Yucca schidigerao* bark, two new phenolic constituents with unusual spiro structures were isolated, called yuccaols D (**C3**) and E (**C4**). To determine their AO properties, the trolox equivalent AO capacity test was developed, obtaining TEAC values of 1.42 and 1.85 mM for compounds **C3** and **C4**, respectively; these results indicate a better activity than the positive quercetin control, which offered a value of 2.60 mM (see Fig. 3).[27]

Yucca gloriosa is a member of the Asparagaceae family, which mainly grows in Eastern Georgia and has a rich source of steroidal saponins. The fraction of saponins found in its leaves has been used as the primary raw material for the synthesis of steroid hormones.[28] An investigation in 2006 of the bark of *Y. gloriosa* revealed two very unusual phenolic constituents called gloriosaols A (**C5**) and B (**C6**). In 2007 three new phenolic derivatives of gloriosaols C (**C7**), D (**C8**), and E (**C9**) were isolated. The AO activities of compounds **C5–C9** were evaluated using the TEAC test; the values were 5.55, 3.00, 5.60, 4.91, and 4.91 mM, respectively, compared to the positive quercetin control with a value of 2.60 mM (see Fig. 3).[29] It is important to mention that no information was found related to the synthesis of compounds **C3–C9**.

Uncaria tomentosa is a tropical medicinal vine in the Rubiaceae family, widely distributed in the Amazon rainforest and other areas of South and Central America. *U. tomentosa* is a powerful complementary herb for the treatment of most parasites; it has also shown a wide variety of biological activities that include cardiovascular, anticancer, AO, antimicrobial, and anti-inflammatory effects.[30–35] The compound spiro [4.4.0] (**C11**) called pteropodine was isolated from *U. tomentosa*, and its AO activity was evaluated using the DPPH assay. Compound **C11** presented a radical inhibition percentage of 98.00 percent at a concentration of 250 μg mL^{-1}.[36] Total synthesis of pteropodine (**C11**) was published in 1990, and the general procedure is shown in Scheme 4.[37]

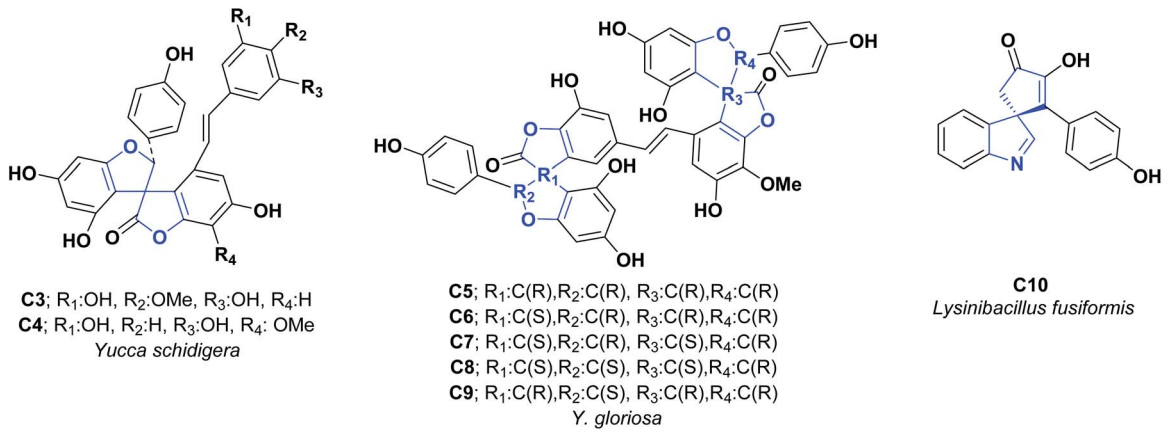
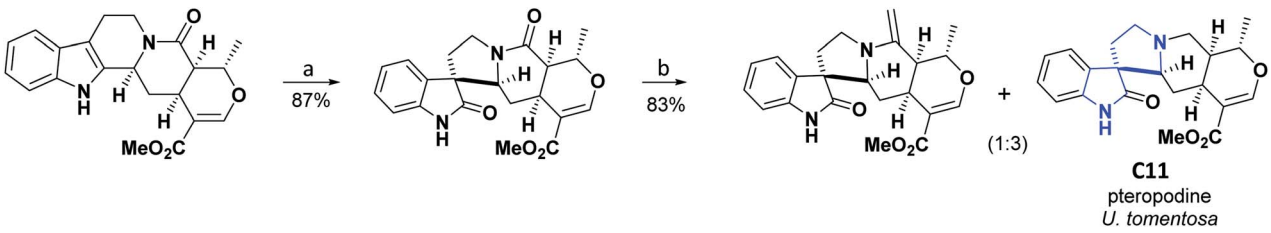


Fig. 3 Structures of the spiro heterocycles [4.4.0] compounds **C3–C10**.



Scheme 4 Structures, reagents and conditions for the synthesis of spiro heterocycle [4.4.0] **C11**. (a) (1) *tert*-BuOCl, Et_3N, rt; (2) $AgClO_4$; MeOH–H_2O, $HClO_4$, rt; (b) (1) AlH_3; THF; −50 °C, 1 h; (2) $NaBH_3CN$, MeOH–H_2O, HOAc, rt, 1 h.

[4.4.0] Spirocyclic system (C); compounds of synthetic origin

Isatin or 1*H*-indole-2,3-dione is a metabolic by-product of epinephrine found in mammalian tissues and fluids. This molecule has excellent synthetic versatility, which has generated a growing interest in the development of new derivative compounds.[38] For this reason, there have been several reports of studies on a wide range of biological activities of isatin-derived molecules, such as analgesic, anti-inflammatory, antipyretic, and cytotoxic activities.[39–41] Moreover, thanks to its lactam ring, isatin and its derivatives are responsible for having free radical scavenging activity due to their N–H and C=O residues.[42]

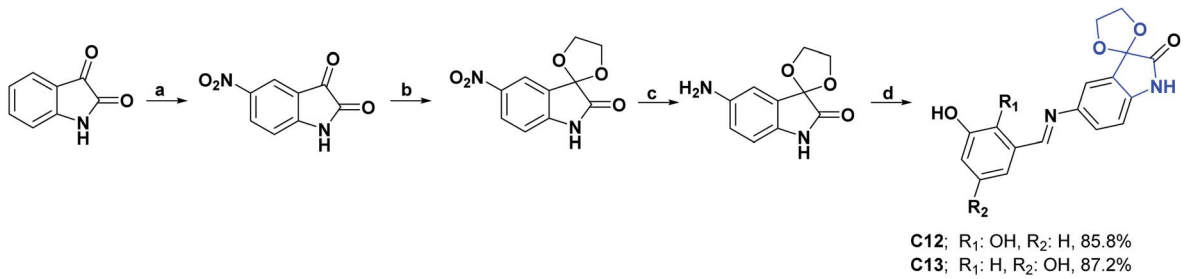
Schiff bases are another important class of organic compounds with pharmacological activities, such as antibacterial, antifungal, antimalarial, anti-inflammatory, and antipyretic.[43,44] Therefore, due to the interest that has arisen in the mentioned compounds, these two pharmacophore blocks have been unified in two new Schiff bases derived from spiroisatin (**C12** and **C13**), and their AO capacities were determined using DPPH cationic radical scavenging tests, CUPRAC and ABTS.[45] Results obtained for **C12** and **C13** showed IC_{50} values of 4.49 and 18.65 μM in the DPPH test, 0.39 and 0.86 μM in the ABTS test, and A_{050} values of 0.42 and 1.35 μM in the CUPRAC test, respectively.

The AO capacities of these compounds were compared with quercetin (positive control), which showed IC_{50} values of 8.69, 15.49, and A_{050} of 18.47 μM in the DPPH, ABTS, and CUPRAC tests, respectively. At the end of this study, the authors determined that these compounds showed better AO activity in all tests than the positive control. The synthesis of compounds **C12** and **C13** is shown in Scheme 5.[45]

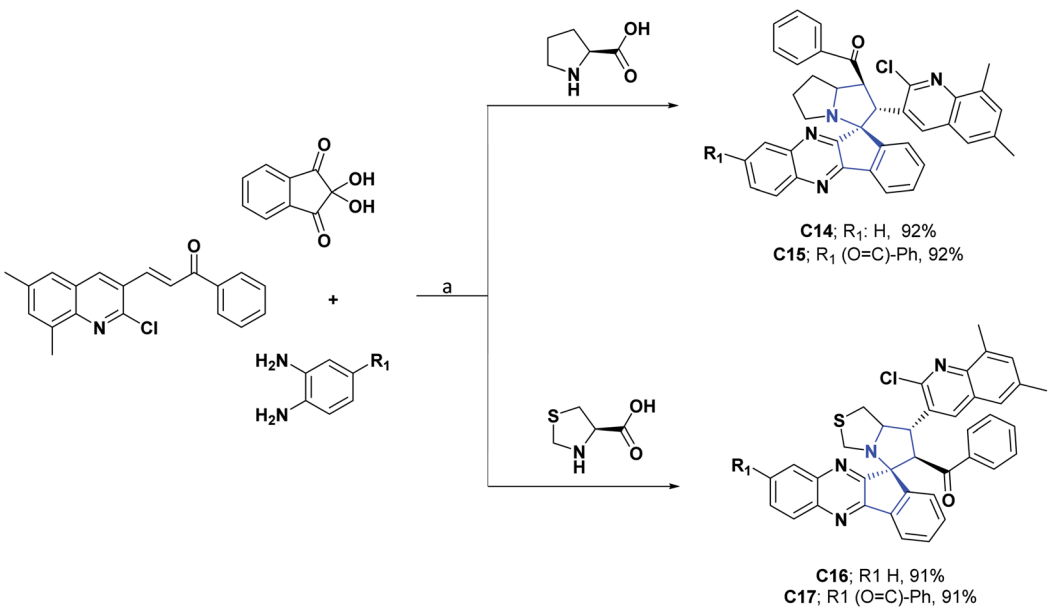
Pyrrolizidines and pyrrolothiazoles make up another important group of nitrogenous heterocycles that also stand out for their wide range of pharmacological activities such as antimycobacterial, hepatoprotective, antibiotic, antidiabetic, anticonvulsant, and anti-acetylcholinesterase (AChE).[46–52]

The generation of molecules with these structural residues is, therefore, of great interest. Indenoquinoxalines and their derivatives also exhibit a spectrum of biological activities such as antimicrobial, antifungal, anticancer, and anthelmintic properties.[53] This led in 2017 and 2018 to the unifying of these pharmacophoric nuclei into two new spiro-indenoquinoxaline pyrrolizines (**C14** and **C15**),[54] and two spiro-indenoquinoxaline pyrrolothiazoles (**C16–C17**),[53] whose AO capacities were evaluated through the DPPH, NO, and SOA tests.

The IC_{50} values obtained for compounds **C14–C17** were, respectively, 2.96, 3.56, 3.09 and 3.11 μg mL^{-1} for the DPPH



Scheme 5 Structures, reagents and conditions for the synthesis of spiro heterocycles [4.4.0] **C12** and **C13**. (a) KNO_3, H_2SO_4, rt, 2 h; (b) ethylene glycol, PTSA, benzene, reflux, 24 h; (c) cyclohexene, 10% Pd–C, EtOH, reflux, 2 h; (d) aldehyde derivatives, Et_3N, EtOH, reflux, 8 h.



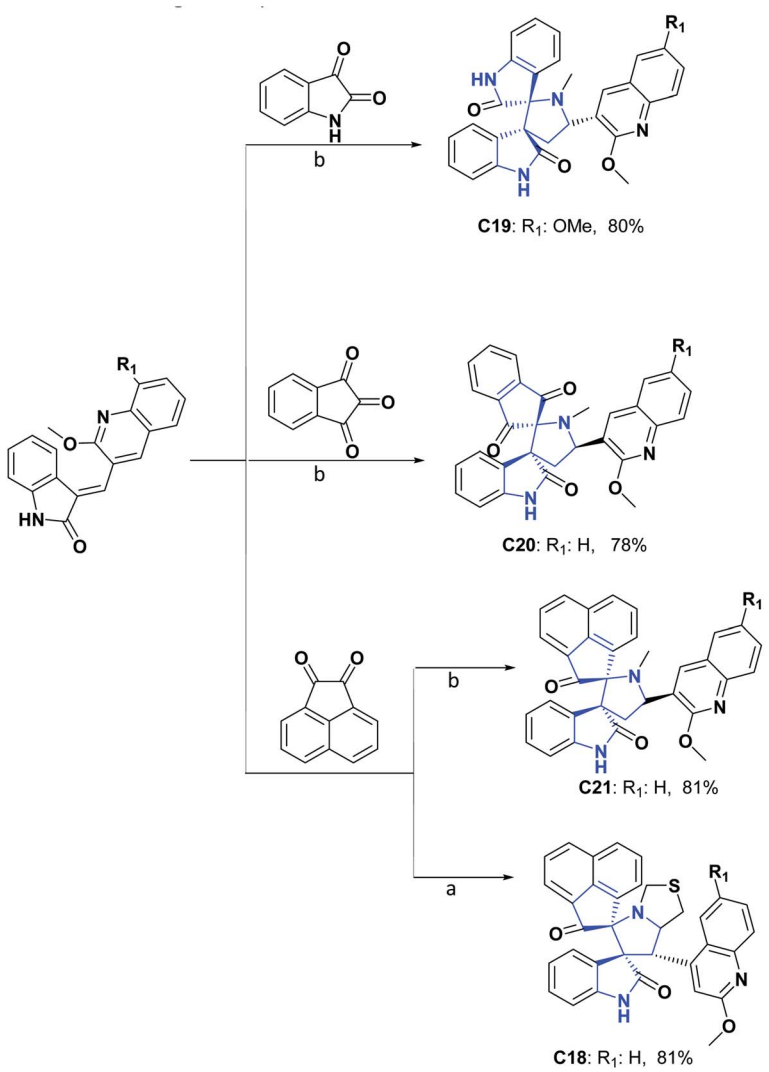
Scheme 6 Structures, reagents and conditions for the synthesis of spiro heterocycles [4.4.0] **C14–C17**. (a) MeOH, L-proline, reflux 1.5 h for **C14**, 1 h for **C15**, 2 h for **C16**, 3 h for **C17**.

assay, 1.34, 3.56, 2.58 and 3.26 μg mL^{-1} in the NO test and 4.00, 3.80, 4.29 and 4.34 μg mL^{-1} in the SOA test. For all compounds and tests, the AO activity was better than the positive control (BHT), which presented IC_{50} values of 7.93, 7.19, and 9.30 μg mL^{-1} in the DPPH, NO, and SOA tests. The general procedure for obtaining compounds **C14–C17** is shown in Scheme 6.[53,54]

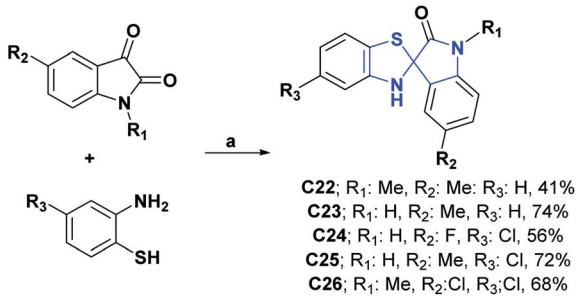
Like the molecules above, spirooxindoles are compounds of great pharmacological interest due to their wide variety of biological activities, including anti-inflammatory, antidiabetic, antitumor, antiviral, antimalarial, antifungal, antitubercular, and AChE inhibitors.[55–61] Many of these activities have been mainly related to the well-defined three-dimensional structure of spiroxyindoles and their conformational limitations generated by spirocarbon causing structural stiffness. However, spirooxindoles are undoubtedly the group of spiro molecules of synthetic origin whose AO activities have been most studied. Therefore, the synthesis and study of the AO activity of spiro compounds [4.4.0] derived from oxindoles (**C18–C36**) have been reported.

Compounds **C18–C21** are hybrid double spiros containing heteroatoms; their AO activities were evaluated by DPPH and LPO tests.[62] IC_{50} values reported for these compounds (**C18–C21**) are, respectively, 14.66, 15.03, 15.14, and 14.88 μM in the DPPH assay, while 13.75, 14.20, 16.00, and 16.74 μM in the LPO. All compounds presented good AO activity, in comparison with the positive controls, vitamin C, quercetin, and BHA, which repeatedly presented IC_{50} values of 14.99, 14.74, and 14.76 μM in the DPPH test and 18.34, 13.91, and 24.00 μM in the LPO assay.[62]

The authors emphasized that the good AO activity presented by the compounds could be due to the methoxy group in the *ortho* position of quinoline, which serves as a source of electrons, which could improve the stabilization of the oxygen radical resulting from DPPH. Also, they highlighted that the AO properties of the compounds coincided with vitamin C, which has a cyclic ester (lactone), and that this is because oxindoles have a very close structural similarity since they contain a cyclic amide (lactam) that makes them good candidates for exhibiting AO properties. Syntheses of compounds **C18–C21** are shown in Scheme 7.[62]



Scheme 7 Structures, reagents and conditions for the synthesis of spiro heterocycles [4.4.0] **C18–C21**. (a) MeOH, thiazolidine-4-carboxylic acid, reflux; (b) MeOH, methylglycine, reflux.

