https://doi.org/10.31925/farmacia.2019.6.4 **ORIGINAL ARTICLE**

MICROWAVE ASSISTED SYNTHESIS AND SPECTROSCOPIC CHARACTERIZATION OF SOME NOVEL SCHIFF BASES OF CARPROFEN HYDRAZIDE

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Abstract

A new series of Schiff bases was synthesised by the treatment of (2*RS*)-2-(6-chloro-9*H*-carbazol-2-yl)propanehydrazide (carprofen hydrazide) with few benzaldehyde derivatives under microwave irradiation. The IR, ^{1}H NMR and ^{13}C NMR spectroscopic characterization of newly synthesised compounds is reported. The Schiff bases were tested for antibacterial activity, the strongest effect being against *S. aureus*.

Rezumat

A fost sintetizată o serie nouă de baze Schiff, prin tratarea (2*RS*)-2-(6-cloro-9*H*-carbazol-2-il)propanohidrazidei (hidrazida carprofenului) cu derivați ai benzaldehidei, prin iradiere cu microunde. Este raportată caracterizarea spectrală IR, ^{1}H RMN și ^{13}C RMN a compușilor nou sintetizați. Bazele Schiff au fost testate din punct de vedere al activității antibacteriene efectul cel mai pronunțat înregistrându-se împotriva *S. aureus*.

Keywords: Schiff bases, carbazol derivatives, microwave-irradiation, spectral data

Introduction

The azometin functional group (C=N) of the Schiff base structure is considered to be a versatile pharmacophore in the design and development of the bioactive compounds [6].

Due to their characteristic properties, such as structural variety, thermal stability and coordination capacity, these compounds have potential applications in different fields [28].

Schiff bases present various biological activities such as antimicrobial [8, 16, 18], antitubercular [23], anti-helmintic [12], anticancer [25], antioxidant [21], analgesic [9], anti-inflammatory [17], anticonvulsant [20], antidiabetic [26], antidepressant [30].

These compounds are also used as catalysts, pigments and dyes, intermediates in organic synthesis, polymer stabilizers and corrosion inhibitors [2, 4, 7, 11]. They are also used in other fields such as coordinating chemistry, analytical chemistry and agriculture as fungicides, pesticides and bactericides [3, 5, 13].

Synthesis reaction of the Schiff bases has numerous applications in research such as the synthesis of new heterocycles, the identification, detection and analysis of aldehydes or ketones, the purification of the compounds with carbonyl group or amine group or the protection of these functional groups in the process of complex synthesis.

Schiff bases interfere in cellular processes by forming a hydrogen bond between the active moieties of the cellular constituents and the sp^2 nitrogen atom of the azomethine group [31, 32].

A novel series of 5-substituted Schiff bases of isatin derivatives, 7-(4-((3-(4-(benzylideneamino)phenyl-imino)-5-fluoro-2-oxindolin-1-yl)methyl)piperazin-

1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid derivatives, were synthesized and tested in order to characterize theirs *in vitro* anti-microbial activity, establishing the minimal inhibitory concentration, as compared to standard antimicrobial drugs such as ciprofloxacin and ketoconazole [24].

6-Bromo-2-[2-(2,6-dichlorophenyl)amino]benzyl-3-(benzylideneamino) quinazolin-4(3H)-one derivatives were synthesized and then tested for *in vitro* antimicrobial activity on *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Bacillus subtilis* and *Candida albicans*, using penicillin G and amphotericin B as standards. The results demonstrated that all compounds exhibit mild to moderate antibacterial and antifungal activity [22].

The Schiff bases of substituted pyrazole, 4-[(3-substituted-1*H*-pyrazol-3-yl)methyleneamino]-5-substituted-4*H*-1,2,4-triazole-3-thiols were tested for antibacterial activity against microbial strains of *S. aureus*, *P. aeruginosa*, *B. subtilis* and *Escherichia coli*. Following the tests, one of the compounds proved to be as active as ceftriaxone (the substance used as a standard), an antibiotic used against *P. aeruginosa*, *B. subtilis* and *E. coli* strains, but the strongest effect was against *S. aureus* [14].

Many Schiff base ligands are potentially excellent chelating agents capable to forming stable complexes with metal ion. Thus, the complexes of La(III), Ce(III), Pr(III), Nd(III), Sm(III) and Gd(III) with 4-hydroxy-3-(1-{2-(2-hydroxy-benzylidene)-aminophenyl-imino}-ethyl)-6-methy-pyran-2-one were synthesized, characterized and tested for antimicrobial activity against *S. aureus*, *E. coli*, *Bacillus* sp. and were screened for fungicidal activity against *Aspergillus niger*, *Trichoderma* and *Fusarium oxysporum.* According to the results, the complexes have better antifungal properties than the free ligand (Schiff base) [27].

In this paper we have studied the possibility of carrying out chemical reactions to obtain Schiff bases by condensing (2*RS*)-2-(6-chloro-9*H*-carbazol-2-yl)-propanehydrazide (carprofen hydrazide) with aromatic aldehydes, using the advantages of microwave irradiation, in order to reduce the reaction time, and to increase the reaction yield and purity of the final products by diminishing undesirable side reactions, compared to conventional heating methods.

The use of microwaves also includes other advantages: an uniform and efficient heating of the reaction mixture, an improved reproducibility of the synthesis method, avoiding heat loss, low cost of use and, last but not least, the reduction of environmental pollution, this method being part of the principles of "green" concept introduced in order to reduce or eliminate the use and formation of hazardous substances for human health and the environment [15]. This justifies the other purpose of our work, to optimize the micro-wave synthesis of Schiff bases.

Materials and Methods

All reagents were used as received from Merck or Aldrich (Darmstadt și Steinheim, Germania).

The microwave assisted synthesis was performed with a Biotage® Initiator Classic 2.0 (Biotage, Uppsala, Sweden).

Melting points were determined by Electrothermal 9100 apparatus (Bibby Scientific Ltd, Stone, UK) and were uncorrected.

The IR spectra were recorded on a Bruker Vertex 70 FT-IR spectrometer (Bruker Corporation, Billerica, MA, USA). These were obtained using the ATR technique and are rendered as: w – weak band; m – medium band; s – intense band; vs – very intense band.

The ^{1}H NMR and ^{13}C NMR spectra were recorded in deuterated dimethyl sulfoxide (DMSO-d6) on a Bruker Fourier 300 MHz instrument (Bruker Corp., Billerica, MA, USA), operating at 300 MHz for ^{1}H NMR and at 75 MHz for ^{13}C NMR and on a Bruker Avance III 500 MHz instrument (Bruker Corporation, Billerica, MA, USA) operating at 500 MHz for proton and 125 MHz for carbon.

In NMR spectra, chemical shifts were recorded as δ values, in parts per million (ppm), relative to tetra-methylsilane as internal standard, and coupling constants (J) in Hertz. Standard abbreviations that indicate the multiplicity of signals are used as follows: s (singlet), d (doublet), t (triplet), q (quartet), spt (septet), m (multiplet), dd (double doublet), td (triple doublet). The ^{1}H NMR data are reported in the following order: chemical shifts, multiplicity, signal/ atom attribution and the coupling constants. For ^{13}C NMR data the order is as follows: chemical shifts and signal/ atom attribution.

Chemical shifts for hydrogen and carbon atoms were also confirmed by 2D-NMR experiments.

