Synthesis, characterization and antimicrobial properties of two derivatives of pyrrolidine-2,5-dione fused at positions-3,4 to a dibenzobarrelene backbone

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Abstract

Background : The present study describes for the first time, the synthesis of two pyrrolidine-2,5-dione derivatives that belong to N-arylsuccinimid (compound **5**) and of azo (compound **8**) class of molecules. The initial step of the reaction involved the preparation of the intermediate compound (9R, 10R, 11S)-9, 10-dihydro-9, 10-[3, 4] furanoanthracene-12, 14-dione (**3**) through [4 + 2]-cycloaddition between anthracene and maleic anhydride in xylene which was then condensed with *para*-hydroxyaniline to give compound **5**. Subsequent coupling of **5** with the aryldiazonium ion of aniline gave compound **8**.

Results: These compounds were characterized by their physical, elemental, and spectroscopic data. 2D-NMR (COSY, HSQC, and HMBC) techniques were used to complete the elucidation of their structures. Compounds **5** (MIC = 32–128µg/mL) and **8** (MIC = 16–256µg/mL) along with the precursor **3** (MIC = 64–128µg/mL) displayed moderate antimicrobial activities against selected bacterial and fungal species when compared with those of nystatin (MIC = 0.50–2µg/mL) and ciprofloxacin (MIC = 0.50–16µg/mL) used as reference drugs.

Conclusion: The results of biological tests showed that compounds **3**, **5**, **8** possess antimicrobial activities. Although being less active than the compound taken as a reference, the azo compound has better antibacterial activity than the other two compounds especially on *Staphylococcus aureus*, *V. cholerae*SG24 and, *V. cholerae*CO6 strains. These results show that the azo function (N = N) is indeed a pharmacophore and would be responsible for the biological activity in the azo molecules.

Introduction

Pyrrolidines, also known as azolidines, are the simplest compounds in the azolidine group. They are cyclic amines with four carbon atoms having the general formula C_4H_9N. Pyrrolidine derivatives known as succinimid are cyclic imides with five vertices; the simplest compound of this family is the succinimid of formula $C_4H_5NO_2$. The substitution of the nitrogen proton with aromatic groups yielded N-arylsuccinimid type compounds. Pyrrolidines and their derivatives (scheme 1) [7] are essential structural units of many important compounds useful in the pharmaceutical field because of they possess biological functions such as anti-microbial [1, 2], anti-tumor [3], anti-convulsant [4], anti-tubercular [5], and analgesic activities [6].

Another groups synthetic compounds containing Azo moieties have been found to possess biological functions similar in certain ways to those of N-arylsuccinimid (e.g. antimicrobial [8, 9], anti-inflammation [10], anti-oxidant [11]). In addition to these two groups of synthetic biological compounds, many natural molecules are biological active. Concerning natural products, phenols and polyphenols are been extending studied in various models and some their activities including antioxidants but also anti-tumor anti-inflammation and anti-microbial [12] [13] [14].

Antibiotics have been widely used in the past decade to treat a variety of infectious diseases that remain one of the leading causes of mortality and morbidity in the world. Nevertheless, the massive use of these antibiotics has led to the emergence of pathogens multi resistant to conventional antibiotics [15]. Such resistant pathogens include the case of methicillin resistant *Staphylococcus aureus*, vancomycin resistant *Enterococcus*; which sets the limits of the therapeutic treatments currently used [16]. One of the possible ways to fight the phenomenon of antibiotic resistance is the development of new molecules. Previous work on pyrrolidine derivatives and azo compounds show that these compounds are very important because of their multiple biological activities [17, 18, 19, 20, 21, 22]. Furthermore, Mkpenie and co-workers [23] recently found that the azo moiety (-N = N-) was a pharmacophores responsible for activities in azo compounds. The motivation of this work is that to the best of our knowledge, azo compounds having the nucleus of dibenzobarrelene have hitherto not been reported in the literature. Furthermore, in contrary to pyrrolidines, phenols and azo compounds, very few is known about the biological activity of dibenzobarrelene derivatives [24] (scheme 2).