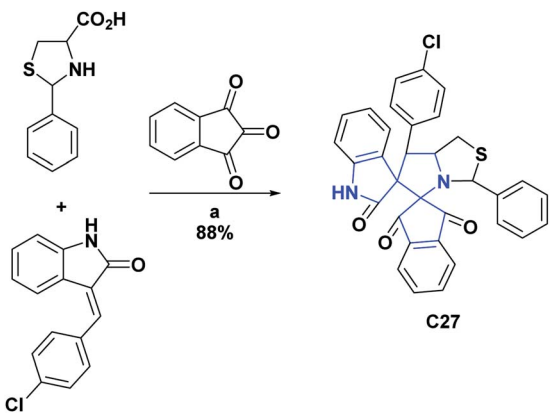


Scheme 8 Structure, reagents, and conditions for the synthesis of spiro heterocycles [4.4.0] **C22–C26**. (a) EtOH, reflux, 5 h for **C22** and **C23**, 3–6 h for **C24–C26**.

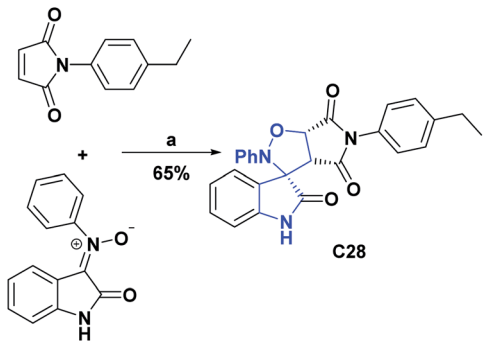
DPPH, ABTS, and anti-liposomal peroxidation tests were assessed for spiroxindoles **C22–C26.**[63,64] The results obtained showed that these compounds have EC_{50} values of 0.98, 1.30, 13.00, 8.33 and 4.19 mM, respectively, in the DPPH assay, EC_{50} of 0.98, 1.02, 0.99, 1.16 and 1.55 mM in the ABTS test and EC_{50} of 0.04, 0.03, 0.11, 0.12 and 0.12 mM in the anti-LPO test. Additionally, compounds **C22–C26** were compared with vitamin C and tocopherol as positive controls that respectively presented EC_{50} values of 0.36 and 0.35 mM in the DPPH test and 1.20 and 1.20 mM in the ABTS test. In the case of the anti-LP test, the molecules were only compared with tocopherol, which presented an EC_{50} value of 0.15 mM. Syntheses of compounds **C22–C26** are shown in Scheme 8.[63,64]

Likewise, the AO activities of oxindoles **C27–C30** were determined by the DPPH radical scavenging test. For compounds **C27** and **C28**, IC50 values were determined, which were respectively 32.50 μM and 0.44 μg mL^{-1}. Additionally, these compounds (**C27** and **C28**) were compared, respectively, with BHA that presented an IC_{50} of 58.60 μM and BHT that presented an IC_{50} of 5.37 μg mL^{-1}. General procedures for obtaining compounds **C27** and **C28** are shown in Schemes 9 and 10.[65,66]

In compounds **C29** and **C30**, only the percentage of DPPH radical scavenging at 450 μM was determined and presented values of 77.45 and 77.78%.[67] Compounds **C29** and **C30** were better



Scheme 9 Structures, reagents, and conditions for the synthesis of spiro heterocycle [4.4.0] **C27**. (a) Eutectic mixture of quaternary ammonium salt, acetylcholine iodide–ethylene glycol, stirring, 50 °C, 1 h.

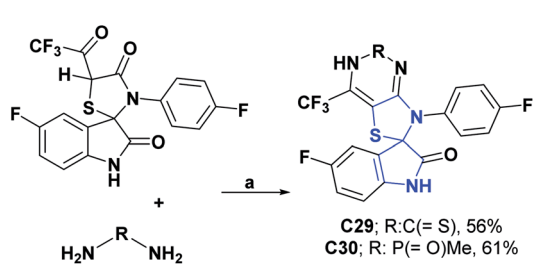


Scheme 10 Structures, reagents, and conditions for the synthesis of spiro heterocycle [4.4.0] **C28**. (a) CH_3CN, reflux, 1.5 h.

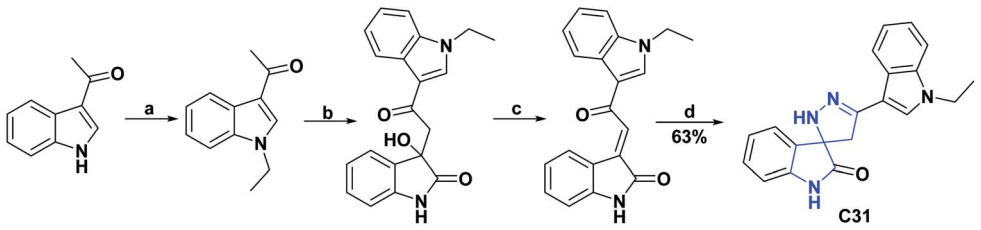
as compared to vitamin C as a positive control, which at the equivalent concentration presented a value of 55.20%. Compound **C31** at a concentration of 20 μg L^{-1} showed a percentage of DPPH radical uptake of 65.55% and was compared with vitamin C, which at an equivalent concentration showed a percentage of uptake of 99.67%.[68] General procedures for obtaining compounds **C29–C31** are shown in Schemes 11 and 12.[67,68]

In contrast, the activity of spiroxyindole **C32** was studied "*in vitro*" in the spontaneous LPO model in liver homogenate. The intensity of the lipid oxidation processes was evaluated by accumulating compounds that reacted with thiobarbituric acid (TBA reagents). The decrease in the content of TBA reagents in the liver sample indicated the presence of the AO activity of the studied compound. Thus, compound **C32** at 50 μM had a TBA reagent content of 8.45 mmol g^{-1} of tissue and was compared to an intact sample that had a TBA reagent content of 0.37 mmol g^{-1} of tissue. The synthesis of compound **C32** is shown in Scheme 13.[69]

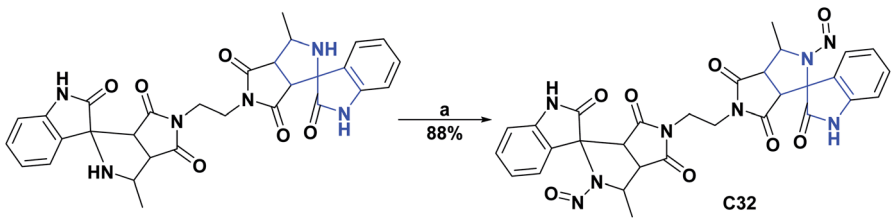
It is important to remember that oxidation processes do not only affect biological organisms; an example of this is the oxidation reactions that predominantly occur in lubricating oils in service, which are responsible for various lubrication problems, including an increase in the total acid number, the formation of varnishes, sludge and sediment and the depletion of additives. The AO activities of compounds **C33**,[70] and **C34** (ref. 71) were studied according to the standard method ASTMD-943 and according to the change in the total acid number (TAN) that they generated in the mother sample. Compounds **C33** and **C34** at 200 ppm showed TAN values of 2.31–140.72 and 1.57–61.50 mg KOH per g of sample × 10^2, respectively, in the test range of 24–96 h. The compounds were compared with



Scheme 11 Structures, reagents, and conditions for the synthesis of spiro heterocycles [4.4.0] **C29** and **C30**. (a) EtOH, reflux, 10 h.

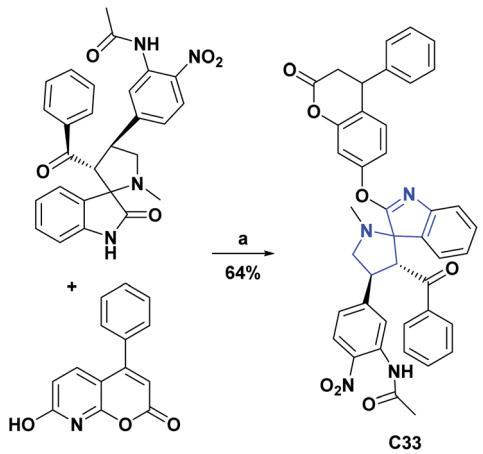


Scheme 12 Structures, reagents and conditions for the synthesis of spiro heterocycle [4.4.0] **C31**. (a) Bromoethane, DMSO, NaOH, stirring, rt; (b) indoline-2,3-dione, EtOH, diethylamine, reflux, 5 h; (c) AcOH, HCl (2 drops), 80 °C, 30 min; (d) $N_2H_4 \cdot H_2O$ (98%), EtOH, AcOH (2 drops) reflux.

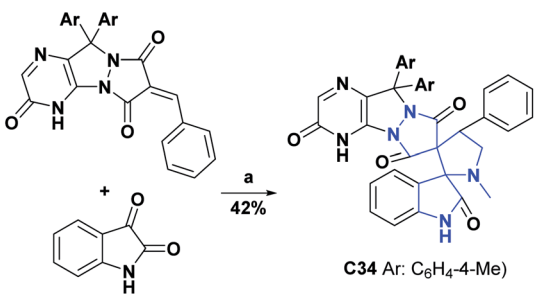


Scheme 13 Structures, reagents, and conditions for the synthesis of spiro heterocycle [4.4.0] **C32**. (a) AcOH, 10 °C, $NaNO_2$, after 12 h; water was added.

vitamin C as a positive control that at the same concentration and in the same time interval showed TAN values of 10.14 to 94.63 mg KOH per g sample $\times 10^2$. The general syntheses of compounds **C33** and **C34** are shown in Schemes 14 and 15.[70,71]



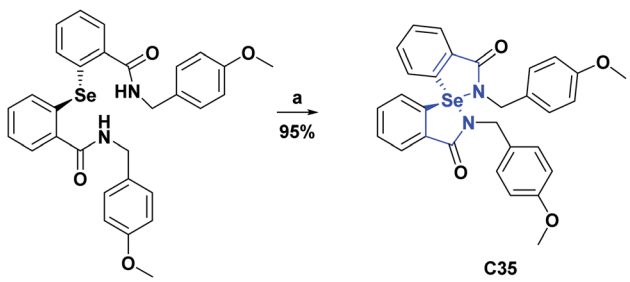
Scheme 14 Structures, reagents, and conditions for the synthesis of spiro heterocycle [4.4.0] **C33**. (a) $POCl_3$, rt.



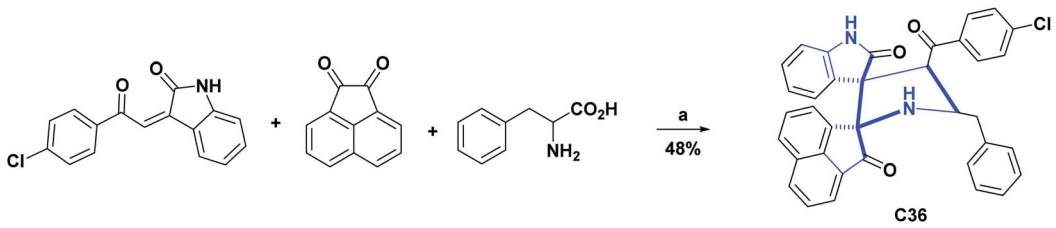
Scheme 15 Structures, reagents, and conditions for the synthesis of spiro heterocycle [4.4.0] **C34**. (a) MeOH–H_2O (3 : 1) in boiling, methylglycine, MCDC.

Compound **C35**, an epiroselenide derived from oxindole, was evaluated for its AO activity through the peroxynitrite (PN) inhibition test. Compound **C35** had an IC_{50} of 12.83 μM, compared to the Ebselen positive control that showed an IC_{50} of 0.92 μM. The process of obtaining compound **C35** is shown in Scheme 16.[72] Finally, the AO activity of spiroxyindole **C36** was subjected to the DPPH test, in which it showed inhibition percentages of 24.05, 33.30, 44.25, 52.75, 62.80, and 75.00 percent at concentrations of 10, 20, 40, 60, 80, and 100 μg mL^{-1} respectively, in comparison with vitamin C used as a positive control, and presented inhibition percentages of 45.00, 53.10, 51.70, 76.00, 82.45 and 95.00 at the same concentrations, respectively. The synthesis of the molecule **C36** is shown in Scheme 17.[73]

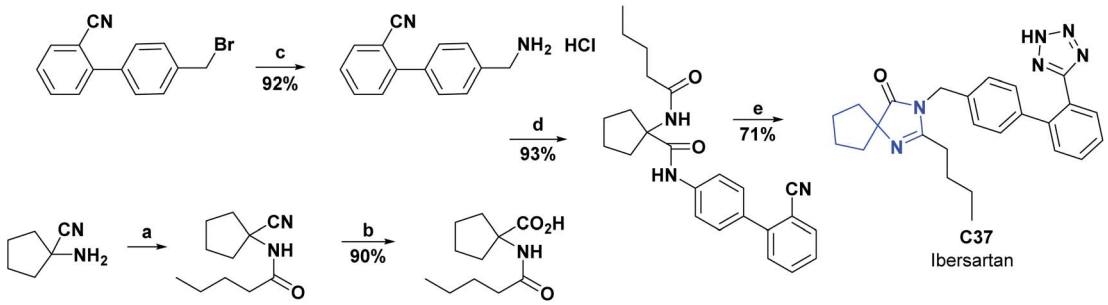
C37, known as Irbesartan, is an angiotensin receptor that has been studied in rats and found to be a possible drug suitable for inhibiting oxidative stress in atherosclerosis, myocardial infarction, atrial fibrillation, diabetes, and diabetic nephropathy, used frequently for the treatment of hypertension (see Scheme 18).[74] The AO capacity of **C37** was evaluated in Wistar rats, to which small doses of intragastric Irbesartan were administered for 28 days, and then in blood serum and liver



Scheme 16 Structure, reagents, and conditions for the synthesis of spiro heterocycle [4.4.0] **C35**. (a) H_2O_2.



Scheme 17 Structures, reagents and conditions for the synthesis of spiro heterocycle [4.4.0] **C36**. (a) MeOH, reflux, 30 min.



Scheme 18 Structures, reagents and conditions for the synthesis of spiro heterocycle [4.4.0] irbesartan, (**C37**). (a) (1) Et_3N, DCM, stirring, 0–5 °C, 15 min; (2) stirring, 0–5 °C, 2 h; (b) (1) HCl, stirring, 55–60 °C, 2 h; (2) EtOAc–H_2O, stirring, 25–35 °C; (c) (1) NaN_3, DMF, stirring, 30–40 °C; (2) TPP, ethyl acetate H_2O, stirring, 25–35 °C, 2 h; (3) HCl, stirring, 0–5 °C, 1 h; (d) (1) DCC, methylene chloride, HOBT, diisopropylamine, reflux, 7 h → rt; (2) stirring, 0–5 °C, 1 h; (e) (1) Bu_3SnCl, NaN_3, N_2 atmosphere, stirring, rt, 30 min; (2) DMF, stirring, rt, 30 min; (3) *O*-xylene, stirring, 150–155 °C, 20 h → rt; (4) CH_2Cl_2, *O*-xylene, HCl, stirring, rt, 3 h.

tissue, the changes in indicators such as superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), catalase (CAT), and malondialdehyde (MDA) were measured.

The activities of SOD (U mL^{-1}), GSH-Px (U mL^{-1}), CAT (U mL^{-1}) and MDA (nmol mL^{-1}) at 28 days were 210.73 ± 2.62, 1312.63 ± 87.89, 11.19 ± 4.29 and 8.81 ± 0.86, respectively, as compared to their controls with 206.96 ± 3.46, 1101.70 ± 66.54, 5.68 ± 1.62 and 10.39 ± 2.32.