Synthesis

*Methyl (2RS)-2-(6-chloro-9H-carbazol-2-yl)-propanoate(carprofen methyl ester) (**3**)*

10 g (*RS*)-2-(6-Chloro-9*H*-carbazol-2-yl)propanoic acid (carprofen) (Mr 273.71; 0.037 mol) was dissolved with stirring in 400 mL methanol absolute. After the mixture became homogeneous, 1.2 mL concentrated sulfuric acid (98%) was dropwise added as a catalyst, and stirring was continued at room temperature for 8 hours. The reaction mixture was left overnight at room temperature, and then the methanol was evaporated at low pressure until a precipitate appeared. Over the reaction mixture, 200 mL of water was added and the precipitate was filtered off at low pressure and washed well with water on the filter to remove the acid traces. The white or slightly yellow precipitate was air dried for 24 hours.

10 g (Yield 95%) of carprofen methyl ester (Mr 287.71) with m.p. 107-110°C were obtained.

The compound is soluble at room temperature in methanol, ethanol, isopropanol, isobutanol, xylene, chloroform, ethyl acetate, dimethylsulfoxide, dimethylformamide, pyridine, insoluble in hexane and water.

*(2RS)-2-(6-chloro-9H-carbazol-2-yl)propanehydrazide (carprofen hydrazide) (**4**)*

In a 100 mL round bottom flask equipped with a water-cooling cooler, 6 g carprofen methyl ester (Mr 287,71; 0,021 mol) in 40 mL of ethanol (96% or absolute) is added. Under magnetic stirring, 7 mL of 100% hydrazine hydrate is added, and the reaction mixture is refluxed for 8 hours with continuous stirring. After several hours of refluxing, the hydrazide may precipitate as white crystals. After the reaction time has ended, the mixture is cooled and the carprofen hydrazide is filtered off at low pressure and wash with cold alcohol on the filter; 4.2 g of white carprofen hydrazide (Mr 287.75) are obtained with a melting point of 241-243ºC (yield of 70%).

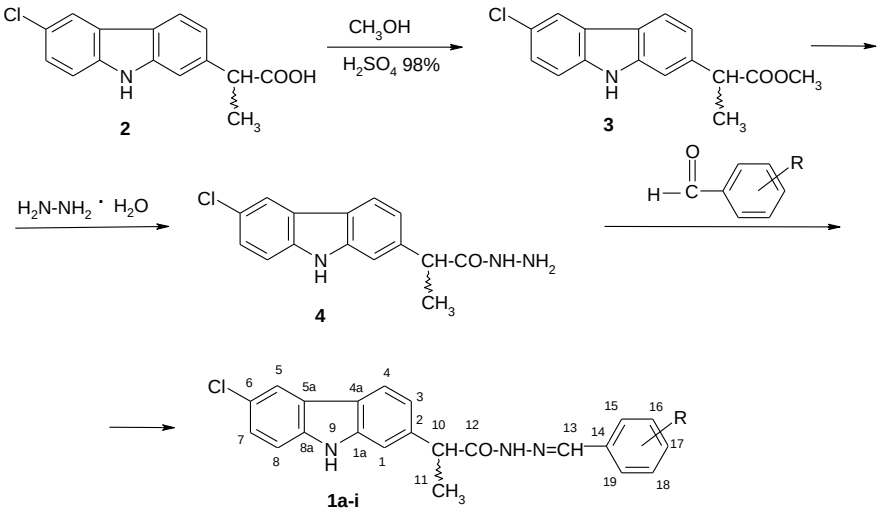
The compound is soluble at room temperature in dimethylsulfoxide, dimethylformamide, pyridine, by heating in isobutanol, hardly soluble by heating in methanol, ethanol, ethyl acetate, insoluble in isopropanol, methylene chloride, chloroform, xylene, acetonitrile, hexane and water.

It may happen that the traces of methyl ester remaining unreacted to co-precipitate with the hydrazide. The presence of traces of unreacted methyl ester in the hydrazide may be readily observed from the ^{1}H NMR and ^{13}C NMR spectra of the hydrazide. When it is found that the ester is present in the final product, it can be easily removed by stirring the hydrazide slurry in a solvent in which it does not dissolve (methylene chloride, chloroform, acetonitrile, etc.) but wherein the ester is readily soluble. Filtration of the suspension produces a sufficiently hydrazide which can be used further in the reactions.

*General microwave procedure for the synthesis of novel Schiff bases (**1a-i**)*

A microwave-vial (5 mL) was charged with a mixture of (2*RS*)-2-(6-chloro-9*H*-carbazol-2-yl)propanehydrazide (carprofen hydrazide) (**4**) (Mr 287.737; 0.001 mol) and substituted aromatic aldehyde (0.001 mol) in 3 mL methanol absolute, catalytic amount of glacial acetic acid was added and the vial was capped and the sample was subjected to microwave irradiation (pre-stirring: 5 minutes, absorption level setting very high) to 90°C for 25 min. The reaction mixture was allowed to cool to ambient temperature, and then in the refrigerator overnight. The obtained product was filtered; the solid obtained was crystallized from isopropanol or isopropanol:water 1:2.

The general scheme for the synthesis of the novel Schiff bases from carprofen hydrazide is shown in Figure 1.



R= -H, 4-isopropyl, 2-F, 3-F, 4-F, 2-Cl, 3-Cl, 4-CF_3, 4-phenoxy

Figure 1.
Synthesis of novel Schiff bases from carprofen hydrazide

Results and Discussion

We have synthesized new Schiff bases (**1a-i**) that bring together in the same molecule the 9*H*-carbazole nucleus and the active pharmacophore fragment –CONH–N=CH–. In order to optimize the reaction conditions, the microwave synthesis were performed at different temperatures (40ºC, 70ºC, 90ºC) and varying the reaction times (15 minutes, 20 minutes, 25 minutes), using the NMR spectroscopy to check the result of the reaction. So we have determined that the best yield is obtained using a heating temperature of 90ºC for 25 minutes.

In Figure 1, the compounds methyl (2*RS*)-2-(6-chloro-9*H*-carbazol-2-yl)propanoate (carprofen methyl ester) (**3**) was prepared according to the literature method [10].

The synthesis and physico-chemical characterization of carprofen hydrazide (**4**) is presented in a patent request [29].

The final compounds (*EZ*)-N'-substituted-benzylidene-(2*RS*)-2-(6-chloro-9*H*-carbazol-2-yl)propanehydrazide (**1a-i**) were synthesized by the reaction between **4** with substituted aromatic aldehyde (benzaldehyde, 4-isopropylbenzaldehyde, 2-, 3- and 4-fluorobenzaldehyde, 2- and 3-chlorobenzaldehyde, 4-trifluoromethylbenzaldehyde, 4-phenoxy-benzaldehyde), in molar ratio of 1:1, under microwave irradiation, in the presence of acetic acid as catalyst. Studies have been carried out to optimize reaction conditions, the best yields being obtained using molar ratio of carprofen hydrazide: corresponding benzaldehyde in absolute methanol as the reaction medium, heating at 90ºC for 25 minutes, with 5 minutes pre-stirring. In presence of acetic acid catalyst, the reaction is more efficiently, in milder conditions and it gives better yields. Moreover, the work up and purification procedures are simple as the catalyst is water soluble [1, 19].

All the novel compounds were synthesized in good yields. The new compounds are soluble at normal temperature in DMSO, DMF and pyridine, by heating in benzene, toluene, xylene, ethylacetate, 1,4-dioxane and inferior alcohols, insoluble at cold and boiling in water, methylene chloride and hexane.