Despite the individual biological function of N-arylsuccinimid, azo compounds and phenol molecules, synthesis strategies to incorporate them into a single molecule may be advantageous. That's why we combined in this work the pyrrolidine-2,5-dione, phenol, fragment of dibenzobarrelene and the azo bridge in a single molecular architecture, with the expectation to obtain an hybrid molecule with an improved antibacterial and antifungal activity on selected microorganisms.

Results And Discussion

Chemistry

The preparation of compound **5** was done by the following procedure: a Diels-Alder reaction between anthracene **1** and maleic anhydride **2** leads to compound **3** which was subsequently condensed with *para*nitroaniline **4** in acetic acid at reflux to give the desired compound **5** with yield of 92 % (scheme 3).

UV-visible spectrum shows that this compound **5** absorbs between 200 and 400 nm, the near UV range. This spectrum has several absorption bands; λ_{1max} = 250 nm, λ_{2max} = 355 nm, λ_{3max} = 395 nm corresponding respectively to the electronic transitions π-π* of chromophores C = C of benzene present in the base of dibenzobarrelene, of C = O and C = C of benzene present in succinimid. The high value of λ_{3max} is explained by the presence of auxochrome OH on benzene.

Its IR spectrum shows a characteristic broad absorption band around 3363 cm^{-1} attributable to the OH function of phenol. At 2973 cm^{-1}can also be observed a band corresponding to the valence = C-H bonds of the benzene ring; the absorption band at 1696 cm^{-1} is attributable to the carbonyls (C = O) of the amides. Those at 1600 cm^{-1} and 1562 cm^{-1} are attributable to the valence bonds C = C of the aromatic cycle. The C-N and C-O functions are characterized by the presence of the bands at 1273 cm^{-1} and at 1202 cm^{-1} respectively.

Its mass spectrum shows two peaks of pseudo molecular ions, one at 390 (100%) corresponding to $[M + Na]^+$ and the other at 757 (90 %) corresponding to $[2M + Na]^+$ from which the molar mass of the compound was deduced to be m/z: 367 corresponding to the raw formula $C_{24}H_{17}NO_3$. Its ^{1}HNMR spectrum shows, despite the symmetry, that the aromatic protons in dibenzobarrelene moiety are not equivalent due to the molecular arrangements [25]; so they have different signals. The doublet split at 7.32 (dd, 2H, J = 5.3 and 3.3 Hz) is assigned to the protons H-3, H-7 while that at 7.23 (dd, 2H, J = 5.4 and 3.3 Hz) is assigned to the protons H-2, H-6. The multiplet at 7.11 is attributed to the protons H-1, H-4, H-5, H-8. The singlet at 4.75 (s, 2H) is assigned to the benzylic protons H-9, H-10 and the other benzylic protons H-11, H-15 give a singlet at 3.25 (s, 2H). The benzylic protons H-9, H-10, H-11, H-15 were expected to give doublets, but rather give singlets due to the presence of a more electronegative phenyl group adjacent to each proton [25]. In the phenolic moiety, we have an AA'BB' proton system. The doublet at 6.62 (d, 2H, J = 8.8 Hz) is assigned to the proton H-2', H-6' and that at 6.17 (d, 2H, J = 8.8 Hz) is assigned to the protons H-3', H-5'. The low values of the chemical shifts of these benzenic protons are due to the mesomeric effect on the one hand of the OH group which shields in *ortho* position the protons H-3 ', H-5' and on the other hand the mesomeric effect of the nitrogen contained in the pyrrolidine cycle which also *ortho* shields the protons H-2', H-6'. The mesomeric effect of OH is greater than that of nitrogen, hence the strong shielding of the H-3', H-5' protons compared to those of H-2', H-6'. The COSY spectrum of this compound shows squares of correlation between the protons H-3 and H-4, H-2 and H-1, H-2'and H-3', H-9 and H-11. The ^{13}C NMR spectrum of compound **5** has thirteen signals instead of twenty four as in the molecular formula which confirm that there is symmetry in the molecule. Four signals are observed corresponding to quaternary carbons at 177.9 (C = O), 157.4 (C-OH), 141.2 (C = C), 138.8 (C = C) and 122.7 (C-N). There are also six signals attributable to protonated benzenic carbons at 127.6, 127.1, 126.8, 125.1, 124.3, 115.9 and two signals attributable to benzylic carbons at 46.9 and 45.8.