AO capacity of **C37** was also studied through the oxidation of erythrocytes induced by 2,2-[azobis(2-amidinopropane)] hydrochloride (AAPH) and H_2O_2, in addition to radical scavenging (ABTS). The inhibition time of **C37** in the hemolysis induced by AAPH at a concentration of 100 μM was 77 minutes of the 217 minutes of the hemolysis time, while for trolox as a positive control at the same concentration it presented an inhibition time of 160 minutes with a hemolysis time of 290 minutes.[74]

The inhibition rate of **C37** in H_2O_2-induced hemolysis was at a concentration of 100 μM of 85.75% at a hemolysis rate of 28.95%, as compared to trolox at the same concentration with a hemolysis rate of 30.14% and an inhibition rate of 94.21%. Finally, the IC_{50} value for the ABTS assay was 7.60 μM, compared to trolox with an IC_{50} of 11.80 μM.[74] The results of the different experiments show that irbesartan can effectively scavenge ABTS radicals, and inhibit AAPH, H_2O_2-induced hemolysis of erythrocytes. Irbesartan can also increase GSH-Px, SOD, CAT activities and decrease MDA content in rats, showing that **C37** is a good AO.[74] In 2007, Korrapati *et al.* reported a method for obtaining compound **C37**, and the general procedure is shown in Scheme 18.[75]

Table 2 summarizes the AO test results for compounds **C12–D37** and the positive controls against which they were contrasted.

[4.5.0] Spirocyclic system (D)

[4.5.0] Spirocyclic system (D); compounds of natural origin

Ribes nigrum is a small perennial shrub, commonly known as black currant, which belongs to the Grossulariaceae family and is distributed mainly in Northern Europe and Asia.[76,77] The black currant is commonly cultivated to obtain its red fruits, which are of particular interest in the generation of food products (juices, jams, and syrups), due to their flavor and their relatively high amount of vitamin C. Hence, they have exceptional AO activity as compared to other fruits and vegetables.[78] The leaves of *R. nigrum* have been used in traditional medicine for the treatment of rheumatic disease in Europe, and are recognized because of their AO and anti-inflammatory effects.[79] In *R. nigrum* leaves, several prodelphinidins, procyanidins, and proanthocyanidins have been found. According to several studies, they prevent aging of the skin and heart disease, in addition to scavenging free oxygen radicals and inhibiting lipid peroxidation (LPO) induced by UV radiation.[80]

The spiro compound [4.5.0] **D1**, called Ribesin H, was isolated from *R. nigrum* leaves; its AO activity was assessed using SOA and DPPH tests. During the SOA test, compound **D1** presented better results for concentration (EC_{50} 3.26 μM) as compared to the butylated hydroxyanisole (BHA) used as a positive control (EC_{50} 17.02 μM). Additionally, in the DPPH test, compound **D1** showed an EC_{50} value of 50 μM, in contrast to the BHA, which presented an EC_{50} value of 26.71 μM (see Fig. 4).[76] Total synthesis for the compound **D1** was not found.

The rhizome of *Acorus tatarinowii* is a well-known traditional Chinese medicine that plays an essential role in clinical therapy due to its high pharmacological activity, low toxicity, infrequent

Table 2 Results of antioxidant tests for molecules C12–C37[a]

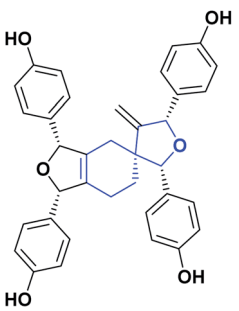
Antioxidant assay								
Entry/positive control (units)	DPPH	ABTS	LPO	NO	SOA	CUPRAC	TAN	PN
C12[45]/quercetin (IC_{50} μM)	4.49/8.69	0.39/15.49	N.A	N.A	N.A	0.42/18.47 (A_{050})	N.A	N.A
C13[45]/quercetin (IC_{50} μM)	18.65/8.69	0.86/15.49	N.A	N.A	N.A	1.35/18.47 (A_{050})	N.A	N.A
C14[54]/BHT (IC_{50} μg mL^{-1})	2.96/7.93	N.A	N.A	1.34/7.19	4.00/9.30	N.A	N.A	N.A
C15[54]/BHT (IC_{50} μg mL^{-1})	3.56/7.93	N.A	N.A	3.56/7.19	3.80/9.30	N.A	N.A	N.A
C16[53]/BHT (IC_{50} μg mL^{-1})	3.09/7.93	N.A	N.A	2.58/7.19	4.29/9.30	N.A	N.A	N.A
C17[53]/BHT (IC_{50} μg mL^{-1})	3.11/7.93	N.A	N.A	3.26/7.19	4.34/9.30	N.A	N.A	N.A
C18[62]/vitamin C (IC_{50} μM)	14.65/14.99	N.A	13.75/18.34	N.A	N.A	N.A	N.A	N.A
C19[62]/vitamin C (IC_{50} μM)	15.03/14.99	N.A	14.20/18.34	N.A	N.A	N.A	N.A	N.A
C20[62]/vitamin C (IC_{50} μM)	15.14/14.99	N.A	16.00/18.34	N.A	N.A	N.A	N.A	N.A
C21[62]/vitamin C (IC_{50} μM)	14.88/14.99	N.A	16.74/18.34	N.A	N.A	N.A	N.A	N.A
C22[63,64]/tocopherol (EC_{50} mM)	0.98/0.35	0.98/1.20	0.04/0.15	N.A	N.A	N.A	N.A	N.A
C23[63,64]/tocopherol (EC_{50} mM)	1.30/0.35	1.02/1.20	0.03/0.15	N.A	N.A	N.A	N.A	N.A
C24[54]/tocopherol (EC_{50} mM)	13.00/0.35	0.99/1.20	0.11/0.15	N.A	N.A	N.A	N.A	N.A
C25[54]/tocopherol (EC_{50} mM)	8.33/0.35	1.16/1.20	0.12/0.15	N.A	N.A	N.A	N.A	N.A
C26[54]/tocopherol (EC_{50} mM)	4.19/0.35	1.55/1.20	0.12/0.15	N.A	N.A	N.A	N.A	N.A
C27[65,66]/BHA (IC_{50} μM)	32.50/58.60	N.A	N.A	N.A	N.A	N.A	N.A	N.A
C28[65,66]/BHT (IC_{50} μg mL^{-1})	0.44/5.37	N.A	N.A	N.A	N.A	N.A	N.A	N.A
C29[67]/vitamin C % inh (400 μM)	77.45/55.2%	N.A	N.A	N.A	N.A	N.A	N.A	N.A
C30[67]/vitamin C % inh (400 μM)	77.78/55.2%	N.A	N.A	N.A	N.A	N.A	N.A	N.A
C31[68]/vitamin C % inh (20 μg L^{-1})	65.55/99.6%	N.A	N.A	N.A	N.A	N.A	N.A	N.A
C32[69]/intact sample (TBA mmol per g tissue)	N.A	N.A	8.52/0.37	N.A	N.A	N.A	N.A	N.A
C33[70]/vitamin C (mg KOH per g sample to 24 h)	N.A	N.A	N.A	N.A	N.A	N.A	2.31/10.14	N.A
C34[71]/vitamin C (mg KOH per g sample to 24 h)	N.A	N.A	N.A	N.A	N.A	N.A	1.57/10.14	N.A
C35[72]/ebselen (IC_{50} μM)	N.A	N.A	N.A	N.A	N.A	N.A	N.A	12.30/0.92
C36[73]/vitamin C % inh (100 μg L^{-1})	75.0/95.0%	N.A	N.A	N.A	N.A	N.A	N.A	N.A
C37[74]/trolox (IC_{50} μM)	N.A	7.60/11.80	N.A	N.A	N.A	N.A	N.A	N.A

[a] N.A, not applicable. N.F., not found. % inh, inhibition percentage.

complications, and outstanding performance in the treatment of disorders related to the central nervous system.[81] Several studies have supported its usefulness in pharmacological actions related to the central nervous system, such as epilepsy, cerebrovascular diseases, and senile dementia, including Alzheimer's disease.[82] Various studies have reported its sedative, antidepressant, digestive, analgesic, diuretic, and antifungal effects.[83–86]

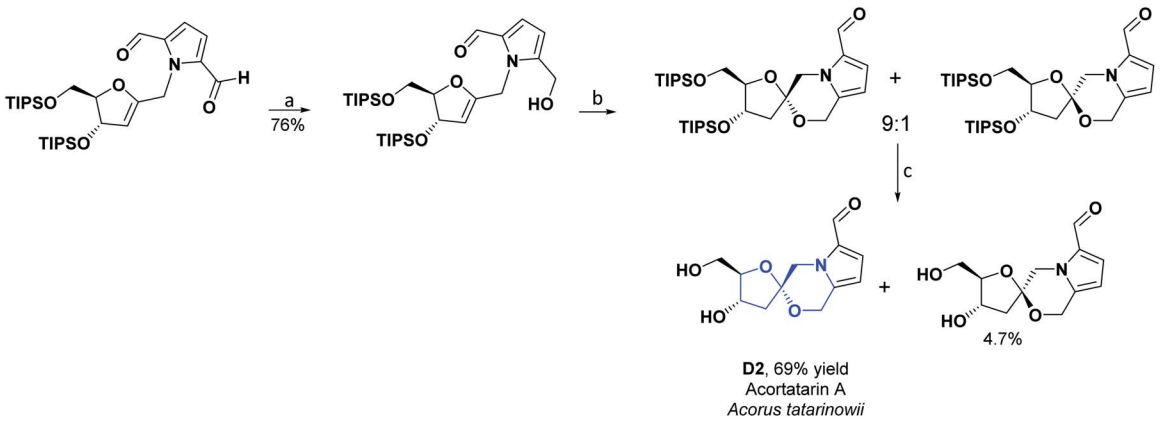
Two new spiro alkaloids that have a naturally unusual morpholine ring in their structure, called Acortatarins A (**D2**) and B (**D3**), were isolated in 2011 from the rhizome of *Acorus tatarinowii*. The AO capacities of compounds **D2** and **D3** were determined, according to the percentage of ROS production inhibition induced by glucose in mesangial cells. Compound **D2**, at a concentration of 50 μM, inhibited ROS generation by approximately 50%, while compound **D3** at the same value of concentration inhibited ROS generation by around 30%.[87] In 2015, compound **D2** was found in the EtOH extract of the dried mycelium of the edible medicinal mushroom *Xylaria nigripes*. The AO capacity was reckoned by preventing oxidative stress-induced cytotoxicity of rat A7r5 vascular smooth muscle cells. At a concentration of 25 μM, compound **D2** generated 94% cell viability as compared to the hydrated catechin used as a positive control, which at the same concentration caused 97.1% cell viability.[88] In 2017, a synthesis route was proposed for compounds **D2** and **D3**. Researchers of that study estimated the AO activity of these two compounds according to the inhibition of glucose-induced ROS production in mesangial cells. Compound **D2** had an IC_{50} of 4.60 μM, while compound D3 had an IC_{50} of 11.00 μM.[89] The total synthesis of compounds **D2** and **D3** is shown in Schemes 19 and 20, respectively.[90]

Lysidice rhodostegia is a traditional Chinese shrub plant that belongs to the Leguminosae family's genus *Lysidice*. Provinces in China such as Guangdong, Guangxi, and Yunnan[91] distribute the *L. rhodostegia*. Its roots have been used in Chinese alternative

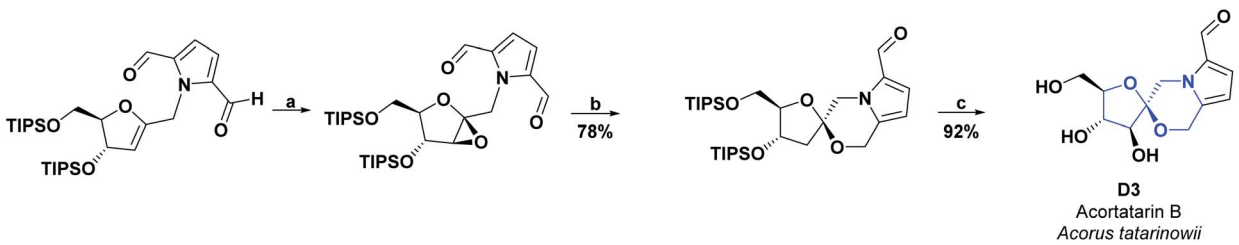


D1
Ribesin H
Ribes nigrum

Fig. 4 Structure of spiro heterocycle [4.5.0] Ribesin H (**D1**).



Scheme 19 Structures, reagents and conditions for the synthesis of spiro heterocycle [4.5.0] Acortatarin A (**D2**). (a) $NaBH_4$, THF, 0 °C; (b) (1) THF, NaHMDS, $Hg(OAC)_2$, stirring, −78 °C, 25 min; (2) stirring, −78 °C → 0°, 1 h; (3) stirring, 0 °C → rt, 5 h. (4) $NaBH_4$, stirring, rt, 2 min; (c) THF, TBAF, stirring, 0 °C, 2 h.



Scheme 20 Structures, reagents and conditions for the synthesis of spiro heterocycle [4.5.0] Acortatarin B (**D3**). (a) Dimethyldioxirane, DCM, stirring, 1 h, 0 °C; (b) (1) Bu_4NBH_4, DCM, stirring, 1 h, 0 °C; (2) stirring, 2 h, rt; (c) THF, TBAF, stirring, 2.5 h, rt.

medicine to treat pain, fractures, and bleeding. Previous investigations related to this plant have led to the isolation of an array of structurally diverse compounds, including phloroglucinols, flavonoids, stilbenes, and triterpenoids, some of which have displayed potent vasodilatory and antioxidative activities.[92]

A new acylfloroglucinol, was isolated from the roots of *Lysidice rhodostegia*, called lysidicins J (**D4**). The AO activity of the mentioned compound was determined by the content of malondialdehyde (detected by the thiobarbituric acid method), produced during microsomal LPO induced by ferrous cysteine. Compound **D4** showed AO activity with inhibition rates of 100% at a concentration of 0.10 μM. However, its AO capacity disappeared at lower concentrations (0.01 and 0.001 μM). We compared this compound with vitamin E as a positive control, which presented an EC_{50} of 33.40 μM (see Fig. 5).[93]

Caesalpinia sappan L. is a tree species belonging to the Leguminosae family, commonly known as Brazilian wood or sappan. *C. sappan* L. is distributed in Southeast Asia, and its dried heartwood has been used as a traditional ingredient in foods or beverages and has a wide variety of medicinal properties.[94] In Indonesia, its material has long been used in folk medicine to treat tuberculosis, diarrhea, dysentery, skin infections, anemia, detoxification, syphilis treatment, an antiseptic to stop bleeding, and pain due to blood circulation disorders.[95]

The investigation of the chemical components of *C. sappan* wood resulted in the isolation of several structural types of phenolic components, including xanthones, coumarins, chalcones, flavones, homoisoflavonoids, and brasilin.[96] Scientific studies validated most of *C. sappan* L.'s folkloric uses as an AO, including its antibacterial, anti-inflammatory, anti-photoaging, hypoglycemic vasorelaxant, hepatoprotective, iron-chelating agent, and anti-acne activities.[96]

The compound spiro [4.5.0] (**D5**) was isolated from the bark of *C. sappan* L. and the AO activity was tested *via* xanthine oxidase (XO), SOA, and HOR tests. The results showed IC_{50} values > 50, <50, and <300 μg mL^{-1}, respectively. The target compound was contrasted with α-tocopherol, β-carotene, and BHT, which presented IC_{50} values > 200 μg mL^{-1} in all the tests (see Fig. 5).[97]

Lysinibacillus is a rod-shaped, Gram-positive mesophilic bacterium. Under harsh conditions, this bacterium can form

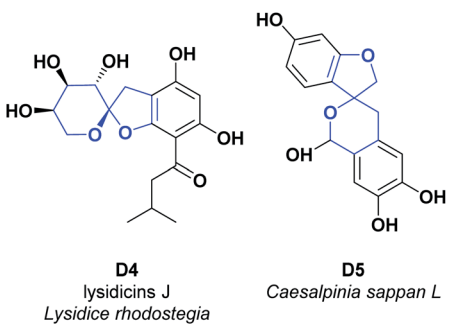
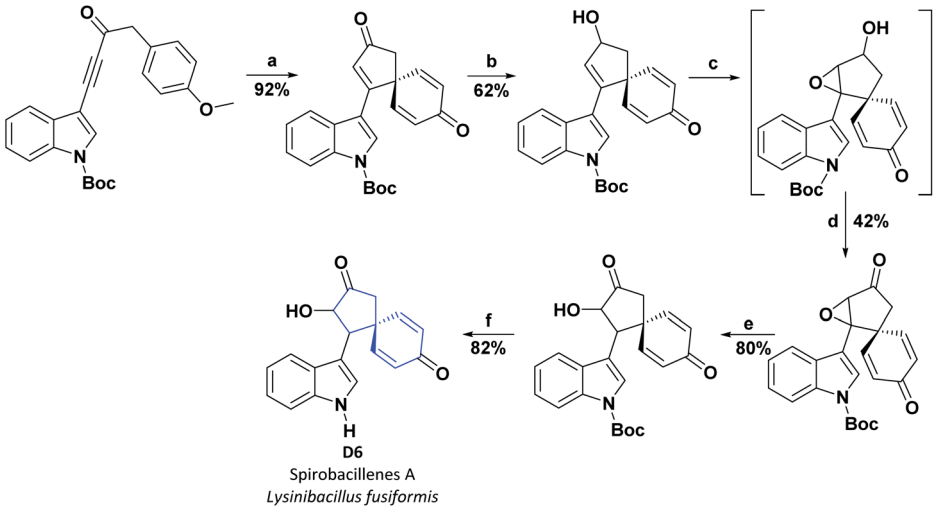


Fig. 5 Structures of spiro heterocycles [4.5.0] lysidicins J (**D4**) and **D5**.