All the synthesis compounds have been characterized by ^{1}H NMR, ^{13}C NMR and IR spectral data.

Spectral data

Spectral data of the intermediates and novel Schiff bases from carprofen hydrazide were in full agreement with the proposed structures.

*Methyl (2RS)-2-(6-chloro-9H-carbazol-2-yl-)-propanoate(carprofen methyl ester) (**3**)*

FT-IR (solid in ATR, ν cm^{-1}): 3450w; 3405vs; 2983w; 2944w; 2875w; 1729vs; 1697m; 1624m; 1448m; 1429m; 1325w; 1269w; 1236w; 1193m; 1172m; 1093w; 1059m; 873w; 806m; 731w; 695w.

^{1} *H-RMN* ($CDCl_3$, δ ppm, *J* Hz): 8.26 (brs, 1H, H-9); 7.96 (brs, 1H, H-5); 7.92 (d, 1H, *J* = 8.1 Hz, H-4); 7.33 (d, *J* = 8.6 Hz, 1H, H-8); 7.31 (brs, 1H, H-1); 7.25 (d, *J* = 8.1 Hz, 1H, H-3); 7.17 (d, 1H, H-7, 8.6); 3.90 (q, *J* = 7.1 Hz, 1H, H-10); 3.71 (s, 3H, H-13); 1.60 (d, *J* = 7.1 Hz, 3H, H-11).

^{13} *C-RMN* ($CDCl_3$, δ ppm): 175.49 (C-12); 140.29 (C-8a); 139.01 (C-1a); 138.00 (C-2); 125.70 (C-7); 124.74 (C-5a); 124.11 (C-4a); 121.53 (C-6); 120.54 (C-4); 119.84 (C-5); 119.47 (C-3); 111.54 (C-8); 109.49 (C-1); 52.17 (C-13); 45.74 (C-10); 18.86 (C-11).

*(2RS)-2-(6-chloro-9H-carbazol-2-yl)propane-hydrazide(carprofen hydrazide) (**4**)*

FT-IR (solid in ATR, ν cm^{-1}): 3347s; 3260m; 2979w; 2873w; 1632vs; 1517m; 1462s; 1428m; 1379w; 1338m; 1269m; 1238s; 1120w; 1061m; 988m; 926w; 885m; 828w; 800m; 733w; 690w.

^{1} *H-RMN* (300 MHz, DMSO-d6, δ ppm, *J* Hz): 11.36 (s, 1H, H-9); 9.24 (s, 1H, HN); 8.15 (d, *J* = 2.2 Hz, 1H, H-5); 8.05 (d, *J* = 8.2 Hz, 1H, H-4); 7.48 (d, *J* = 8.5 Hz, 1H, H-8); 7.47 (brs, 1H, H-1); 7.35 (dd, *J* = 2.2 Hz, *J* = 8.5 Hz, 1H, H-7); 7.16 (dd, *J* = 1.4 Hz, *J* = 8.2 Hz, 1H, H-3); 4.21 (brs, 2H, H-N); 3.70 (q, *J* = 6.9 Hz, 1H, H-10); 1.42 (d, *J* = 6.9 Hz, 3H, H-11).

^{13} *C-RMN* (75 MHz, DMSO-d6, δ ppm): 173.05 (C-12); 140.67 (C-8a); 140.56 (C-1a); 138.36 (C-2); 123.71 (C-5a); 123.56 (C-4a); 122.85 (C-6); 125.02 (C-7); 120.34 (C-4); 119.64 (C-5); 118.90 (C-3); 112.34 (C-8); 109.71 (C-1); 43.81 (C-10); 18.79 (C-11).

The final compounds contain two stereoisomers *E* and *Z* (or *sin* and *anti*). The superscript s/a represents the alternative between *sin* or *anti* stereoisomers, and s + a represents the unique signal for the two isomers.

The presence of the chiral center at C-10 doubles the number of diastereoisomers.

*(EZ)-N'-benzylidene-(2RS)-2-(6-chloro-9H-carbazol-2-yl)propanehydrazide (**1a**)* (M_r = 375.837 g/mol; m.p. 265 - 267ºC; yield 87.8%)

^{1} *H-NMR* (300 MHz, DMSO-d6, δ ppm, *J* Hz): 11.56 (s, H-9$^{s/a}$); 11.38 (s, H-9 $^{s/a}$); 11.34 (s, HN$^{s/a}$); 11.30 (s, HN$^{s/a}$); 8.25 (s, H-13^{s+a}); 8.17 (d, H-5$^{s/a}$, 1.6); 8.14 (d, H-5$^{s/a}$, 1.6); 8.10 (d, H-4$^{s/a}$, 8.1); 8.07 (d, H-4$^{s/a}$, 8.1); 7.94 (s, H-13^{s+a}); 7.70 ÷ 7.64 (m, 2H, H-15, H-19^{s+a}); 7.51 ÷ 7.32 (m, 6H, H-1, H-7, H-8, H-16, H-17, H-18^{s+a}); 7.21 (m, 1H, H-3^{s+a}); 4.83 (q, H-10$^{s/a}$, 7.0); 3.86 (q, H-10$^{s/a}$, 7.0); 1.51 (d, H-11$^{s/a}$, 7.0); 1.48 (d, H-11$^{s/a}$, 7.0).

H-3 protons in the two *sin*/*anti* stereoisomers have very close chemical shift displacement (are quasi-isocrons) and cannot be identified separately. The multiplicity of the signal is doublet of doublets as expected by the H-4 vicinal coupling and the H-1 remote coupling. For the same reason the protons H-15 and H-19 in the *ortho* position relative to the double link present an undetectable signal.

^{13} *C-NMR* (75 MHz, DMSO-d6, δ ppm): 175.11 (C-12$^{s/a}$); 169.89 (C-12$^{s/a}$); 146.54 (C-13$^{s/a}$); 142.54 (C-13$^{s/a}$); 140.57 (C-8a$^{s/a}$); 140.09 (C-8a$^{s/a}$); 138.34 (C-2 $^{s+a}$); 138.27 (C-1a^{s+a}); 134.33 (C-14$^{s/a}$); 134.27 (C-14$^{s/a}$); 129.94 (C-17$^{s/a}$); 129.68 (C-17$^{s/a}$); 128.85 (C-15, C-19$^{s/a}$); 128.77 (C-15, C-19$^{s/a}$); 126.97 (C-16, C-18$^{s/a}$); 126.71 (C-16, C-18$^{s/a}$); 125.09 (C-7$^{s/a}$); 125.00 (C-7$^{s/a}$); 123.62 (C-4a^{s+a}); 122.82 (C-5a^{s+a}); 120.58 (C-4$^{s/a}$); 120.53 (C-4$^{s/a}$) 120.43 (C-6$^{s/a}$); 120.20 (C-6$^{s/a}$); 119.67 (C-5$^{s/a}$); 119.59 (C-5$^{s/a}$); 119.11 (C-3$^{s/a}$); 118.80 (C-3$^{s/a}$); 112.35 (C-8$^{s/a}$); 112.29 (C-8$^{s/a}$); 109.83 (C-1$^{s/a}$); 109.64 (C-1$^{s/a}$); 44.47 (C-10$^{s/a}$); 41.15 (C-10$^{s/a}$); 18.93 (C-11^{s+a}).