The synthesis of the azo compound was done in a two-step process including the diazotization of aniline (**6**) to form the diazonium ion **7** which then copulates with compound **5** to give the azo compound **8** with yield of 67 % (scheme 4).

The UV-visible spectrum of **8** showed a large band around λ_{max} = 385 nm corresponding to the electronic absorption of the chromophores of the system contain azo group. There is also an extension of the peak and an increase in the absorbance of this compound to more than 1.5 compared to that of the compound **5**; moreover the conjugation of the C = C chromophores of arylsuccinimid and aniline by the azo bridge -N = N- promotes the absorption of this compound beyond 400 nm, in the visible region. In its IR spectrum, characteristic absorption bands for phenol and = C-H of the benzene ring are present at 3367 and 3060 cm^{-1}, respectively. The absorption bands at 1768 cm^{-1} and at 1696 cm^{-1} are attributable to the carbonyls (C = O); the higher frequency band is allocated to symmetrical vibrations and the lowest frequency band is allocated to asymmetrical vibrations. The band at 1598 cm^{-1} is attributable to the valence bonds C = C of the aromatic cycle. The azo function (-N = N-) is confirmed by the presence of an absorption band at 1465 cm^{-1}. The C-N and C-O functions are characterized by the presence of the bands at 1274 cm^{-1} and at 1202 cm^{-1} respectively. The absorption at 764 cm^{-1} is attributable to the deformation of (C-H) aromatic.

On its mass spectrum in ESI^+ mode, we observed the pseudo molecular ions at 494 (100%) corresponding to $[M + Na]^+$ from which the molar mass of the compound was deduced to be m/z: 471 corresponding to the gross formula $C_{30}H_{21}N_3O_3$ (Scheme 5). The mass spectrum of compound **8** also contained fragments ions at 454 (20%) $[M^+$-OH], 394 (24%) $[M^+ -C_6H_5]$, 377 (18%) $[M^+$-OH $-C_6H_5]$, 311 (11%) $[M^+$-OH-C_6H_5-CO_2-C-N_2 + $H_2O]$, 278 (15%) $[M^+$-OH-$C_{14}H_{10}]$.

The ^{1} H NMR spectrum of compound **8** also exhibited as in compound **5** the aromatic protons of the dibenzobarrelene moiety respectively at 7.40 (dd, 2H, J = 5.3 and 3.2Hz), 7.32 (dd, 2H, J = 5.3 and 3.3Hz), 7.19 (m, 4H). The benzylic protons appeared at 4.75 (s, 2H) and 3.25 (s, 2H). The phenolic moiety presents three types of protons, two doublets and a singlet. The singlet at 6.98 is attributable to the proton H-6' whereas, the doublets at 6.68 (d, 2H, J = 8.1 Hz) and 6.18 (d, 2H, J = 8.2 Hz) are respectively attributed to the protons H-2' and H-3'. The protons of the aniline moiety H-2 ", H-3", H-4", H-5" and H-6" were exhibited between 7.45 and 7.35 (m, 5H) overlapping with the protons of the dibenzobarrelene nucleus. The ^{13}C NMR of this compound showed more than sixteen carbons instead of thirteen as in compound **5**; confirming therefore the above suggested substitution pattern. In addition to all the carbons present in compound **5**, there are new carbon signals at 160.7 attributable to the depleted carbon C-1" of aniline carrying the azo group; that at 130.8 attributable to carbon C-5' of the

phenolic fragment bearing the azo group. Furthermore, one can notice an overlapping of the signals due to carbons C-2", C-3", C-4 ", C-5", C-6"in the range 129.1-128.8.

DRX Analysis

The spectra of the X-ray diffraction analysis of compounds **5** and **8** are different from each other (Fig. 1). A large number of intense bands or peaks is observed on the spectrum of compound **5**, whereas on the spectrum of compound **8** the number of bands is reduced and the intensities of the latter are low. This suggests that succinimid 5 has a better crystal structure and is therefore more stable than the azo compound [26]. In addition, this stability of compound **5** suggests a better cohesion between atoms compare to the azo compound [26]. This weak cohesion of atoms in the azo compound may be due to presence of the azo bridge (-N = N-). The optimized 3D view of compound **8** is clearly presented in Fig. 2.