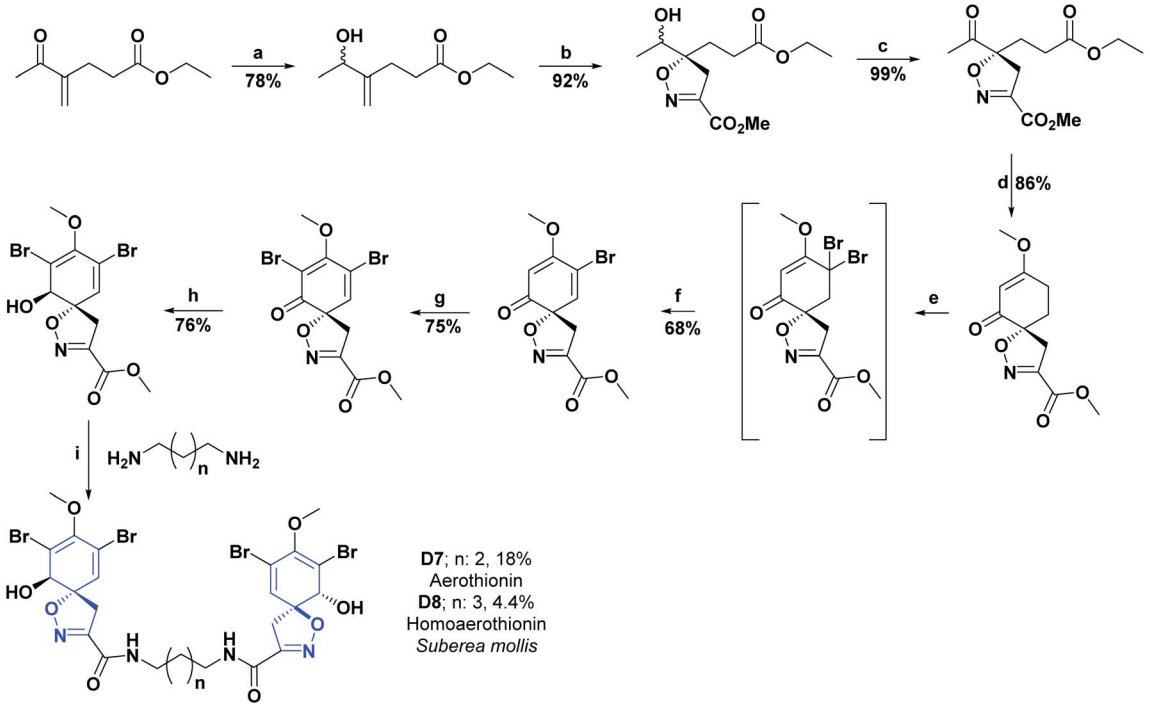


Scheme 21 Structures and reagents for the synthesis of spiro heterocycle [4.5.0] **D6**. (a) $SnCl_2 \cdot 2H_2O$, DCM; (b) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, DCM, MeOH; (c) *m*-CPBA, $NaHCO_3$, DCM; (d) DMP, $NaHCO_3$, DCM; (e) *p*-TsOH, toluene; (f) TFA, DCM.

inactive spores that can resist heat, chemicals, and ultraviolet light. Organisms of this genus were previously considered members of the genus *Bacillus*. However, its taxonomic status, the group 2 rRNA of the genus *Bacillus*, was changed to the genus *Lysinibacillus* in 2007.[98] *Lysinibacillus* is found mainly in soil and has been isolated from plant tissues, fermented plant seed products, and even pufferfish liver specimens. Studies have reported that isolated chemical compounds of the genus *Lysinibacillus* have antimicrobial activities, and they have also been shown to be potential biological control agents for diseases affecting cocoa.[99]

Two previously unreported spiro-cyclopentenones, designated spirobacillenes A (**D6**) and B (**C10**), were isolated from the broth culture of *Lysinibacillus fusiformis*, and inhibition action against NO and ROS production in the LPS-induced RAW 264.70 macrophage cell line was tested. Compound **D6** presented an IC_{50} of 39 and 43 μM for NO and ROS, respectively, while compound **C10** did not display significant AO activities (see Fig. 3).[100] The synthetic process for obtaining **D6** is shown in Scheme 21.[101]

The sea sponge *Suberea mollis* belongs to the order Verongida and the family Aplysinellidae. Marine sponges of the



Scheme 22 Structures, reagents and conditions for the synthesis of the spiro heterocycles [4.5.0] **D7** and **D8**. (a) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, stirring, 0 °C, 1 h; (b) methyl-2-nitroacetate, DABCO, MeOH, reflux, 5 d; (c) PCC/Al_2O_3, DCM. (d) (1) NaOMe, rt, reflux, 12 h; (2) Me_2SO_4, rt, reflux, 24 h; (e) LHMDS, THF, −78 °C, Br_2; (f) DABCO, reflux, 3 h; (g) NBS, DCM, 24 h; (h) $Zn(BH_4)_2$, DCM; (i) MeOH, stirring, rt, overnight.

order Verongida, including the genus *Suberea*, possess an unusual chemical structure due to the extensive amount of sterols and the lack of classic terpenes and brominated compounds associated with tyrosine.[102] Some *Suberea* show diverse bioactivities, including antibacterial, antiviral, enzyme inhibition, and cytotoxic activities.[103–106]

Suberea mollis extract has been reported to have a potent protective effect against liver damage induced by carbon tetrachloride, and it also showed vigorous scavenging activity against free radicals in the DPPH assay.[107]

Researchers who studied the red sea sponge *Suberea mollis*, isolated new compounds known as aerothionin (**D7**), homoaerothionine (**D8**), and two new alkaloids derived from bromotyrosine: subereamolins A (**D9**) and B (**D10**). The AO activities were examined for the isolated compounds using a chemical assay based on DPPH on a TLC plate. The results obtained were qualitative and were evaluated according to the discoloration observed on the chromatographic scale. In addition, the compounds **D7–D10** showed slight activity and were compared with vitamin E as a positive control, which showed intense discoloration on the TLC plate.[102] Schemes 22 and 23 show the syntheses of compounds **D7–D8** and **D9–D10**, respectively.[108–110]

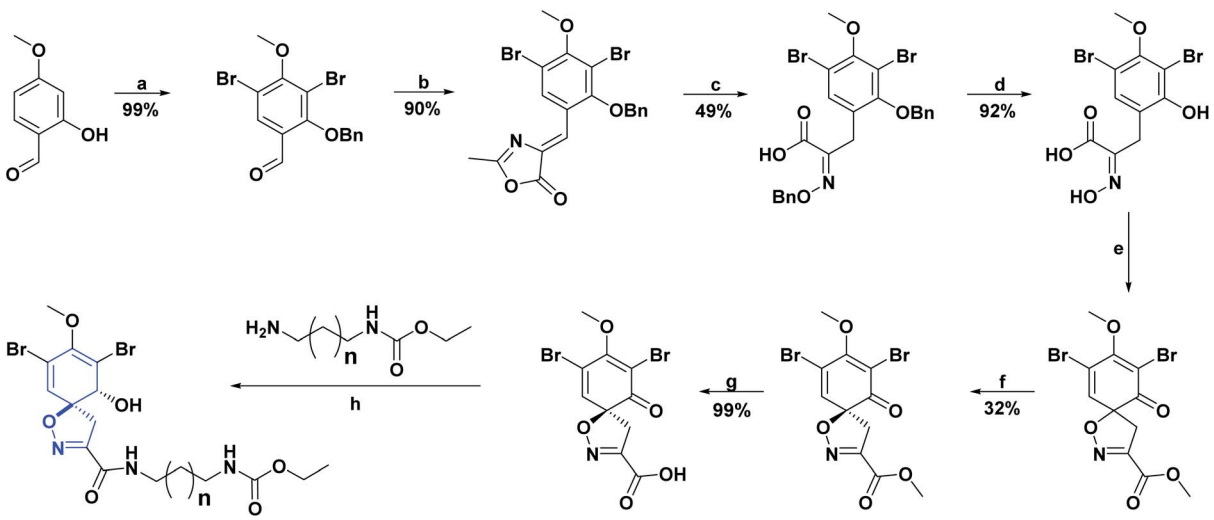
[4.5.0] Spirocyclic system (D); compounds of synthetic origin

As with spirooxindoles [4.4.0], a wide variety of spirooxindoles [4.5.0] (**D11–D31**) were synthesized, and their AO properties have been studied. Compounds **D11–D13** were synthesized in 2018 and, and their AO activities were evaluated through DPPH and peroxide reactive (POR) tests. Compounds **D11–D13** showed IC_{50} values of 20.13, 31.87, and 25.16 μg mL^{-1}, respectively, in the DPPH assay and IC_{50} values of 23.27, 25.37, and 31.82 μg mL^{-1} in the POR assay. All compounds were compared with vitamin C as a positive control, showing IC_{50} values of 19.16 and 20.66 μg mL^{-1}, for the DPPH and POR assays, respectively.[111] The synthesis of compounds **D11–D13** is shown in Scheme 24.[111]

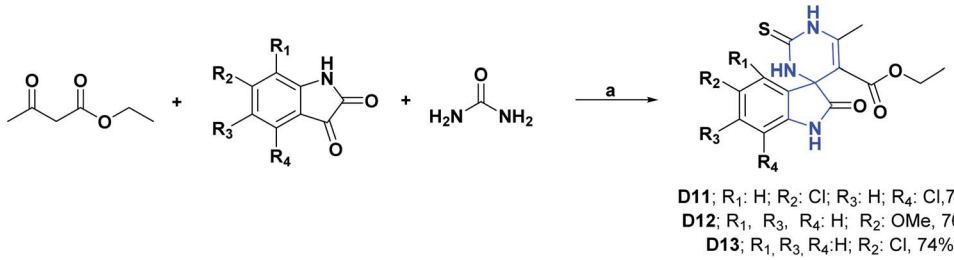
Spirooxindoles [4.5.0] **D14** and **D15** were studied in order to evaluate their AO capacities utilizing the DPPH, ABTS, and NO tests. The authors found that compounds **D14** and **D15** respectively presented IC_{50} values of 619.45 and 539.53 μg mL^{-1} in the DPPH assay, 1597.07 and 1010.20 μg mL^{-1} in the ABTS assay, and 891.09 and 671.95 μg mL^{-1} in the NO assay. Vitamin C was used as a positive control, showing IC_{50} values of 409.75, 550.00, and 544.21 μg mL^{-1} in the DPPH, ABTS, and NO tests, respectively.[112]

In contrast to compounds **D14** and **D15**, the AO activities of compounds **D16** and **D17** were evaluated by the FRAP assay. Compound **D16** presented an IC_{50} value of 405 μg mL^{-1}, while compound **D17** presented an IC_{50} value of 310 μg mL^{-1}. Both compounds (**D16** and **D17**) were compared with Trolox as a positive control, showing an IC_{50} value of 180 μg mL^{-1}.[113] Compounds **D14–D17** were generally synthesized as shown in Scheme 25.[112,113]

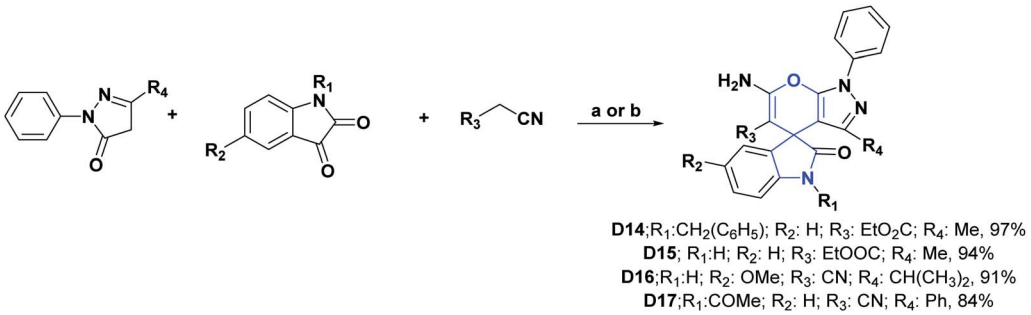
Similarly, the AO activity of iodine-substituted spiropyrrolidine oxindole (**D18**) was studied by the NO test. Compound **D18**, in concentrations of 6 μg mL^{-1} and 10 μg mL^{-1} respectively presented NO radical uptake of 71.43 and 2.80%, where the percentage of radical uptake decreased with concentration. The authors mentioned that this attribute was probably due to the saturation of the carrier molecule to transport the largest number



Scheme 23 Structures, reagents and conditions for the synthesis of the spiro heterocycles [4.5.0] **D9** and **D10**. (a) (1) NBS, DMF, stirring, 0 °C, 50 min (93% yield); (2) BnCl, NaI, K_2CO_3, DMF, stirring, rt, 13 h; (b) *N*-acetylglycine, NaOAC, AC_2O stirring, 120 °C, 6 h; (c) $Ba(OH)_2 \cdot 8H_20$, 1,4-dioxane-H_2O, stirring, 60 °C, 1 h, then *O*-benzylhydroxylamine; (d) (1) $TMSCH_2N_2$, PhMe–MeOH, stirring, 0° → rt, 1 h, 95% yield; (2) Pd-black, H_2, dioxane/AcOH, stirring, rt, 3 h; (e) $PhI(OAc)_2$, MeCN, stirring, 0 °C, 1 h; (f) $Zn(BH_4)_2$, DCM, stirring, rt; (g) LiOH–H_2O, MeOH–H_2O, stirring, rt, 1 h; (h) T3P, DIPEA, stirring, 0 °C, 2 h.



Scheme 24 Structures, reagents and conditions for the synthesis of spiro heterocycles [4.5.0] **D11–D13**. (a) Fe_3O_4-NPs, EtOH, reflux.



Scheme 25 Structures, reagents and conditions for the synthesis of spiro heterocycles [4.5.0] **D14–D17**. (a) H_2O-CAN, ultrasonic irradiation, rt, 10 min for **D14** and 20 min for **D15** (b) H_2O, CeO_2-NPs, stirring, 90 °C, 5 h for **D16** and **D17**.

of drug molecules to the active site of the receptor.[114] The synthesis of compound **D18** is shown in Scheme 26.[114]

Compounds **D19–D30** were studied in order to assess their AO activities using the DPPH assay. In the case of **D19–D22**, they presented IC_{50} values of 29.76, 28.07, 11.60, and 12.19 μg mL^{-1}, respectively, and were compared with vitamin C as a positive control that showed an IC_{50} of 3.89 μg mL^{-1}.[115–117] The syntheses of compounds **D19–D22** are shown in Schemes 27–29, respectively.[118]

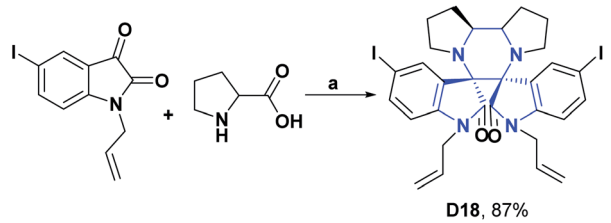
Likewise, compounds **D23–D25** showed, respectively, IC_{50} values of 7.34, 10.06, 10.84, μM and were compared with vitamin C as a positive control that presented an IC_{50} of 3.45 μM.[119] Compound **D26** exhibited an IC_{50} of 0.16 mg mL^{-1}, and it was compared with the positive control quercetin that showed an IC_{50} of 0.55 mg mL^{-1}. The general processes for the syntheses of compounds **D23–D26** are presented in Schemes 30 and 31.[120]

Compounds **D27** and **D28** at a concentration of 400 μg mL^{-1} presented percentages of DPPH radical scavenging of 55 and 58% and were compared with BHA as a positive control that at the same concentration manifested a percentage of scavenging of 99%.[121]

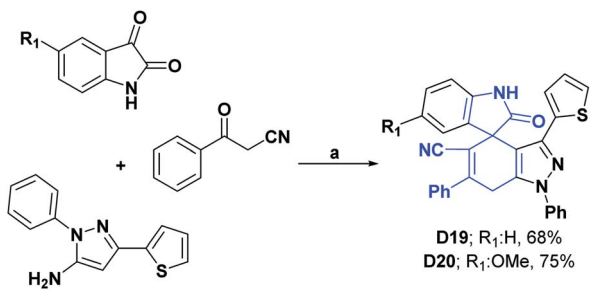
Finally, compounds **D29** and **D30** at a concentration of 1 mg mL^{-1} presented DPPH free radical scavenging percentages of 55.53% and 96.2%, respectively.[122,123] The syntheses of compounds **D27–D30** are shown in Schemes 32–34.