In carbon spectra, due to the presence of *sin*/*anti* stereoisomerism, it can be noticed the doubling of the signals excepting C-1a, C-2, C-4a, C-5a and C-11 respectively.

By heating compound **1a** at 110°C for 24 hours, the *sin-anti* molar ratio does not change, indicating that the rotation barrier is greater than 25 kcal/mol.

The substance is not soluble in deuterated chloroform, but by the addition of TFA, a clear solution is obtained in which the molar ratio (determined from the CH and

CH_3 signal area) *sin*/*anti* becomes 1:4. Isomerisation is likely to occur under the catalytic influence of TFA; the compound decomposes by heating at 60°C.

FT-IR (ATR in solid, ν cm^{-1}): 3267m; 3193m; 3047m; 2973w; 1656s; 1638vs; 1606m; 1560s; 1472m; 1449s; 1376w; 1358m; 1321w; 1273m; 1249m; 1221m; 1198s; 1068m; 1006w; 950w; 922w; 877w; 860w; 822w; 809m; 761m; 738m; 695m; 607m.

*(EZ)-N'-(4-isopropylbenzylidene)-(2RS)-2-(6-chloro-9H-carbazol-2-yl)propanehydrazide (**1b**)* (M_r = 417.827 g/mol; m.p. 252 - 259ºC; yield 69.4%)

[1] H-NMR (300 MHz, DMSO-d6, δ ppm, *J* Hz): 11.57 (s, H-9$^{s/a}$); 11.42(s, H-9$^{s/a}$); 11.37 (s, HN$^{s/a}$); 11.25 (s, HN$^{s/a}$); 8.14 (s, H-13$^{s/a}$); 7.87 (s, H-13$^{s/a}$); 8.16 (d, H-5 $^{s/a}$, 1.8); 8.12 (d, H-5$^{s/a}$, 1.8); 8.08 (d, H-4$^{s/a}$, 8.1); 8.05 (d, H-4$^{s/a}$, 8.1); 7.57 (d, H-15$^{s/a}$, H-19$^{s/a}$, 8.2); 7.56 (d, H-15$^{s/a}$, H-19$^{s/a}$, 8.2); 7.50 ÷ 7.43 (m, 2H, H-1, H-8 $^{s+a}$); 7.36 (dd, 1H, H-7$^{s/a}$, 1.8, 8.2); 7.32 (dd, 1H, H-7$^{a/s}$, 1.8, 8.2); 7.29 (d, 2H, H-16$^{s/a}$, H-18$^{s/a}$, 8.2); 7.26 (d, 2H, H-16$^{s/a}$, H-18$^{s/a}$, 8.2); 7.19 (m, 1H, H-3^{s+a}); 4.80 (q, H-10 $^{s/a}$, 7.0); 3.83 (q, H-10 $^{s/a}$, 7.0); 2.88 (spt, 1H, H-20$^{s/a}$); 2.87 (spt, 1H, H-20$^{s/a}$); 1.48 (d, H-11 $^{s/a}$, 7.0); 1.45 (d, H-11 $^{s/a}$, 7.0); 1.19 (d, 6H, H-21$^{s/a}$); 1.18 (d, 6H, H-21$^{s/a}$).

[13]C-NMR (75 MHz, dmso-d6, δ ppm): 175.15 (C-12$^{s/a}$); 170.00 (C-12$^{s/a}$); 150.70 (C-17$^{a/s}$); 150.37 (C-17$^{a/s}$); 146.76 (C-13$^{s/a}$); 142.78 (C-13$^{s/a}$); 140.64 (C-8a$^{s/a}$); 140.18 (C-8a$^{s/a}$); 138.42 (C-2^{s+a}); 138.34 (C-1a^{s+a}); 132.08 (C-14$^{s/a}$); 131.96 (C-14$^{s/a}$); 127.21 (C-15, C-19$^{s/a}$); 126.90 (C-15, C-19$^{s/a}$); 126.88 (C-16, C-18^{s+a}); 125.23 (C-7$^{s/a}$); 125.14 (C-7$^{s/a}$); 123.70 (C-4a^{s+a}); 122.97 (C-5a$^{s/a}$); 122.91 (C-5a$^{s/a}$); 120.43 (C-6$^{s/a}$); 120.29 (C-6$^{s/a}$); 120.71 (C-4$^{s/a}$); 120.65 (C-4$^{s/a}$); 119.76 (C-5$^{s/a}$); 119.68 (C-5$^{s/a}$); 119.27 (C-3$^{s/a}$); 118.95 (C-3$^{s/a}$); 112.49 (C-8$^{s/a}$); 112.43 (C-8$^{s/a}$); 109.90 (C-1$^{s/a}$); 109.73 (C-1$^{s/a}$); 44.60 (C-10$^{s/a}$); 41.33 (C-10$^{s/a}$); 33.53 (C-20^{s+a}); 23.85 (C-21^{s+a}); 19.07 (C-11^{s+a}).

FT-IR (ATR in solid, ν cm^{-1}): 3357m; 3186m; 3038w; 2928w; 2869w; 1670m; 1643vs; 1604m; 1549s; 1504w; 1463m; 1449s; 1361w; 1306w; 1271w; 1237m; 1200m; 1063m; 1001w; 960w; 872w; 829w; 800w; 732w; 679w; 618w.

*(EZ)-N'-(2-fluorobenzylidene)-(2RS)-2-(6-chloro-9H-carbazol-2-yl)propanehydrazide (**1c**)* (M_r= 393,837 g/mol; m.p. 220 - 227ºC; yield 63,5%)

[1] H-NMR (500 MHz, DMSO-d6, δ ppm, *J* Hz): 11.70 (s, H-9$^{s/a}$); 11.41 (s, H-9$^{s/a}$); 11.38 (s, HN$^{s/a}$); 11.34 (s, HN$^{s/a}$); 8.44 (s, H-13$^{s/a}$); 8.13 (s, H-13$^{s/a}$); 8.17 (d, H-5$^{s/a}$, 1.9); 8.13 (d, H-5$^{s/a}$, 1.9); 8.10 (d, H-4$^{s/a}$, 8.1); 8.06 (d, H-4$^{s/a}$, 8.1); 7.94 (td, H-19$^{s/a}$, *J* (F-H^{19}) = *J* (H^{19}-H^{18}) = 7.7, 1.5); 7.85 (td, H-19$^{s/a}$, *J* (F-H^{19}) = *J* (H^{19}-H^{18}) = 7.7, 1.5); 7.49 (d, H-1$^{s/a}$, 1.6); 7.47 (d, H-1$^{s/a}$, 1.6); 7.48 (d, H-8$^{s/a}$, 8.6); 7.45 (d, H-8$^{s/a}$, 8.6); 7.44 (m, 1H, H-17^{s+a}); 7.36 (dd, H-7$^{s/a}$, 1.9, 8.6); 7.33 (dd, H-7$^{s/a}$, 1.9, 8.6); 7.25 (t, 1H, H-16^{s+a}, *J* (F-H^{16}) = *J* (H^{16}-H^{17}) = 8.6); 7.30 (t, H-18$^{s/a}$, 8.6); 7.24 (t, H-18$^{s/a}$, 8.6); 7.20 (dd, H-3$^{s/a}$, 1.6, 8.1); 7.19 (dd, H-3$^{s/a}$, 1.6, 8.1); 4.82 (q, H-10$^{s/a}$, 7.0); 3.85 (q, H-10$^{s/a}$, 7.0); 1.49 (d, H-11$^{s/a}$, 7.0); 1.48 (d, H-11$^{s/a}$, 7.0).