Biology

Antimicrobial Activity

The antimicrobial activities were evaluated on seven species of microorganisms including bacteria and yeasts and the data are summarized in Table 1. It appears from the results of these analyses that the activity of the compounds varies according to the nature of the microorganisms. Compounds **3**, **5**, **8** showed moderate antimicrobial activities respectively with MICs = (64–128) µg/mL, (32–128) µg/mL and (16–64) µg/mL on bacteria and 128 µg/mL, (64–128) µg/mL, (64–256) µg/mL on yeasts. It is noted that the introduction of the phenol fragment into compound **3** induced an increase in the activity of compound **5** in particular on *Staphylococcus aureus* and on *C. tropicalis* and *C. neoformans* and remains unchanged on the other microorganisms. Furthermore, the introduction of the azo function in compound **5** resulted into an increase of the activity of compound **8**, in particular on *Staphylococcus aureus*, *V. cholerae*SG24, *V. cholerae*CO6. The yeasts have shown a low sensitivity with respect to the azo compound, thus showing that this compound has much better antibacterial than antifungal activity on these types of microorganisms. All the compounds tested showed weak biological activities compared to the reference. The variations in the susceptibilities observed between the microorganisms and the compounds tested would be due to the differences in genetic constitutions that exist between the different microbial strains tested [27].

Table 1
Antimicrobial activity (MIC and MMC in µg/mL) of synthesized compounds as well as reference antimicrobial drugs.

Compounds	Inhibition parameters	*S. aureus*	*V. cholerae*NB2	*V. cholerae*SG24	*V. cholerae*CO6	*C. albicans*ATCC10231	*C. tropicalis* PK233	*C. neoformans* H99
8	MIC	16	64	32	64	256	128	64
	MMC	32	128	64	≥256	≥256	≥256	128
	MMC/MIC	2	2	2	/	/	/	2
5	MIC	32	64	64	128	128	64	64
	MMC	32	128	128	≥256	≥256	≥256	≥256
	MMC/MIC	1	2	2	/	/	/	/
3	MIC	64	64	64	128	128	128	128
	MMC	128	128	128	≥256	≥256	256	256
	MMC/MIC	2	2	2	/	/	2	2
Ref*	MIC	0.50	16	8	16	2	0.50	1
	MMC	0.50	16	8	16	2	0.50	1
	MMC/MIC	1	1	1	1	1	1	1

/: not determined; MIC: Minimum Inhibitory Concentration; MMC Minimum Microbicidal Concentration; *: nystatin for yeasts and ciprofloxacin for bacteria.

Materials And Methods

Instrumental method

All Melting points are corrected and were determined with a STUART SCIENTIFIC Melting Point Apparatus Model SMP3. The TLCs were carried out on Eastman Chromatogram Silica Gel Sheets (13181; 6060) with fluorescent indicator. A mixture of hexane and ethyl acetate (1:2) was used as eluent and iodine was used as revelator for the chromatograms. The IR spectra were measured with a Fourier Transform Infrared spectrometer Brucker Alpha. The UV spectra were recorded with a JENWAY 6715 UV-Vis Spectrophotometer. Combustion analyses were carried out with a C, H, N, and S Euro EA from Hekatech Company, their results were found to be in good agreement (± 0.3%) with the calculated values. XRD data was collected on a STOE Stadi-p X-ray powder diffractometer (STOE &Cie GmbH, Darmstadt, Germany) with Cu $K_{\alpha 1}$ radiation (λ = 1.54056 Å; Gemonochromator; flat samples) in transmission geometry with a DECTRIS® MYTHEN 1K detector (DECTRIS, Baden-Daettwil, Switzerland). HR-ESI-MS spectra were performed with a spectrometer (QTOF Bruker, Germany) equipped with a HR-ESI source. The spectrometer operates in positive ion mode (mass range: 100–1500, with a scan rate of 1.00) with automatic gain control to provide high-accuracy mass measurements within 0.40 ppm deviation using Na formate as calibrant.^{1}HNMR spectra and ^{13}C-NMR spectra were recorded in chloroform on a Bruker SF spectrometer operating respectively at 400 and 100 MHz; TMS was used as internal reference.