The synthesis of compound **D31**, a spiro [4.5.0] derived from tetralin-1,3′-pyrrolidine, was reported, and the general process is shown in Scheme 35. It was evaluated for its AO capacity by the cadmium depletion test in mice, superoxide dismutase, which consisted of intoxication for twenty days by Cd in mice, resulting in a depletion of the AO enzymes glutathione (GSH), superoxide dismutase (SOD), and catalase (CAT) of 49.54%, 67.30%, and 43.30%, respectively, compared to animals under normal conditions.

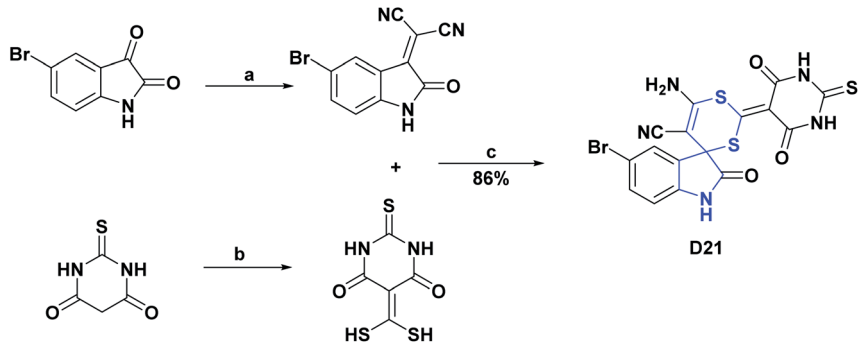
The results of the AO assay showed that in mice treated with **D31**, the amount of depleted AO enzymes was restored to similar values (200 nmol GSH per mg of protein, 50 units of SOD



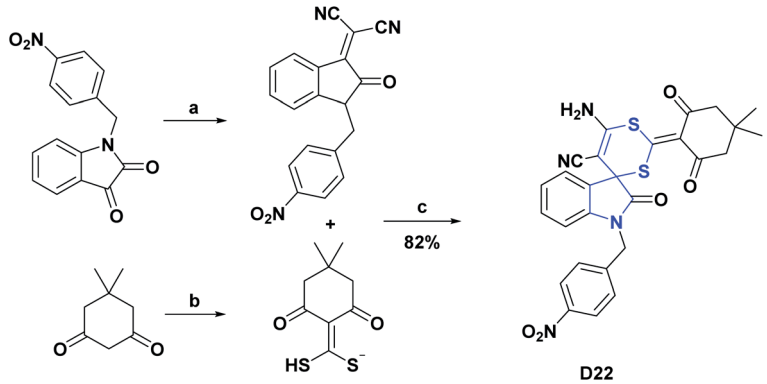
Scheme 26 Structures, reagents and conditions for the synthesis of spiro heterocycle [4.5.0] **D18**. (a) toluene–MeOH, reflux, 2 h.



Scheme 27 Structures, reagents and conditions for the synthesis of spiro heterocycles [4.5.0] **D19** and **D20**. (a) AcOH–H_2O, stirring, 120 °C, 8–11 h.



Scheme 28 Structures, reagents and conditions for the synthesis of spiro heterocycle [4.5.0] **D21**. (a) Malononitrile, MeCN, stirring, rt, 0.5 h; (b) carbon disulfide, Et_3N, acetonitrile, stirring, rt, 1 h. (c) Multicomponent synthesis, Fe_3O_4@gly@CE, stirring, rt, 5.5 h.



Scheme 29 Structures, reagents and conditions for the synthesis of spiro heterocycle [4.5.0] **D22**. (a) Malononitrile, MeCN, rt. (b) Carbon disulfide, MgO NPs, rt. (c) Multicomponent synthesis, rt, 2.5 h.

per mg of protein, and 13 units CAT per mg protein) to those presented by the mice under normal conditions (160 nmol GSH per mg protein, 70 SOD units per mg protein and 14 CAT units per mg protein). The authors attributed the good AO results of the studied compound to the fact that it manages to form a Cd–Se complex that regulates depleted enzymes and at the same time hinders the presence of free Cd in the medium.[124]

Compound **D32**, commonly known as buspirone, is a drug used as an anxiolytic agent. It is believed to be involved in the functioning of the neurotransmitter serotonin in the brain, particularly by acting as a partial agonist of the presynaptic 5-HT_{1A} (dorsal raphe) and postsynaptic 5-HT_{1A} (cortex, hippocampus) receptor.[137] Besides, buspirone has a metabolite 1-pyrimidinyl-piperazine (1-PP) that can contribute to the treatment of neurodegenerative diseases.[138]

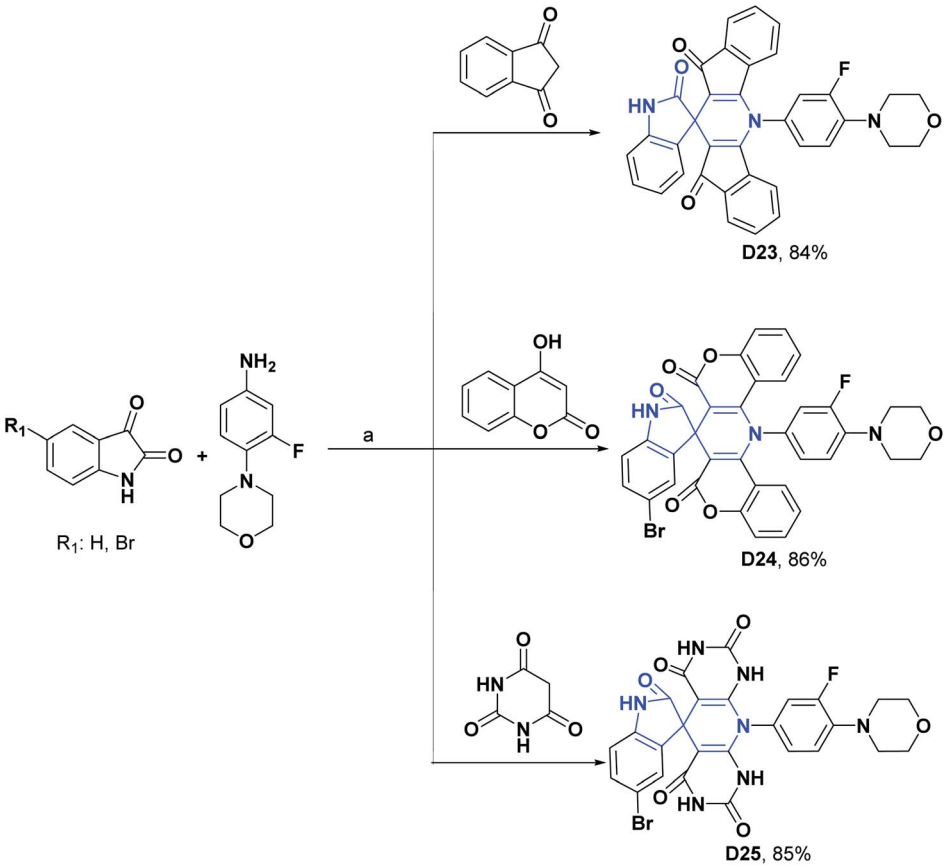
In 2009, to justify oxidative stress as a possible mechanism for pilocarpine-induced seizures, a study was carried out to determine whether buspirone (**D32**) is capable of exerting an anticonvulsant effect and altering the oxidative stress observed after pilocarpine-induced seizures. The effect of buspirone on oxidative stress was studied in the hippocampus of adult male Wistar rats (250–280 g) after seizures and pilocarpine-induced status epilepticus. Oxidative stress was evaluated in terms of the inhibition of lipoperoxidation, decreased amount of nitrite, and increased activity of SOD and CAT. It was found that in the hippocampus of the group of rats that were previously treated with buspirone there was a significant reduction in the level of lipid peroxidation (60.00%) and the content of nitrites (44.00%), as well as an increase in activities of SOD (47.00%) and CAT (40.00%) as compared to rats that were not treated with buspirone.[139] In 2009 the synthesis of buspirone (**D32**) was reported, and the general procedure is shown in Scheme 36.[140]

Table 3 summarizes the AO test results of compounds **D33–D51** and the positive controls against which they were contrasted (See Schemes 37–48).

[4.6.0] Spirocyclic system (E)

[4.6.0] Spirocyclic system (E); compound of synthetic origin

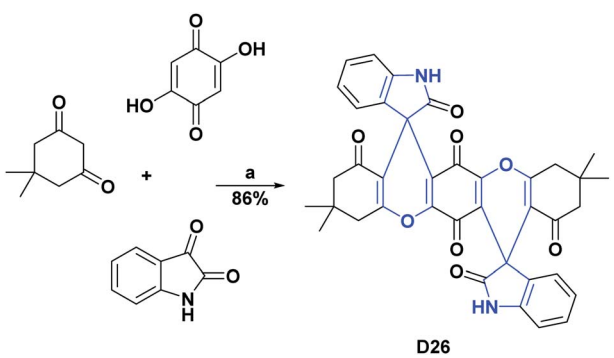
Nitrone spin traps, α-phenyl-*N*-*tert*-butylnitrone (PBN), and structurally related compounds react covalently with short-lived free radicals, such as OH, and are effective against aging ischemic strokes, and in other activities related to oxidative stress. In 2008, a new condensed spirocycle nitrone derivative [4.6.0] (**E1**) was synthesized, characterized, and reported. This compound was shown to inhibit LPO and reduce HOR generated during autoxidation with 6-hydroxydopamine, in addition to inhibiting protein carbonylation (PCO). The IC_{50} (μM) calculated in this study for compound **E1** was 36.00 ± 6.20 for LPO, 53.00 ± 3.90 for PCO, and 7.00 ± 1.20 for OH, presenting a much higher activity



Scheme 30 Structures, reagents and conditions for the synthesis of spiro heterocycles [4.5.0] **D23–D25**. (a) $ZnCl_2$ + urea, 80 °C, 67 min for **D23**, 80 min for **D24**, and 75 min for **D25**.

as compared to PBN positive control, with IC_{50} (μM) of 8500 ± 400, 11 300 ± 182 and 782 ± 39, respectively.[142] The synthesis of compound **E1** is presented in Scheme 49.[143]

In 2017, the synthesis and DPPH radical scavenging activity of 18 spirooxindole derivatives, containing oxazepine moiety, was published. Most of these molecules had AO capacity; however, at 200 μg mL^{-1}, compounds **E2–E6** showed DPPH percentage inhibitions of 78.92, 78.43, 81.50, 81.72, and 73.83%, respectively, values close to that of the positive control, vitamin C, whose inhibition was 98.7%. The synthesis of compounds **E2–E6** is shown in Scheme 50.[144]

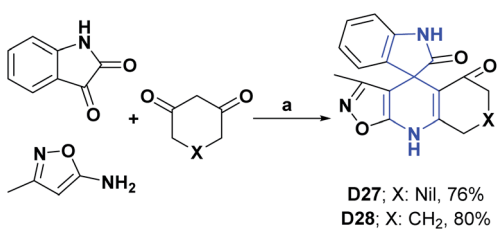


Scheme 31 Structures, reagents and conditions for the synthesis of spiro heterocycle [4.5.0] **26**. (a) (1) GTBSA, H_2O, stirring, reflux, 1 h; (2) 100 °C → rt; (3) MeOH, stirring, reflux, 3 min; (4) centrifuge (1000 rpm) to separate the catalyst.

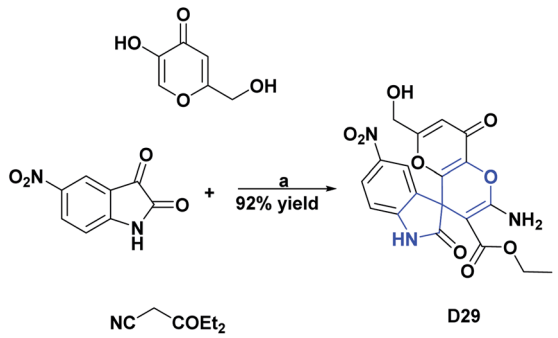
[4.7.0] Spirocyclic system (F)

[4.7.0] Spirocyclic system (F); compounds of synthetic origin

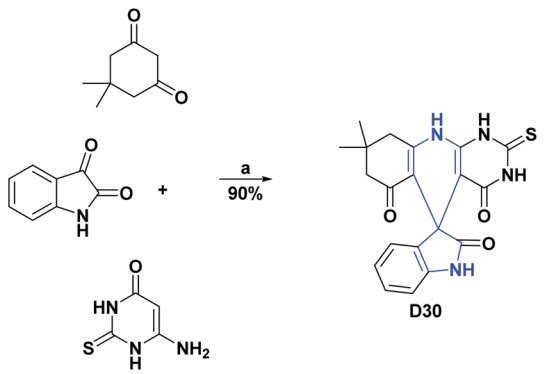
Heterocycles containing the 1,4-thiazepine moiety are important targets in synthetic and medicinal chemistry because this fragment is a key moiety in many natural and synthetic biologically active agents.[145] Six novel spiro (imidazo [4′,5′:4,5′] benzo[1,2-*e*][1,4]thiazepine)-9,3′-indolines (**F1–F5**) were reported. Studies demonstrate that these compounds scavenge the free radical DPPH. The IC_{50} values of all the compounds **F1–F5** ranged from 14.00 to 50.00 μM, with AO activity and were compared with standard vitamin C (IC_{50}: 8.64 μM). In the series, compounds **F2** and **F3** possessing chlorine and bromine groups as substitutions on the benzene ring showed better activity



Scheme 32 Structures, reagents and conditions for the synthesis of spiro heterocycles [4.5.0] **D27** and **D28**. (a) CSA, ultrasonic irradiation, (low power), 70 °C, 30 min, EtOH.



Scheme 33 Structures, reagents and conditions for the synthesis of spiro heterocycle [4.5.0] **D29**. (a) H_2O, SBA-15-DABCO, reflux, 2 h.



Scheme 34 Structures, reagents and conditions for the synthesis of spiro heterocycles [4.5.0] **D30**. (a) EtOH–H_2O, SBA-15-$PhSO_3H$, stirring, 80 °C, 5 h.

against DPPH free radicals (IC_{50}: 20.75 and 14.46 μM, respectively). The authors associate this phenomenon with the increased lipophilicity of molecules, which is due to the substitution of an electronegative atom such as chlorine/bromine at the aromatic rings C5 position. This suggests that C5-substitution with different halides increases the AO activity of spiro(imidazo[4′,5′:4,5′]benzo[1,2-*e*][1,4]thiazepine)-9,3′-indolines. The synthesis of compounds **F1–F5** is shown in Scheme 51.[146]

[5.5.0] Spirocyclic system (G)

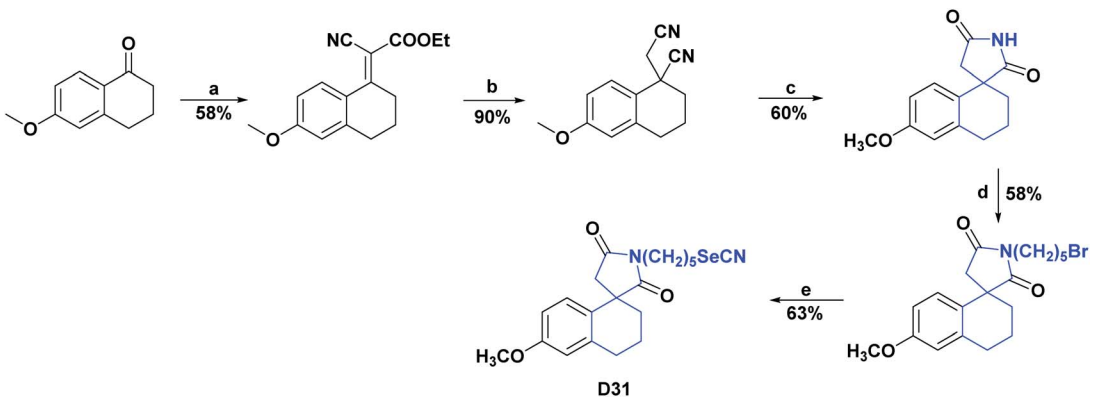
[5.5.0] Spirocyclic system (G); compounds of natural origin

Scientific researchers have reported on the chemistry of specialized metabolites of red algae of the genus *Gracilaria*. The different investigations on organic extracts of "*Gracilaria* sp." have shown that their secondary metabolites have significant anti-inflammatory and AO potential.[147–150] Two new metabolites **G1** and **G2**,[151] were isolated from an ethyl acetate : methanol (EtOAc : MeOH) extract of *Gracilaria salicornia*.