[13] C-NMR (125 MHz, DMSO-d6, δ ppm): 175.22 (C-12$^{s/a}$); 169.97 (C-12$^{s/a}$); 160.67 (d, C-15$^{s/a}$, *J* (F-C^{15}) = 248.3 Hz); 160.57 (d, C-15$^{s/a}$, *J* (F-C^{15}) = 248.3 Hz); 140.57 (C-8a$^{s/a}$); 140.44 (C-8a$^{s/a}$); 139.92 (C-1a^{s+a}); 139.23 (d, C-13$^{s/a}$, *J* (F-C-13$^{s/a}$) = 4.5 Hz); 138.34 (C-2$^{s/a}$); 138.27 (C-2$^{s/a}$); 135.40 (d, C-13$^{s/a}$, *J* (F-C^{13}) = 4.5 Hz); 131.85 (d, C-17$^{s/a}$, *J* (F-C^{17}) = 9.0 Hz); 131.53 (d, C-17$^{s/a}$, *J* (F-C^{17}) = 9.0 Hz); 126.19 (C-19^{s+a}, *J* (F-C^{19}) = 7.5 Hz); 125.10 (C-7$^{s/a}$); 125.01 (C-7$^{s/a}$); 124.92 (d, C-18$^{s/a}$, *J* (F-C^{18}) = 2.6 Hz); 124.89 (d, C-18$^{s/a}$, *J* (F-C^{18}) = 2.6 Hz); 123.60 (C-4a^{s+a}); 122.86 (C-5a^{s+a}); 121.85 (d, C-14$^{s/a}$, *J* (F-C^{14}) = 10.0 Hz); 121.70 (d, C-14$^{s/a}$, *J* (F-C^{14}) = 10.0 Hz); 120.61 (C-6$^{s/a}$); 120.55 (C-6$^{s/a}$); 120.54 (C-4$^{s/a}$); 120.47 (C-4$^{s/a}$); 119.66 (C-5$^{s/a}$); 119.58 (C-5$^{s/a}$); 119.08 (C-3$^{s/a}$); 118.76 (C-3$^{s/a}$ 115.98 (d, C-16$^{s/a}$, *J* (F-C^{16}) = 21.0 Hz); 115.94 (d, C-16$^{s/a}$, *J* (F-C^{16}) = 21.0 Hz); 112.35 (C-8$^{s/a}$); 112.28 (C-8$^{s/a}$); 109.81 (C-1$^{s/a}$); 109.66 (C-1$^{s/a}$); 44.49 (C-10$^{s/a}$); 41.20 (C-10$^{s/a}$); 19.07 (C-11$^{s/a}$); 18.92 (C-11$^{s/a}$).

FT-IR (ATR in solid, ν cm^{-1}): 3337m; 3186w; 3023m; 2967w; 2912w; 1652s; 1637vs; 1615s; 1604s; 1576vs; 1455m; 1432s; 1365m; 1275m; 1241s; 1211m; 1182w; 1153w; 1086w; 1055m; 1016w; 954w; 864w; 802m; 754m; 733m; 697m; 626w.

*(EZ)-N'-(3-fluorobenzylidene)-(2RS)-2-(6-chloro-9H-carbazol-2-yl)propanehydrazide (**1d**)* (M_r = 393.837 g/mol; m.p. 241 - 247ºC; yield 68.5%)

[1] H-NMR (300 MHz, DMSO-d6, δ ppm, *J* Hz): 11.66 (s, H-9$^{s/a}$); 11.40 (s, H-9$^{s/a}$); 11.38 (s, HN$^{s/a}$); 11.33 (s, HN$^{s/a}$); 8.21 (s, H-13$^{s/a}$); 7.91 (s, H-13$^{s/a}$); 8.17 (d, H-5$^{s/a}$, 1.9); 8.13 (d, H-5$^{s/a}$, 1.9); 8.10 (d, H-4$^{s/a}$, 8.1); 8.06 (d, H-4$^{s/a}$, 8.1); 7.43 ÷ 7.51 (m, 5H, H-1, H-8, H-15, H-18, H-19^{s+a}); 7.35 (dd, H-7$^{s/a}$, 1.9, 8.6); 7.33 (dd, H-7$^{s/a}$, 1.9, 8.6); 7.22 ÷ 7.25 (m, 1H, H-17^{s+a}); 7.20 (dd, H-3$^{s/a}$, 1.6, 8.1); 7.19 (dd, H-3$^{s/a}$, 1.6, 8.1); 4.83 (q, H-10$^{s/a}$, 7.0); 3.87 (q, H-10$^{s/a}$, 7.0); 1.49 (d, H-11$^{s/a}$, 7.0); 1.48 (d, H-11$^{s/a}$, 7.0).

[13] C-NMR (75 MHz, DMSO-d6, δ ppm): 175.31 (C-12$^{s/a}$); 170.09 (C-12$^{s/a}$); 162.44 (d, C-16$^{s/a}$, *J* (F-C^{15}) = 242.1 Hz); 160.57 (d, C-16$^{s/a}$, *J* (F-C^{15}) = 242.1 Hz); 145.21 (d, C-13^{s+a}, *J* (F-C^{13}) = 2.6 Hz); 141.19 (d, C-13^{s+a}, *J* (F-C^{13}) = 2.6 Hz); 140.59 (C-8a$^{s/a}$); 140.58 (C-8a$^{s/a}$); 139.99 (C-1a^{s+a}); 138.35 (C-2$^{s/a}$); 138.28 (C-2$^{s/a}$); 136.91 (d, C-14$^{s/a}$, *J* (F-C^{14}) = 9.0 Hz); 136.88 (d, C-14$^{s/a}$, *J* (F-C^{14}) = 9.0 Hz); 130.88 (d, C-19$^{s/a}$, *J* (F-C^{19}) = 8.6 Hz); 130.84 (d, C-19$^{s/a}$, *J* (F-C^{19}) = 8.6 Hz); 125.11 (C-7$^{s/a}$); 125.01 (C-7$^{s/a}$); 123.62 (C-4a^{s+a}); 123.25 (d, C-18 $^{s/a}$, *J*(F-C^{18}) = 7.8 Hz); 123.22 (d, C-18$^{s/a}$, *J* (F-C^{18}) = 7.8 Hz); 122.87 (C-5a^{s+a}); 122.81 (C-6$^{s/a}$); 122.22 (C-6$^{s/a}$); 120.60 (C-4$^{s/a}$); 120.56 (C-4$^{s/a}$); 119.66 (C-5$^{s/a}$); 119.59 (C-5$^{s/a}$); 119.09 (C-3$^{s/a}$); 118.80 (C-3$^{s/a}$); 116.68 (d, C-17$^{s/a}$, *J* (F-C^{17}) = 19.4 Hz); 116.40 (d, C-17$^{s/a}$, *J* (F-C^{17}) = 19.4 Hz); 112.98 (d, C-15$^{s/a}$, *J* (F-C^{15}) = 22.4 Hz); 112.61 (d, C-15$^{s/a}$, *J* (F-C^{15}) = 22.4 Hz); 112.36 (C-8$^{s/a}$); 112.29 (C-8$^{s/a}$);

109.74 (C-1$^{s/a}$); 109.66 (C-1$^{s/a}$); 44.49 (C-10$^{s/a}$); 41.20 (C-10$^{s/a}$); 19.01 (C-11$^{s/a}$); 18.92 (C-11$^{s/a}$).

FT-IR (ATR in solid, ν cm^{-1}): 3334m; 3198w; 3024m; 2968w; 2910w; 1654s; 1638vs; 1608m; 1576vs; 1474m; 1451s; 1375w; 1350m; 1270m; 1243m; 1209s; 1139w; 1096w; 1070m; 1056sh; 1015w; 977w; 956w; 936w; 921w; 871w; 820w; 805w; 790m; 733w; 717w; 684w.

*(EZ)-N'-(4-fluorobenzylidene)-(2RS)-2-(6-chloro-9H-carbazol-2-yl)propanehydrazide (**1e**)* (M_r = 393.837 g/mol): m.p. 239 - 245ºC; yield 65.9%)

^{1} H-NMR (500 MHz, DMSO-d6, δ ppm, *J* Hz): 11.56 (s, H-9$^{s/a}$); 11.37 (s, H-9$^{s/a}$); 11.33 (s, HN$^{s/a}$); 11.29 (s, HN$^{s/a}$); 8.20 (s, H-13$^{s/a}$); 8.16 (d, H-5$^{s/a}$, 1.6); 8.13 (d, H-5$^{s/a}$, 1.6); 8.09 (d, H-4$^{s/a}$, 8.1); 8.05 (d, H-4$^{s/a}$, 8.1); 7.91 (s, H-13$^{s/a}$); 7.75 - 7.69 (m, 2H, H-15^{s+a}, H-19^{s+a}); 7.49 (d, H-1$^{s/a}$, 1.6); 7.47 (d, H-1$^{s/a}$, 1.6); 7.48 (d, H-8$^{s/a}$, 8.6); 7.45 (d, H-8$^{s/a}$, 8.6); 7.35 (dd, H-7$^{s/a}$, 1.9, 8.6); 7.33 (dd, H-7 $^{s/a}$, 1.9, 8.6); 7.23 ÷ 7.28 (m, 2H, H-16^{s+a}, H-18^{s+a}); 7.20 (dd, H-3$^{s/a}$, 1.6, 8.1); 7.19 (dd, H-3$^{s/a}$, 1.6, 8.1); 4.82 (q, H-10$^{s/a}$, 7.0); 3.86 (q, H-10$^{s/a}$, 7.0); 1.49 (d, H-11$^{s/a}$, 7.0); 1.48 (d, H-11$^{s/a}$, 7.0).

^{13} C-NMR (125 MHz, DMSO-d6, δ ppm): 175.11 (C-12$^{s/a}$); 169.91 (C-12$^{s/a}$); 163.02 (d, C-17$^{s/a}$, *J* (F-C^{17}) = 246.8 Hz); 162.83 (d, C-17$^{s/a}$, *J* (F-C^{17}) = 246.8 Hz); 145.45 (C-13$^{s/a}$); 141.39 (C-13$^{s/a}$); 140.56 (C-8a$^{s/a}$); 140.07 (C-8a$^{s/a}$); 138.33 (C-1a^{s+a}); 138.26 (C-2^{s+a}); 130.95 (d, C-14$^{s/a}$, *J* (F-C^{14}) = 3.0 Hz); 130.88 (d, C-14$^{s/a}$, *J* (F-C^{14}) = 3.0 Hz); 129.11 (d, C-15$^{s/a}$, C-19 $^{s/a}$, *J* (F-C$^{15/19}$) = 9.0 Hz); 128.79 (d, C-15$^{s/a}$, C-19$^{s/a}$, *J* (F-C$^{15/19}$) = 9.0 Hz); 125.07 (C-7$^{s/a}$); 124.99 (C-7$^{s/a}$); 123.61 (C-5a^{s+a}); 122.84 (C-4a$^{s/a}$); 122.78 (C-4$^{s/a}$); 120.56 (C-4$^{s/a}$); 120.51 (C-4$^{s/a}$); 120.42 (C-6$^{s/a}$); 120.20 (C-6$^{s/a}$); 119.64 (C-5$^{s/a}$); 119.56 (C-5$^{s/a}$); 119.10 (C-3$^{s/a}$); 118.78 (C-3$^{s/a}$); 115.86 (d, C-16$^{s/a}$, C-18$^{s/a}$, *J* (F-C$^{16/18}$) = 22.3 Hz); 115.82 (d, C-16$^{s/a}$, C-18$^{s/a}$, *J* (F-C$^{16/18}$) = 22.3 Hz); 112.33 (C-8$^{s/a}$); 112.28 (C-8$^{s/a}$); 109.82 (C-1$^{s/a}$); 109.63 (C-1$^{s/a}$); 44.45 (C-10$^{s/a}$); 41.13 (C-10$^{s/a}$); 18.91 (C-11^{s+a}).

FT-IR (ATR in solid, ν cm^{-1}): 3245m; 3215m; 3051w; 1641vs; 1603s; 1556s; 1507s; 1472m; 1450m; 1429w; 1346w; 1274m; 1235s; 1198s; 1155w; 1068m; 1009w; 953w; 937w; 864w; 836m; 809m; 738w; 701w.

*(EZ)-N'-(2-chlorobenzylidene)-(2RS)-2-(6-chloro-9H-carbazol-2-yl)propanehydrazide (**1f**)* (M_r = 410.29 g/mol; m.p. 268 - 271ºC; yield 70.73%)

^{1} H-NMR (300 MHz, DMSO-d6, δ ppm, *J* Hz): 11.80 (s, H-9$^{s/a}$); 11.49 (s, H-9$^{s/a}$); 11.39 (s, HN$^{s/a}$); 11.34 (s, HN $^{s/a}$); 8.59 (s, H-13$^{s/a}$); 8.30 (s, H-13$^{s/a}$); 8.16 (d, H-5$^{s/a}$, 1.6); 8.13 (d, H-5$^{s/a}$, 1.6); 8.10 (d, H-4$^{s/a}$, 8.1); 8.06 (d, H-4$^{s/a}$, 8.1); 7.99 (dd, H-19$^{s/a}$, 2.3, 7.9); 7.92 (dd, H-19$^{s/a}$, 2.3, 7.9); 7.62 ÷ 7.31 (m, 6H, H-1, H-7, H-8, H-16, H-17, H-18^{s+a}); 7.19 (dd, H-3^{s+a}, 1.3, 8.1); 4.82 (q, H-10$^{s/a}$, 7.0); 3.85 (q, H-10$^{s/a}$, 7.0); 1.49 (d, H-11$^{s/a}$, 7.0); 1.47 (d, H-11$^{s/a}$, 7.0).