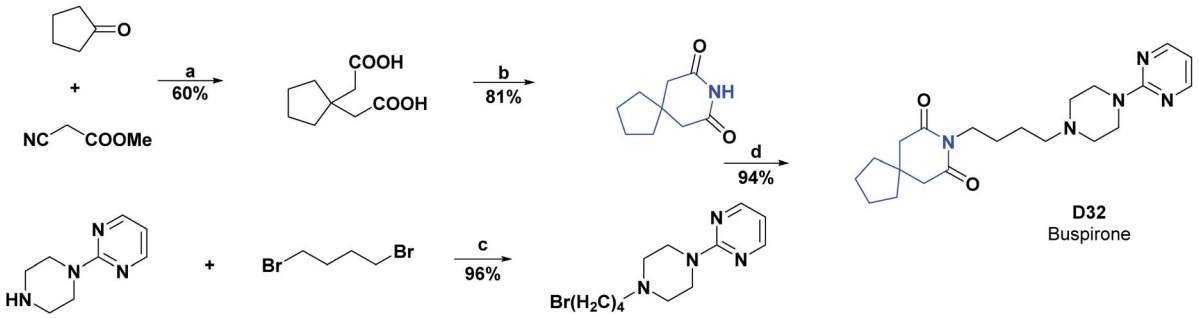
The ability of the isolated compounds to scavenge DPPH and ABTS radicals was also determined. Compounds **G1** and **G2** presented IC_{50} (mM) of 1.61 ± 0.03 and 1.13 ± 0.01, respectively, in stabilizing the DPPH. In the stabilization of the radical ABTS, they presented IC_{50} (mM) 1.72 ± 0.04 and 1.24 ± 0.02, respectively. Both compounds showed better results than α-tocopherol, which displayed an IC_{50} (mM) of 1.42 ± 0.04 for the DPPH test and 1.79 ± 0.05 for the ABTS test (see Fig. 6).[151]

Xylaria nigripes, also known as Wu Ling Shen, belongs to the Xylariaceae family of fungi; it is used in traditional Chinese medicine and grows in nature around abandoned nests of termites, *Odontotermes formosanus*.[152,153] This medicinal mushroom contains many bioactive molecules such as steroids, glycosides, alkaloids, and amino acids.[154] *Xylaria nigripes* is traditionally used to treat depression, trauma, sleep disorders, and also as a nerve tonic.[155] Various "*in vivo*" and "*in vitro*" investigations have shown that *Xylaria nigripes* has biological activities such as antitumor,[156] prevention of spatial memory impairment,[157] anti-inflammatory,[158] immunomodulatory, hepatoprotective,[159] antidepressant activity in epileptic patients,[152] improvements of sensitivity to insulin, neuroprotective,[160] and AO activities.[153,161]

In 2015, a spirocyclic pyrrole alkaloid known as xilapirosides **G3** was isolated for the first time from the EtOH extract of *X. nigripes*. A new analog of compound **G3** was also synthesized, named by the authors as xilapirosides **A2** (**G4**). The AO capacity



Scheme 35 Structures, reagents and conditions for the synthesis of spiro heterocycle [4.5.0] **D31**. (a) (1) Ethyl cyanoacetate, NH_4OAc–AcOH, benzene, stirring, 90 °C, 4 h. (2) Reflux, Dean–Starkwater trap, 24 h; (3) NH_4OAc–AcOH, stirring, 90 °C, 1 h; (4) reflux, 24 h and cold to rt; (b) KCN, EtOH–H_2O, stirring, 60 °C, 17 h; (c) AcOH, H_2SO_4, stirring, 110 °C, 2 h; (d) 1,5-dibromopentane, acetone, K_2CO_3, reflux, 24 h; (e) KSeCN, crown ether, THF, stirring, rt, 1 h.



Scheme 36 Structures, reagents and conditions for the synthesis of spiro heterocycle [4.5.0] **D32**. (a) (1) NH_3, MeOH, −5 °C, 20 h; (2) H_2SO_4–H_2O, 170 °C, 1 h; (b) $(NH_4)_2CO_3$, stirring, 200 °C, 30 min; (c) polyethylene glycol-400, Na_2CO_3, reflux, 7 h; (d) MeCN, TBAB, K_2CO_3, microwave, 120 °C, 4 min.

Table 3 Results of antioxidant tests for molecules **D33–D51**[a]

Antioxidant assay							
Entry/positive control (units)	Scheme	DPPH	ABTS	FRAP	LPO	XO	POR
D33[125]/vitamin C (IC_{50} mg mL^{-1})	37	0.17/0.15	N.A	N.A	N.A	N.A	N.A
D34[125]/vitamin C (IC_{50} mg mL^{-1})	37	0.16/0.15	N.A	N.A	N.A	N.A	N.A
D35[126]/trolox % inh (10 μM)	38	82.30/82.45%	N.A	N.A	N.A	N.A	N.A
D36[127]/BHT (IC_{50} mg mL^{-1})	39	0.90/0.72	2.31/0.93	N.A	N.A	N.A	N.A
D37[127]/BHT (IC_{50} mg mL^{-1})	39	0.50/0.72	0.43/0.93	N.A	N.A	N.A	N.A
D38[128]/α-tocopherol (EC_{50} mM)	40	0.28/0.28	0.88/1.02	2.66/2.75	0.12/0.13	N.A	N.A
D39[128]/α-tocopherol (EC_{50} mM)	40	0.29/0.28	0.96/1.02	2.33/2.75	0.12/0.13	N.A	N.A
D40[128]/α-tocopherol (EC_{50} mM)	40	1.19/0.28	1.61/1.02	0.135/2.75	0.25/0.13	N.A	N.A
D41[128]/α-tocopherol (EC_{50} mM)	40	0.97/0.28	1.63/1.02	1.34/2.75	0.25/0.13	N.A	N.A
D42[129]/vitamin C % inh (2 mM)	41	N.A	79.60/88.90%	N.A	N.A	N.A	N.A
D43[129]/vitamin C % inh (2 mM)	41	N.A	66.70/88.90%	N.A	N.A	N.A	N.A
D44[129]/vitamin C % inh (2 mM)	41	N.A	25.90/88.90%	N.A	N.A	N.A	N.A
D45[130]/4-hydroxycoumarin (IC_{50} μM)	42	97.80/124.10	N.A	N.A	N.A	% inh: 63.50/19.30%	N.A
D46[131]/BHA % inh (100 μg mL^{-1})	43	92.52/93.60%	N.A	N.A	N.A	N.A	N.A
D47[132]/vitamin C (% inh)	44	81.92/82.33%	N.A	N.A	N.A	N.A	N.A
D48[133]/vitamin C (IC_{50} μM)	45	48.49/20.05	N.A	N.A	N.A	N.A	N.A
D49[134]/vitamin C % inh	46	88.80/99.10%	N.A	N.A	N.A	N.A	N.A
D50[135]/vitamin C % inh (2000 μM)	47	60.00%/N·F	N.A	N.A	N.A	N.A	N.A
D51[136]/vitamin C (IC_{50} μg mL^{-1})	48	8.81/145.4	N.A	N.A	N.A	N.A	25.12/73.13

[a] N. A, not applicable. N. F, not found. % inh, inhibition percentage.

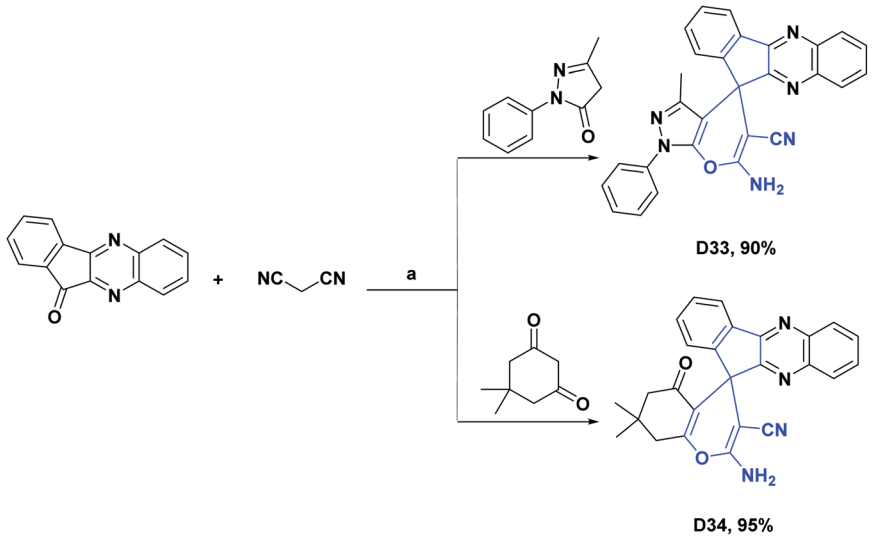
for both compounds was evaluated at different concentrations (25, 50, and 100 μM) to prevent cytotoxicity induced by the oxidative stress of A7r5 rat vascular smooth muscle cells. *tert*-Butyl hydroperoxide (*t*BHP) was used as a soluble source of peroxide radicals (POR) and caused 40.40% vascular smooth muscle cell death at a concentration of 200 mM. It is reasonable to say that the cytotoxicity induced by oxidative stress was notably attenuated when the vascular smooth muscle cells were pretreated with the spiro-alkaloids **G3** and **G4**. Compound **G3** presented cell viabilities of 64.70, 71.52, 95.36%, and **G4** presented cell viabilities of 74.90, 90.30, and 97.10%. Both compounds were compared with hydrated catechin (positive control) that showed 97.10% and 103.90% of cell viability at concentrations of 50 and 100 μM (see Fig. 7).[88]

The total synthesis of compound **G3** is shown in Scheme 52.

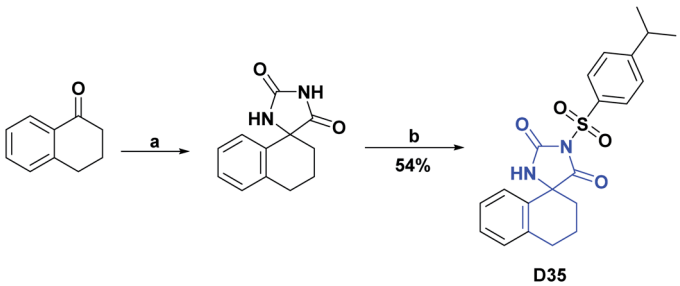
[5.5.0] Spirocyclic system (G); compounds of synthetic origin

Coumarin rings are important secondary metabolites of plants and have been extensively studied for their wide variety of biological activities. The recorded activities of coumarins and their derivatives are, among others, antitumor, anti-inflammatory, AO, analgesic, and anti-HIV.[162–164] Also, they have been reported to be helpful in the treatment of asthma and have been used against lymphedema.[165–167] Among the most representative compounds of coumarins, the derivatives of 4-hydroxycoumarin stand out, which have been proven to be powerful pharmacological centers, such as the drugs warfarin and acenocoumarol, used for more than 20 years in anticoagulant therapy.[168]

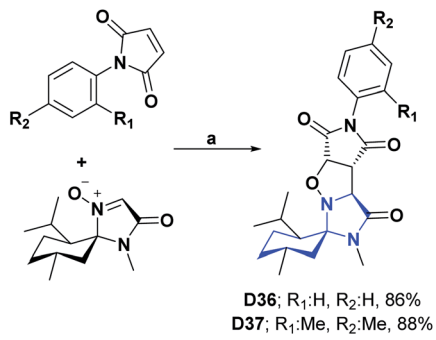
Two new compounds derived from spiro of 4-hydroxypyranocoumarin (**G5** and **G6**)[130,168] were synthesized, and their AO activities were evaluated by the DPPH test. The spiro **G5** presented an IC_{50} value of 161.40 μM as compared with the positive controls 4-hydroxycoumarin, 7-hydroxycoumarin, and BHT with



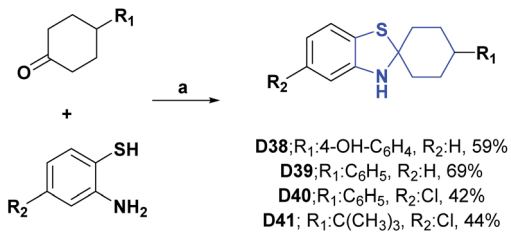
Scheme 37 Structures, reagents and conditions for the synthesis of spiro heterocycles [4.5.0] **D33** and **D34**. (a) APVPB, H_2O, reflux, 5 h.



Scheme 38 Structures, reagents and conditions for the synthesis of spiro heterocycle [4.5.0] **D35**. (a) KCN, $(NH_4)_2CO_3$, EtOH, stirring, 55–60 °C, 15 h. (b) Arylsulfonyl chloride, Et_3N, DCM, DMAP, stirring, rt, 15 h.



Scheme 39 Structures, reagents and conditions for the synthesis of spiro heterocycles [4.5.0] **D36** and **D37**. (a) Toluene, stirring, 110 °C, 48 h.



Scheme 40 Structures, reagents and conditions for the synthesis of spiro heterocycles [4.5.0] **D38–D41**. (a) EtOH, reflux, 8 h.

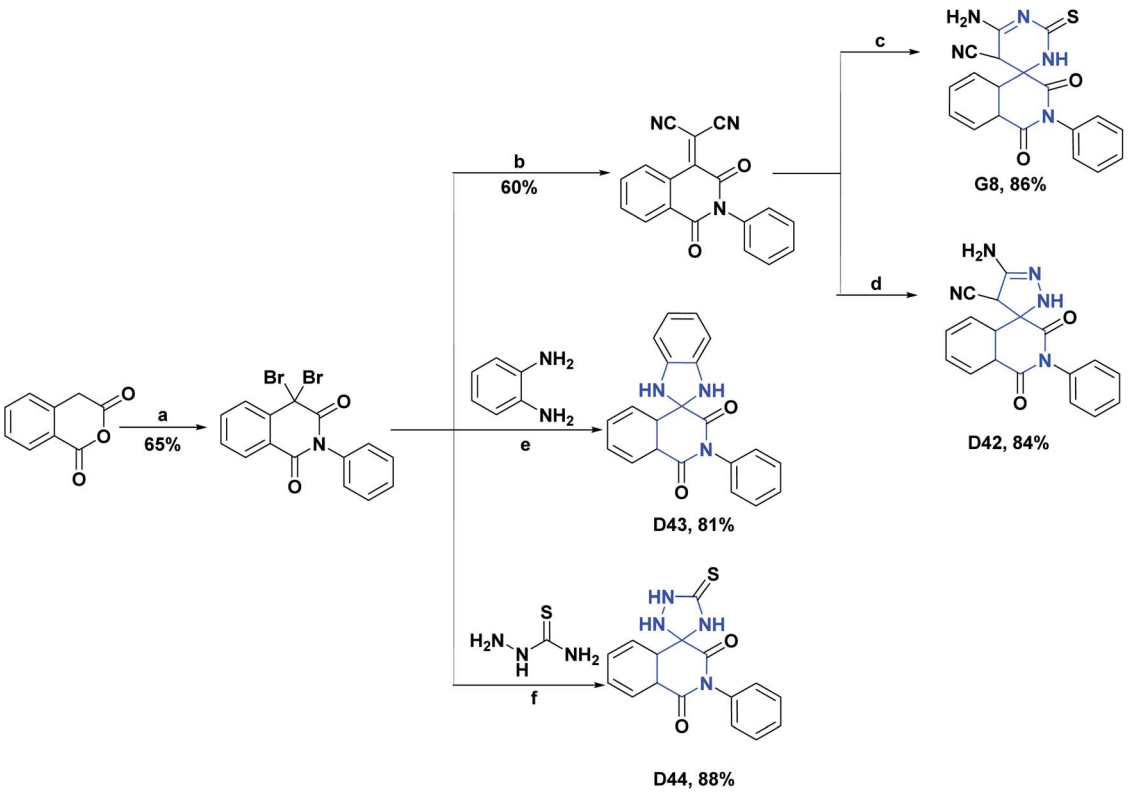
IC_{50} >124.10, 400, and 83.80 μM, respectively. The process for obtaining compound **G5** is described in a general way in Scheme 42.[130]

In the DPPH test, compound **G6** presented an inhibition percentage of 41.00% at a concentration of 400 μM; also, this compound was evaluated by the HOR scavenging test, where it presented an inhibition percentage of 93.00% as compared to 7-hydroxycoumarin, which at the same concentration showed a percentage of inhibition of 60.00%. The general synthesis for obtaining compound **G6** is shown in Scheme 53.

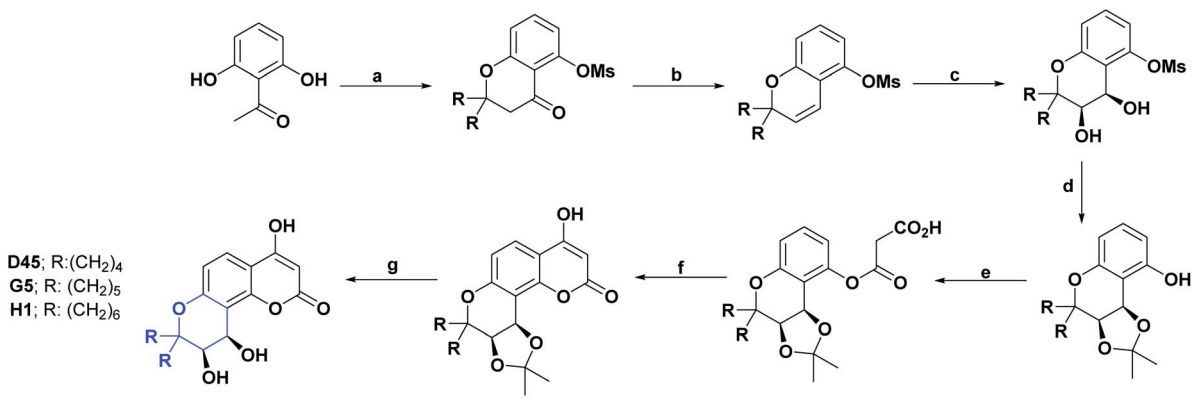
Like coumarins, quinolines are important secondary metabolites of plants that have a large body of research supporting a wide variety of biological activities such as antimalarial, anticancer (including breast cancer), antibiotic, anti-HIV, potent liver X receptor agonist, a potent competitive inhibitor of nucleotide mimicking virus hepatitis C NS3 helicase, Pim-1 kinase inhibitor, and vascular endothelial growth factor receptor 2 inhibitor.[169–177]

The synthesis of two spiroquinoline derivatives, **G7** and **G8**, has been reported.[129,178] The AO activity of compound **G7** was evaluated by the free radical scavenging DPPH assay, showing an IC_{50} value of 20.65 μM and was compared with vitamin C as a positive control that presented a value of 43.9 μM. The synthesis of compound **G7** is shown in Scheme 54.[178]

The AO activity of compound **G8** was evaluated by the erythrocyte hemolysis test and the ABTS radical stabilization test. In the erythrocyte hemolysis test with compound **G8**, a hemolysis percentage of 5.00% was obtained, compared to vitamin C, with which a hemolysis percentage of 3.93% was obtained. In the ABTS test, the spiro compound exhibited a percent inhibition of 81.50%, while vitamin



Scheme 41 Structures, reagents and conditions for the synthesis of spiro heterocycles [4.5.0] **D42–D44**. (a) (1) Aniline; (2) Br_2, AcOH, reflux, 2 h. (b) Malononitrile, EtOH-piperidine. (c) Thiourea, EtOH-piperidine, microwave at 500 W and 140 °C for 15 min. (d) Hydrazine, EtOH-piperidine, microwave at 500 W and 140 °C for 15 min. (e) and (f) Sodium ethoxide, EtOH, microwave at 500 W and 140 °C for 15 min.

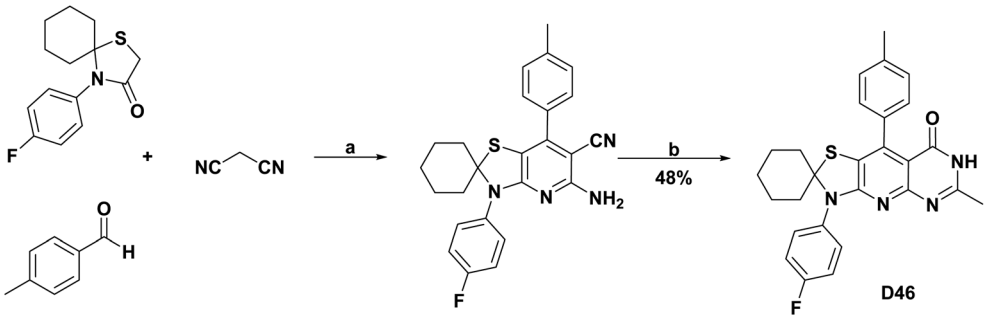


Scheme 42 Structures, reagents and conditions for the synthesis of spiro heterocycles [4.5.0] **D45**, [5.5.0] **G5** and [5.6.0] **H1**. (a) (1) Cyclopentanone (**D45**) or cyclohexanone (**G5**), or cycloheptanone (**H1**), pyrrolidine, toluene, reflux, 2 h. (2) MsCl, Et_3N, DMC, rt, 12 h; (b) (1) $NaBH_4$, MeOH, reflux, 1 h; (2) *p*-TsOH, toluene, reflux, 1 h; (c) OsO_4, *N*-methylmorpholine-*N*-oxide, *t*-BuOH, THF, H_2O, rt, 2 d; (d) acetone, H_2SO_4, 80 °C, 3 h; (e) (1) NaOH 10%, EtOH, reflux 48 h; (2) Meldrum's acid, toluene, reflux, 1 h; (f) $(CF_3CO)_2O$, DMC, rt, 20 h; (g) CF_3CO_2H, MeOH, rt, 24 h.

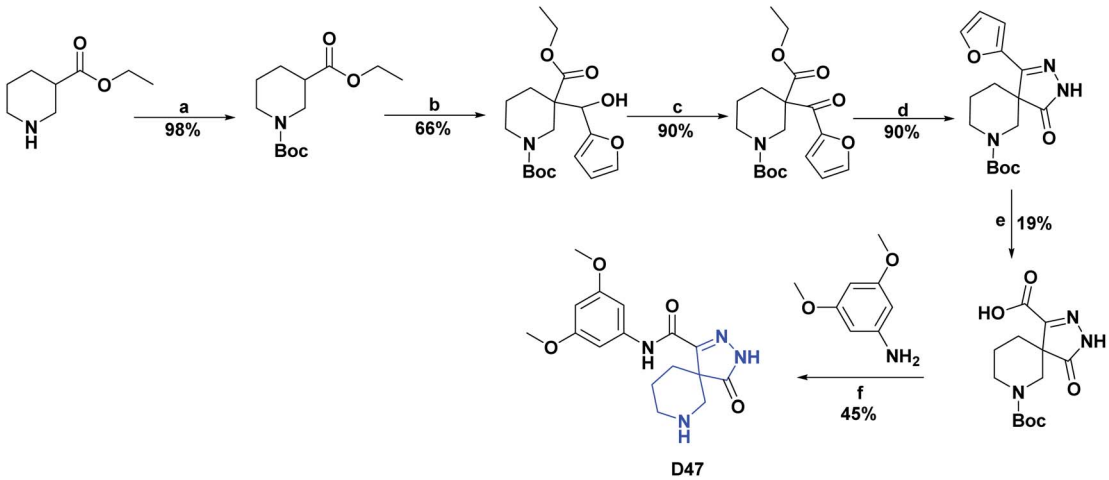
C exhibited a percent inhibition of 88.90% for the same test. The synthesis of compound **G8** is shown in Scheme 41.[129]

Chromone scaffold molecules are substructures that possess a wide variety of biological activities, including AO, antifungal, antiviral, antimicrobial, antiallergic, anti-inflammatory, antiproliferative, and antitumor activity.[162,179–181] Chromones represent an attractive source of compounds of pharmacological interest due to their low toxicity. Furthermore, several spirochromanone derivatives have been reported to exhibit a wide range of biological activities: acetyl CoA carboxylase inhibitor,[182] antiarrhythmic activity,[183] delta-opioid receptor agonists for the treatment of pain.[184]

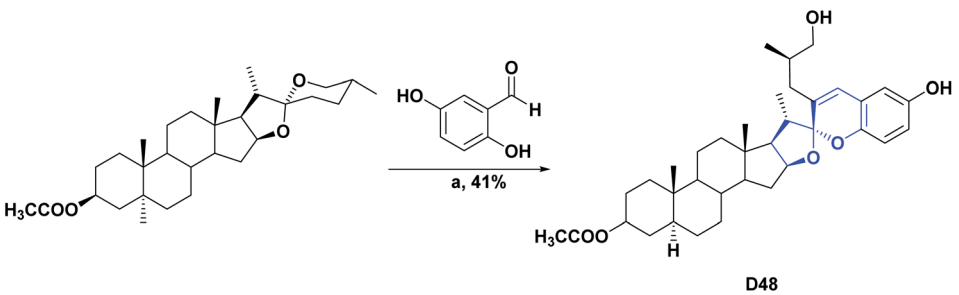
A series of 2′-substituted-3′-methylpyro [cyclohexane-1,7′-furo [3,2-*g*] chroman]-5′(7′*H*)-one spiros (**G9–G11**) have been synthesized. Their AO activities were studied by the DPPH radical scavenging test and the hydrogen POR test. In the DPPH assay, the compounds **G9–G11** showed IC_{50} values (μg mL^{-1}) of



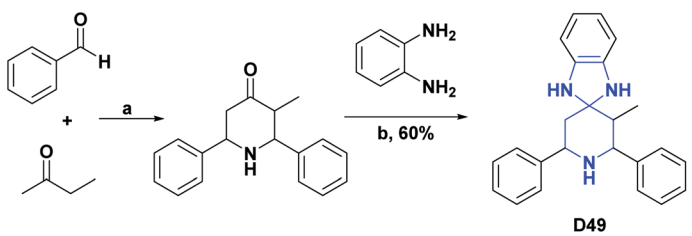
Scheme 43 Structures, reagents and conditions for the synthesis of spiro heterocycle [4.5.0] **D46**. (a) $AcNH_4$, AcOH, reflux, 24 h. (b) AcOH, AC_2O, reflux, 9 h.



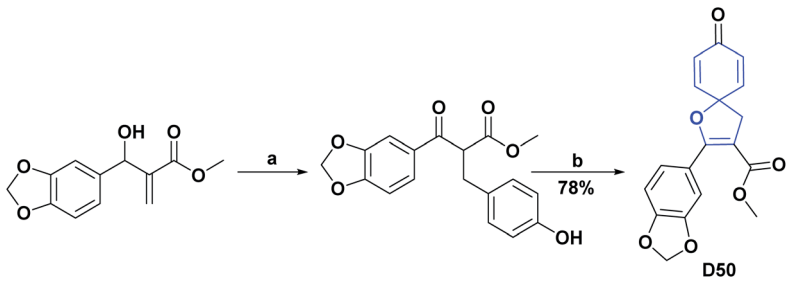
Scheme 44 Structures, reagents and conditions for the synthesis of spiro heterocycle [4.5.0] **D47**. (a) BOC_2O, DCM, TEA, rt, 2 h; (b) LDA, furan-2-carbaldehyde, −78 °C, 30 min; (c) MnO_2, DCM, rt, 4 h; (d) NH_2NH_2–H_2O, EtOH, AcOH, rt, 4 h; (e) $KMnO_4$, acetone, water, 60 °C, 4 h; (f) DMF, DIPEA, HATU; HCl in 1,4-dioxane, rt, 5 h.



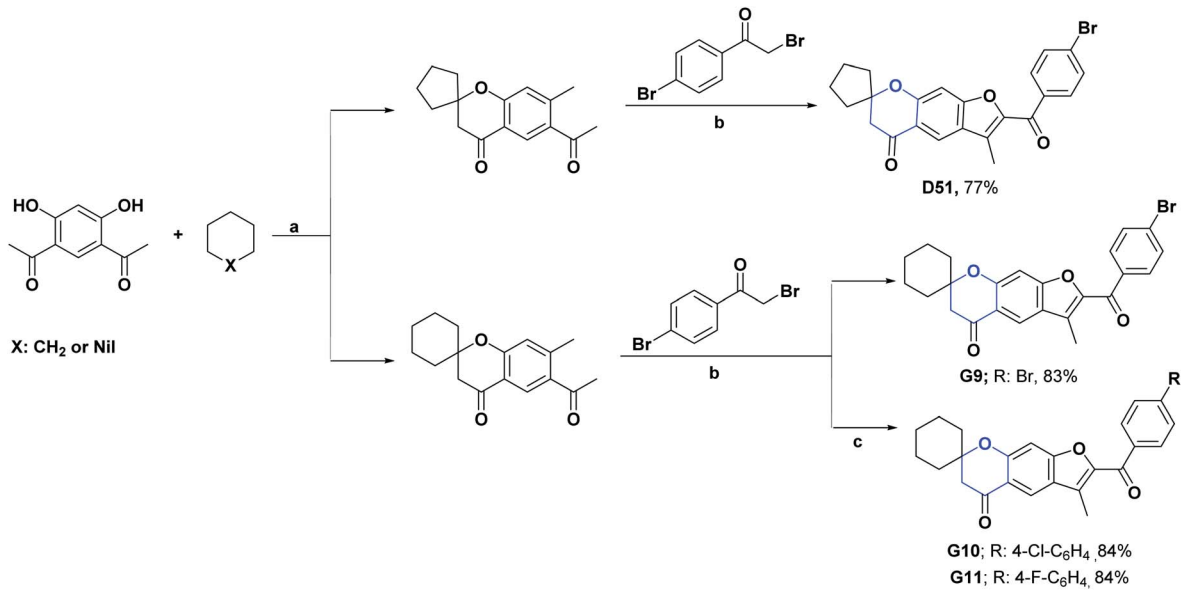
Scheme 45 Structures, reagents and conditions for the synthesis of spiro heterocycle [4.5.0] **D48**. (a) BF_3OEt_2·DCM, 24 h.



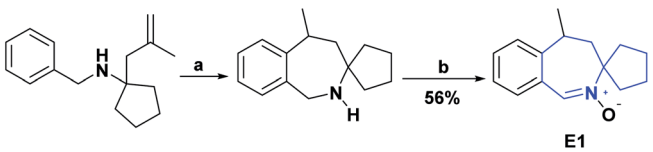
Scheme 46 Structures, reagents and conditions for the synthesis of spiro heterocycle [4.5.0] **D49**. (a) $AcNH_4$, EtOH; (b) benzene, anhydrous K_2CO_3, reflux, 24 h.



Scheme 47 Structures, reagents and conditions for the synthesis of spiro heterocycle [4.5.0] **D50**. (a) 4-Iodophenol, Et_3N, Nájera's catalyst,[141] DMF, 110 °C, 3 h. (b) PIFA, anhydrous CH_3CN, −10 °C, N_2, 10–15 min.



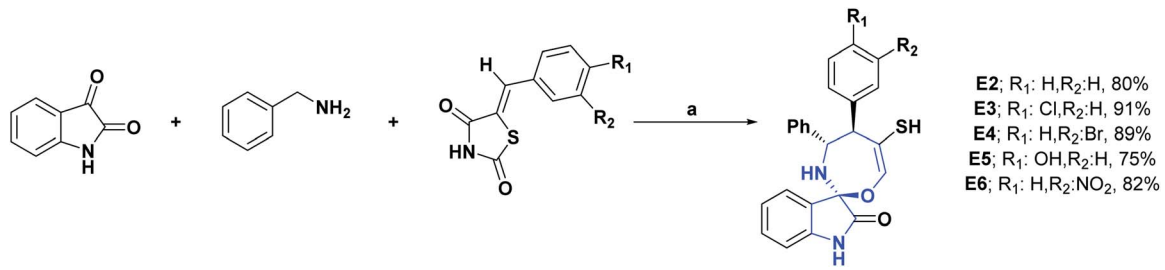
Scheme 48 Structures, reagents and conditions for the synthesis of spiro heterocycles [4.5.0] **D51**, [5.5.0] **G9–G11**. (a) Toluene, pyrrolidine, reflux, 3 h; (b) K_2CO_3, microwave at 100 W for 5 min; (c) (4-chlorophenyl)boronic for **G10**, (4-fluorophenyl)boronic acid for **G11** Toluene, EtOH, H_2O, $Pd(PPh_3)_4$, Na_2CO_3, microwave at 100 W for 20 min.