^{13} C-NMR (75 MHz, DMSO-d6, δ ppm): 175.30 (C-12$^{s/a}$); 175.19 (C-15$^{s/a}$); 170.10 (C-12$^{s/a}$); 170.00 (C-15$^{s/a}$); 142.42 (C-13$^{s/a}$); 138.62 (C-13$^{s/a}$); 140.59 (C-8a$^{s/a}$); 139.91 (C-8a$^{s/a}$); 140.45 (C-1a^{s+a}); 138.29 (C-2$^{s/a}$); 138.14 (C-2$^{s/a}$); 133.05 (C-14$^{s/a}$); 132.85 (C-14$^{s/a}$); 131.46 (C-17$^{s/a}$); 131.12 (C-17$^{s/a}$); 128.23 (C-18$^{s/a}$); 127.79 (C-18$^{s/a}$); 127.73 (C-16$^{s/a}$); 127.61 (C-16$^{s/a}$); 126.79 (C-19$^{s/a}$); 126.64 (C-19$^{s/a}$); 125.14 (C-7$^{s/a}$); 125.05 (C-7$^{s/a}$); 123.62 (C-5a$^{s/a}$); 123.58 (C-5a$^{s/a}$); 122.89 (C-4a$^{s/a}$); 122.83 (C-4a$^{s/a}$); 120.47 (C-6$^{s/a}$); 120.25 (C-6$^{s/a}$); 120.66 (C-4$^{s/a}$); 120.60 (C-4$^{s/a}$); 119.69 (C-3$^{s/a}$); 119.61 (C-3$^{s/a}$); 119.07 (C-5$^{s/a}$); 118.79 (C-5$^{s/a}$); 112.32 (C-8$^{s/a}$); 112.26 (C-8$^{s/a}$); 109.76 (C-1$^{s/a}$); 109.64 (C-1$^{s/a}$); 44.61 (C-10$^{s/a}$); 41.25 (C-10$^{s/a}$); 18.97 (C-11$^{s/a}$); 18.91 (C-11$^{s/a}$).

FT-IR (ATR in solid, ν cm^{-1}): 3255m; 3204m; 3060m; 2972w; 2933w; 1640vs; 1603s; 1555vs; 1503w; 1469s; 1445s; 1376w; 1357m; 1316m; 1269m; 1247m; 1220m; 1199s; 1067m; 1049m; 1004w; 951w; 924w; 862w; 826w; 803m; 748m; 736m; 698w; 670w.

*(EZ)-N'-(3-chlorobenzylidene)-(2RS)-2-(6-chloro-9H-carbazol-2-yl)propanehydrazide (**1g**)* (M_r = 410.29 g/mol): m.p. 249 - 255ºC; yield 80.5%)

^{1} H-NMR (300 MHz, DMSO-d6, δ ppm, *J* Hz): 11.69 (s, H-9$^{s/a}$); 11.40 (s, H-9$^{s/a}$); 11.38 (s, HN$^{s/a}$); 11.33 (s, HN$^{s/a}$); 8.18 (s, H-13$^{s/a}$); 8.17 (d, H-5$^{s/a}$, 1.6); 8.13 (d, H-5$^{s/a}$, 1.6); 8.08 (d, H-4$^{s/a}$, 8.1); 8.06 (d, H-4$^{s/a}$, 8.1); 7.88 (s, H-13$^{s/a}$); 7.70 (bs, 1H, H-15$^{s/a}$); 7.68 (bs, 1H, H-15$^{s/a}$); 7.64 ÷ 7.60 (m, H-19^{s+a}); 7.49 ÷ 7.31 (m, 5H, H-1, H-7, H-8, H-17, H-18^{s+a}); 7.21 (m, 1H, H-3^{s+a}); 4.81 (q, H-10$^{s/a}$, 7.0); 3.86 (q, H-10$^{s/a}$, 7.0); 1.49 (d, H-11$^{s/a}$, 7.0); 1.47 (d, H-11$^{s/a}$, 7.0).

The ratio of the E/Z diastereoisomers is equal, as shown by the H-10 and H-11 integrals. In the carbon spectrum, some signals are attributed to the E or Z isomers, suffering a dedoublation, indicating a discrimination of all of the E-R, E-S, Z-R and Z-S diastereoisomers.

^{13} C-NMR (75 MHz, DMSO-d6, δ ppm): 175.34 (C-12$^{s/a}$); 175.23 (C-12$^{s/a}$); 170.15 (C-12$^{s/a}$); 170.05 (C-12$^{s/a}$); 144.92 (C-13$^{s/a}$); 140.98 (C-13$^{s/a}$); 140.62 (C-8a$^{s/a}$); 140.44 (C-8a$^{s/a}$); 138.37 (C-1a^{s+a}); 138.30 (C-2^{s+a}); 136.58 (C-16^{s+a}); 133.68 (C-14$^{s/a}$); 133.60 (C-14$^{s/a}$); 130.72 (C-18^{s+a}); 129.60 (C-17$^{s/a}$); 129.34 (C-17$^{s/a}$); 126.30 (C-15$^{s/a}$); 126.11 (C-15$^{s/a}$); 125.63 (C-19$^{s/a}$); 125.37 (C-19$^{s/a}$); 125.14 (C-7$^{s/a}$); 125.04 (C-7$^{s/a}$); 123.63 (C-4a^{s+a}); 122.89 (C-5a^{s+a}); 120.48 (C-6$^{s/a}$); 120.24 (C-6$^{s/a}$); 120.58 (C-4^{s+a}); 119.69 (C-5$^{s/a}$); 119.62 (C-5$^{s/a}$); 119.15 (C-3$^{s/a}$); 118.82 (C-3$^{s/a}$); 112.33 (C-8^{s+a}); 109.67 (C-1^{s+a}); 44.49 (C-10$^{s/a}$); 41.28 (C-10$^{s/a}$); 19.01 (C-11$^{s/a}$); 18.94 (C-11$^{s/a}$).

FT-IR (ATR in solid, ν cm^{-1}): 3259s; 3212m; 3190m; 3053m; 2972w; 2898w; 1640vs; 1610m; 1559vs; 1470m; 1449m; 1429m; 1358m; 1346m; 1274m; 1247m; 1216m; 1196vs; 1069m; 1006w; 956m; 923w; 902w; 878w; 856w; 804m; 786m; 739m; 696m; 682m; 650w; 608m.

*(EZ)-N'-(4-trifluoromethylbenzylidene)-(2RS)-2-(6-chloro-9H-carbazol-2-yl)propanehydrazide (**1h**)* (M_r = 443.847 g/mol; m.p. 241 - 246ºC; yield 63.1%)

^{1} H-NMR (300 MHz, DMSO-d6, δ ppm, *J* Hz): 11.79 (s, H-9$^{s/a}$); 11.51 (s, H-9$^{s/a}$); 11.41 (s, HN$^{s/a}$); 11.36 (s,

HN$^{s/a}$); 8.28 (s, H-13$^{s/a}$); 8.18 (d, H-5$^{s/a}$, 1.9); 8.14 (d, H-5$^{s/a}$, 1.9); 8.11 (d, H-4$^{s/a}$, 8.2); 8.07 (d, H-4$^{s/a}$, 8.2); 7.98 (s, H-13$^{s/a}$); 7.91 (d, H-15$^{s/a}$, H-19$^{s/a}$, 8.1); 7.88 (d, H-15$^{s/a}$, H-19$^{s/a}$, 8.1); 7.80 (d, 2H, H-16$^{s/a}$, H-18$^{s/a}$, 8.1); 7.79 (d, 2H, H-16$^{s/a}$, H-18$^{s/a}$, 8.1); 7.52 ÷ 7.44 (m, 2H, H-1, H-8^{s+a}); 7.37 (dd, 1H, H-7$^{a/s}$, 1.9, 8.2); 7.34 (dd, 1H, H-7$^{a/s}$, 1.9, 8.2); 7.22 (bd, 1H, H-3$^{s/a}$, 8.2); 7.20 (bd, 1H, H-3$^{s/a}$, 8.2); 4.84 (q, H-10$^{s/a}$, 7.0); 3.89 (q, H-10 $^{s/a}$, 7.0); 1.51 (d, H-11$^{s/a}$, 7.0); 1.49 (d, H-11$^{s/a}$, 7.0).