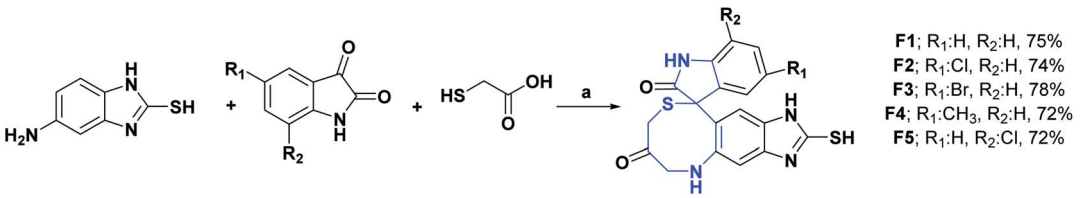
Scheme 49 Structures, reagents and conditions for the synthesis of spiro heterocycle [4.6.0] **E1**. (a) H_2SO_4 98%, 0 °C → 40–45 °C, 1 h (for 8 d); 75–80 °C, 3 h; (b) acetone–H_2O, $Na_2WO_4 \cdot 2H_2O$, H_2O_2 50%, rt, 5 h.

2.64, 3.93, and 11.03, respectively. In the POR test, IC_{50} of (μg mL^{-1}) 83.14, 96.65, and 32.11, respectively, were obtained. The compounds were compared with vitamin C as a positive control, which presented an IC_{50} of 145.4 μg mL^{-1} in the DPPH assay and 77.13 μg mL^{-1} in the hydrogen POR assay.

It is important to highlight that in the DPPH test, all compounds presented IC_{50} values lower than vitamin C, with compounds **G9** and **G10** giving the best results. In the hydrogen POR test, only compound **G11** showed lower IC_{50} values than



Scheme 50 Structures, reagents and conditions for the synthesis of spiro heterocycles [4.6.0] **E2–E6**. (a) Et_3N, THF, reflux, 20 min.



Scheme 51 Structures, reagents and conditions for the synthesis of spiro heterocycles [4.6.0] **F1–F5**. (a) MeCN-PTSA, reflux, 80 °C, 24 h.

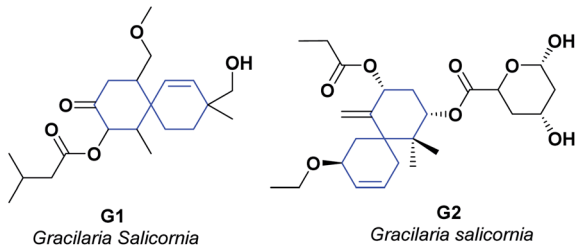


Fig. 6 Structures of spiro heterocycles [5.5.0] **G1** and **G2**.

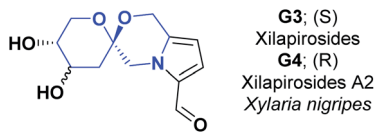
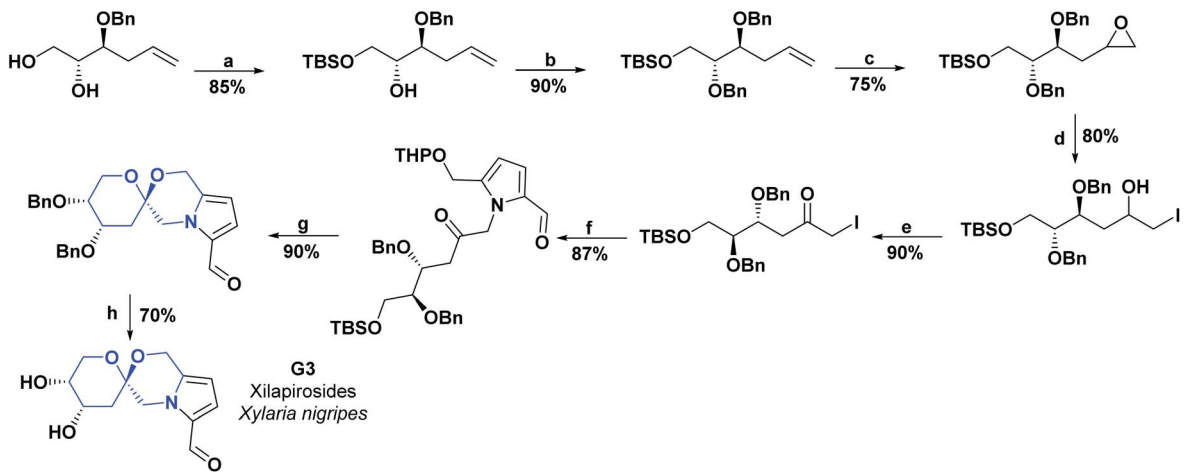


Fig. 7 Structures of spiro heterocycles [5.5.0] xilapirosides (**G1**) and xilapirosides A2 (**G2**).

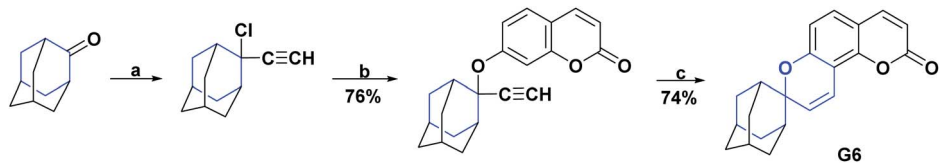
the positive control.[136] In Scheme 48 the syntheses of compounds **G9–G11** are presented.

Spirochroman compounds [5.5.0] **G12** and **G13** were reported in 2015 and 2016.[185,186] The AO activities of compounds **G12** and **G13** were determined by the DPPH radical trapping test. Spiro compounds **G12** and **G13** presented excellent AO activity with IC_{50} values of 0.50 and 1.25 μM, respectively, compared to vitamin C (positive control), which presented an IC_{50} of 8.64 μM. Schemes 55 and 56 present the synthesis of compounds **G12** and **G13**, respectively.

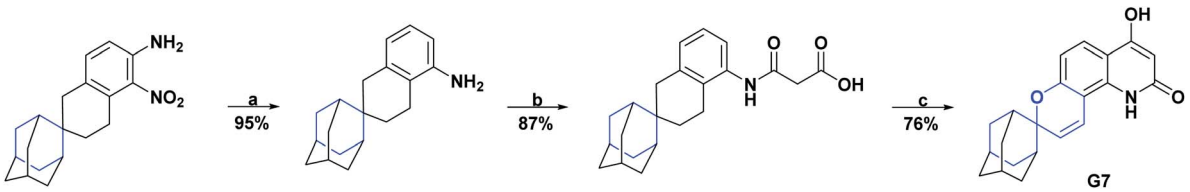
The functionalized heterocycle compounds are of great interest for the design and development of drugs. Many of the fused pyridine compounds have been reported to be valuable compounds that possess a wide variety of biological properties such as anticonvulsant, antibacterial, antipsychotic, antifungal, antileishmanial, antidiabetic activities, antimicrobial, AO, anticancer, antiviral, antihypertensive, antimalarial, anti-inflammatory, and antitumor.[187–189]



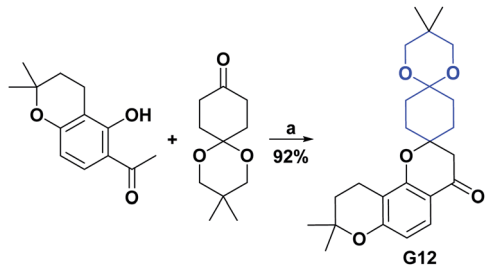
Scheme 52 Structures, reagents and conditions for the synthesis of spiro heterocycle [5.5.0] xilapirosides (**G3**). (a) TFA, DCM, stirring, 2 h; (b) TBSCl, Et_3N, DCM, stirring, r.t, overnight; (c) BnBr, NaH, DMF, stirring, 0 °C, 30 min; (d) $CeCl_3 \cdot 7H_2O$, NaI, MeCN, stirring, rt, 5 h; (e) DMP, DCM, stirring, rt, 3 h; (f) K_2CO_3, DMF, stirring, rt, 6 h; (g) 4 N, HCl, THF, 0 °C, 4 h; (h) $TiCl_4$, DCM, stirring, −78 °C, 40 h.



Scheme 53 Structures, reagents and conditions for the synthesis of spiro heterocycle [5.5.0] **G6**. (a) (1) C_2HK, THF, stirring, rt; (2) HCl, $CaCl_2$, hydroquinone, stirring; (b) K_2CO_3, KI, CuI, acetone, stirring, 60 °C, 4 h; (c) *N*,*N*-diethylaniline, stirring, 180 °C, 1 h.



Scheme 54 Structures, reagents and conditions for the synthesis of spiro heterocycle [5.5.0] **G7**. (a) (1) $NaNO_2$, H_2SO_4–H_2O, rt, 1 h; (2) EtOH, $CuSO_4$, reflux, 30 min; (3) $SnCl_2 \cdot 2H_2O$, acetone, reflux, 12 h; (b) (1) diethyl malonate, 190 °C, 15 h; (2) NaOH, EtOH, rt, 2 h; (c) $(CF_3CO)_2O$, DCM, rt, 24 h.



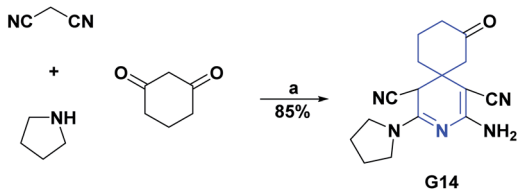
Scheme 55 Structures, reagents and conditions for the synthesis of spiro heterocycle [5.5.0] **G12**. (a) Pyrrolidine, EtOH, microwave, 4 min.

Through a multicomponent reaction, a functional spiropyridine compound [5.5.0] (**G14**) was synthesized. The AO activity of compound **G14** was evaluated by the DPPH radical scavenging test. This compound presented excellent AO capacity with an IC_{50} value of 0.07 μM. Spiro compound **G14** was compared with vitamin C as a positive control, which had an IC_{50} for the DPPH assay of 0.05 μM. The synthesis of compound **G14** is shown in Scheme 57.[189]

[5.6.0] Spirocyclic system (H)

[5.6.0] Spirocyclic system (H); compounds of synthetic origin

Compound **H1** is a spiro [5.6.0], which, like compounds **G5** and **G6**, belongs to the hydroxycoumarin family. In 2008, Panteleon *et al.* synthesized and evaluated the AO capacity of compound **H1** using the DPPH test, finding that said compound had an IC_{50} of 157.70 μM. These results were compared with the positive controls 4-hydroxycoumarin, 7-hydroxycoumarin, and BHT with IC_{50} > 124.10, 400, and 83.80 μM respectively (see Fig. 8). The synthesis of compound **H1** is shown in Scheme 42.[130]



Scheme 57 Structures, reagents and conditions for the synthesis of spiro heterocycle [5.5.0] **G14**. (a) EtOH, reflux, 18 h.

Conclusions

The syntheses and AO activities of many spiro compounds of natural and synthetic origin have been reviewed. Table 1s of ESI† summarizes some features of the 119 spiro compounds reviewed; it is shown that the most abundant spiro heterocycles with information about AO properties were [4.5.0], followed by [4.4.0], and most of the spiro [4.4.0] compounds studied had better results than the positive controls used in the respective assays. In general, the revised compounds demonstrated some AO activities that were mainly limited to the DPPH, ABTS, FRAP, anti-LPO, superoxide, xanthine oxidase, peroxide, hydroxyl, and

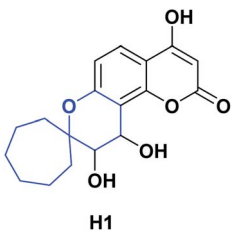
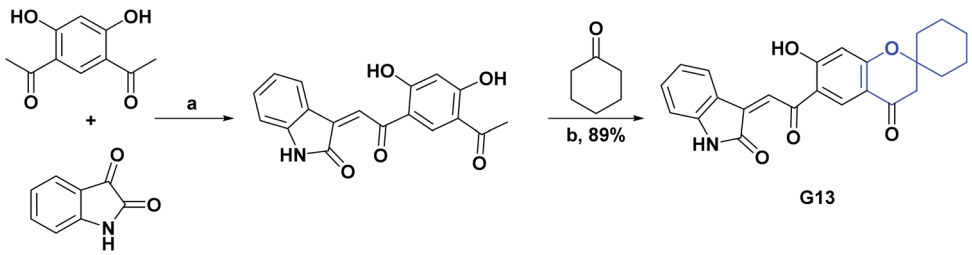


Fig. 8 Structure of the spiro heterocycle [5.6.0] **H1**.



Scheme 56 Structures, reagents and conditions for the synthesis of spiro heterocycle [5.5.0] **G13**. (a) KOH, microwave; (b) pyrroline-[bmim]Cl·$FeCl_3$, microwave, 60 °C, 5 min.

nitric oxide tests. The molecules that presented the best results for these tests were the spiro compounds **G14**, **C12**, **D41**, **C18**, **C15**, **D5**, **D11**, **E1**, and **C14**. The most active compounds were characterized for having at least one oxygen atom; a number of them (around 35%) are phenolic compounds, and in the molecules where this functional group was absent, aryl ethers and nitrogen functional groups such as amine and amides could be found. It is important to note that spirocyclic compounds of synthetic origin have better AO activity in most of the reviewed tests as compared to compounds of natural origin. However, the discovery of the latter has increased in recent years. Therefore, they are likely to inspire new pathways for the design of drugs based on AO properties and the development of new synthetic libraries. Thus, in terms of their development, spiro heterocycles will continue to be an essential structural scaffold in medicinal chemistry.

Abbreviations

ABTS	2,2′-Azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)
APVPB	Acetic acid-functionalized poly (4-vinylpyridinium) bromide
Ac_2O	Acetic anhydride
AChE	Acetylcholinesterase
AO	Antioxidant (s)
BF_3OEt_2	Boron trifluoride etherate
BHA	Butylated hydroxyanisole
BHT	Butylhydroxytoluene
bmim	1-Butyl-3-methylimidazolium
t-BOC	*tert*-Butyloxycarbonyl protecting group
CAN	Ceric ammonium nitrate
CAT	Catalase
CSA	Camphorsulfonic acid
CTAB	Cetyltrimethylammonium bromide
CUPRAC	Cupric ion reducing antioxidant capacity assay
DABCO	1,4-Diazabicyclo[2.2.2]octane
DCC	Dicyclohexylcarbodiimide
DCM	Dichloromethane
DIPEA	*N*,*N*-Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DMP	Dess–Martin periodinane
DMSO	Dimethyl sulfoxide
DPPH	2,2-Diphenyl-1-picrylhydrazyl
EC_{50}	Half maximal effective concentration
EtOH	Ethanol
GSH	Glutathione
GTBSA	Glycoluril tetrakis(butane-1-sulfonic acid)
HATU	Hexafluorophosphate azabenzotriazole tetramethyl uronium
HOBT	1-Hydroxybenzotriazole
HOR	Hydroxyl radicals
IC_{50}	Half maximal inhibitory concentration
LHMDS	Lithium bis(trimethylsilyl)amide
LPO	Lipid peroxidation
MCDC	The multicomponent 1,3-dipolar cycloaddition
m-CPBA	*meta*-Chloroperoxybenzoic acid
MeOH	Methanol
mg	Milligram
mL	Millilitre
mM	Millimolar
NaHMDS	Sodium hexamethyldisilazane
NBS	*N*-Bromosuccinimide
Nil	Null
NO	Nitric oxide
NPs	Nanoparticles
PBN	α-Phenyl-*N*-*tert*-butylnitrone
PCO	Protein carbonylation
PIFA	[Bis(trifluoroacetoxy)iodo]benzene
PN	peroxynitrite
POR	Peroxide reactive
PTC	Phase transfer catalyst
PTSA	*p*-Toluenesulfonic acid
ROS	Reactive oxygen species
rt	Room temperature
SOA	Superoxide anion
SOD	Superoxide dismutase
T3P	Propylphosphonic anhydride
TAN	Total acid number
TBA	Acid thiobarbituric
TBAB	Tetrabutylammonium bromide
TBAF	Tetrabutylammonium fluoride
*t*BHP	*tert*-Butyl hydroperoxide
TEAC	Trolox equivalent antioxidant capacity
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin-layer chromatography
TPP	Triphenylphosphine
μM	Micromolar
XO	Xanthine oxidase

Conflicts of interest

There are no conflicts to declare.

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