At H-3, it can be observed the vicinal coupling with H-4, but the *meta* coupling is not visible, the line appears wider; for this reason is a broad doublet signal.

^{13} *C-NMR* (75 MHz, DMSO-d6, δ ppm): 175.50 (C-12$^{s/a}$); 170.40 (C-12$^{s/a}$); 145.01 (C-13$^{s/a}$); 141.03 (C-13$^{s/a}$); 140.64 (C-8a$^{s/a}$); 140.49 (C-8a$^{s/a}$); 139.96 (C-14$^{s/a}$); 138.43 (C-14$^{s/a}$); 138.35 (C-1a^{s+a}); 138.11 (C-2^{s+a}); 129.56 (q, C-17^{s+a}, *J* (3F-C^{17}) = 21.7 Hz); 127.67 (C-15, C-19$^{s/a}$); 127.38 (C-15, C-19$^{s/a}$); 125.79 (C-16, C-18^{s+a}); 125.26 (C-7$^{s/a}$); 125.18 (C-7$^{s/a}$); 123.98 (q, C-20^{s+a}, *J* (3F-C^{20}) = 272.1 Hz); 123.67 (C-4a^{s+a}); 123.00 (C-5a$^{s/a}$); 122.94 (C-5a$^{s/a}$); 120.59 (C-6$^{s/a}$); 120.34 (C-6$^{s/a}$); 120.78 (C-4$^{s/a}$); 120.72 (C-4$^{s/a}$); 119.77 (C-5$^{s/a}$); 119.68 (C-5$^{s/a}$); 119.17 (C-3$^{s/a}$); 118.93 (C-3$^{s/a}$); 112.50 (C-8$^{s/a}$); 112.44 (C-8$^{s/a}$); 109.99 (C-1$^{s/a}$); 109.76 (C-1$^{s/a}$); 44.65 (C-10$^{s/a}$); 41.48 (C-10$^{s/a}$); 19.05 (C-11^{s+a}).

FT-IR (ATR in solid, ν cm^{-1}): 3449w; 3416m; 3175w; 3019w; 2897w; 1660s; 1643vs; 1566m; 1469w; 1449w; 1421w; 1327vs; 1271w; 1232w; 1193m; 1133vs; 1102m; 1066s; 1014w; 947w; 861w; 831m; 796w; 728w.

(EZ)-N'-(4-phenoxybenzylidene)-(2RS)-2-(6-chloro-9H-carbazol-2-yl)propanehydrazide ***(1i)*** (M_r = 467.937 g/mol; m.p. 269 - 277ºC; yield 62%)

^{1} *H-NMR* (300 MHz, DMSO-d6, δ ppm, *J* Hz): 11.51 (s, H-9$^{s/a}$); 11.38 (s, H-9$^{s/a}$); 11.33 (s, HN$^{s/a}$); 11.24 (s, HN$^{s/a}$); 8.18 (s, H-13$^{s/a}$); 7.88 (s, H-13$^{s/a}$); 8.17 (d, H-5$^{s/a}$, 1.6); 8.13 (d, H-5$^{s/a}$, 1.6); 8.09 (d, H-4$^{s/a}$, 8.1); 8.05 (d, H-4$^{s/a}$, 8.1); 7.69 ÷ 7.65 (m, 2H, H-15, H-19^{s+a}); 7.49 ÷ 7.31 (m, 5H, H-1, H-7, H-8, H-22, H-24^{s+a}); 7.22 ÷ 7.16 (m, 2H, H-3, H-23^{s+a}); 7.13 ÷ 6.99 (m, 4H, H-16, H-18, H-21, H-25^{s+a}); 4.81 (q, H-10$^{s/a}$, 7.0); 3.84 (q, H-10$^{s/a}$, 7.0); 1.48 (d, H-11$^{s/a}$, 7.0); 1.46 (d, H-11$^{s/a}$, 7.0).

^{13} *C-NMR* (75 MHz, DMSO-d6, δ ppm): 175.04 (C-12$^{s/a}$); 174.93 (C-12$^{s/a}$); 169.84 (C-12$^{s/a}$); 169.74 (C-12$^{s/a}$); 158.47 (C-17$^{s/a}$); 158.19 (C-17$^{s/a}$); 155.89 (C-20$^{s/a}$); 155.76 (C-20$^{s/a}$); 145.99 (C-13$^{s/a}$); 141.93 (C-13$^{s/a}$); 140.65 (C-8a$^{s/a}$); 140.60 (C-8a$^{s/a}$); 140.44 (C-1a$^{s/a}$); 140.15 (C-1a$^{s/a}$); 138.37 (C-2$^{s/a}$); 138.28 (C-2$^{s/a}$); 138.22 (C-2$^{s/a}$); 138.13 (C-2$^{s/a}$); 130.38 (C-15$^{s/a}$, C-19$^{s/a}$); 130.25 (C-15$^{s/a}$, C-19$^{s/a}$); 129.86 (C-14$^{s/a}$); 129.71 (C-14$^{s/a}$); 128.89 (C-22$^{s/a}$, C-24$^{s/a}$); 128.58 (C-22$^{s/a}$, C-24$^{s/a}$); 125.13 (C-7$^{s/a}$); 125.03 (C-7$^{s/a}$); 123.64 (C-4a$^{s/a}$); 123.61 (C-4a$^{s/a}$); 122.89 (C-5a$^{s/a}$); 122.82 (C-5a$^{s/a}$); 120.60 (C-4$^{s/a}$); 120.56 (C-4$^{s/a}$); 119.61 (C-6$^{s/a}$); 119.53 (C-6$^{s/a}$); 119.68 (C-5^{s+a}); 119.65 (C-3$^{s/a}$); 119,59 (C-3$^{s/a}$); 119.45 (C-16, C-18$^{s/a}$); 119.35 (C-16, C-18$^{s/a}$); 119.12 (C-23$^{s/a}$); 118.84 (C-23$^{s/a}$); 118.38 (C-21, C-25$^{s/a}$); 118.21 (C-21, C-25$^{s/a}$); 112.37 (C-8$^{s/a}$); 112.34 (C-8$^{s/a}$); 112.28 (C-8$^{s/a}$); 112.24 (C-8$^{s/a}$); 109.89 (C-1$^{s/a}$); 109.87 (C-1$^{s/a}$); 109.64 (C-1$^{s/a}$); 109.60 (C-1$^{s/a}$); 44.46 (C-10$^{s/a}$); 41.21 (C-10$^{s/a}$); 18.94 (C-11^{s+a}).

FT-IR (ATR in solid, ν cm^{-1}): 3243m; 3047w; 2975w; 2895w; 1649m; 1638m; 1605m; 1586m; 1565m; 1503m; 1488s; 1452m; 1241vs; 1199m; 1162m; 1092w; 1069w; 874w; 822w; 742w; 689w.

Conclusions

Novel Schiff bases containing carprofen moiety were synthesized using microwave synthesis, a green chemical method, eco-friendly, simple, sensitive, reducing solvent amount and reaction time.

The reaction of (2*RS*)-2-(6-chloro-9*H*-carbazol-2-yl)propanehydrazide with different aldehydes in presence of methanol as a solvent and glacial acetic acid as catalyst, gave a novel series of Schiff bases, with lower yields than expected, despite using a method that is noticeable by increased reaction yields.

These compounds were characterized with the aid of spectral (FT-IR, ^{1}H NMR, and ^{13}C NMR) analysis.

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