Synthesis of (9R, 10R, 11S)-9, 10-dihydro-9,10-[3, 4]*furanoanthracene-12,14-dione* (**3**)

4.92 g (27.76 mmol) of anthracene and 2.43 g (23.80 mmol) of maleic anhydride are refluxed for 40 min in 50 ml of xylene. The solution obtained is filtered hot and left to stand for about a day for gentle and gradual crystallization of the product.The latter is then filtered, dried and crystallized from xylene to give 6.30 g (83%) of white crystals; mp: 315°C (Lit. [25] 261–262°C from xylene).

Synthesis of (9R, 10R, 11S)-13-(4-hydroxyphenyl)-9,10-dihydro-9,10[3, 4]*epipyrrolo- anthracene-12,14-dione* (**5**)

4 g (0.0145 mol) of **3** are dissolved in 50 ml of acetic acid while hot. Excess *para* hydroxyaniline (4 g, 0.0367 mol) previously dissolved in 30 ml of acetic acid is added and the mixture is heated under reflux for 3 hours and then cooled to room temperature. The solution is filtered and washed with aqueous ethanol (50%) and dried to give 4.84 g of a gray-colored product **5**; mp: 337°C, yield 92%; ESI-MS: 390.11 (M + Na, 100%). UV-Vis: λ_{max} (DMSO): 250, 355, 395 nm. IR (potassium bromide): 3363 cm^{-1} (OH), 2973 (CH), 1696 (C = O), 1600 – 1562 (C_{Ar}=C_{Ar}), 1273 (C-N), 1202 (C-O), 764 (= C_{Ar}H) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 7.32 (dd, 2H, J = 5.3 and 3.3 Hz, H-3, H-7), 7. 23 (dd, 2H, J = 5.4 and 3.3 Hz, H-2, H-6), 7.11 (m, 4H, H- 1, H-4, H-5, H-8). 4.75 (s, 2H, H-9, H-10), 3.25 (s, 2H, H-11, H-15), 6.62 (d, 2H, J = 8.8 Hz, H-2', H-6'), 6.17 (d, 2H, J = 8.8 Hz, H-3', H-5'). ^{13}C (^{1}H)-NMR ($CDCl_3$) δ177.9 (C-12, C-14), 157.4 (C-4'), 141.2 (C-4a, C-8a), 138.8 (C-1a, C-5a), 122.7 (C-1'), 127.6 (C-3', C-5'), 127.1 (C-1, C-5), 126.8 (C-4, C-8), 125.1 (C-3, C-7), 124.3 (C-2, C-6), 115.9 (C-2', C-6'), 46.9 (C-11, C-15) and 45.8 (C-9, C-10). Anal. Calcd. for $C_{24}H_{17}NO_3$ (367.12): C, 78.56; H, 4.66; N, 3.8; found: C, 78.35; H, 4.83; N, 3.91.

Synthesis of (9R, 10R, 11S) -13-(4-hydroxy 3-(phenyldiazenyl) phenyl)-9,10-dihydro-9,10-[3, 4] *epipyrroloanthracene-12,14–dione* (**8**)

Preparation Of Diazonium Salt Solution

Dry sodium nitrite (1.38g, 2 mmol) was slowly added over a period of 30 minutes to concentrated sulphuric acid (5 mL) with occasional stirring. The solution was cooled to 0–5°C. 1g (1.07 mmol) of aniline (**6**) was dissolved in DMSO (5 mL) and cooled to 0–5°C. The nitrosyl sulphuric acid solution was added to the amine solutionand the temperature was maintained to 0–5°C.

Procedure For The Preparation Of The Coupling Product

Compound **5** (0.367 g, 1 mmol) was dissolved in DMSO (5 mL) and then cooled in an ice-bath at 0–5°C. The diazonium solution **7** previously prepared was added drop wise over 1 hour before neutralizing the sulfuric acid present with a 10 ml sodium acetate (10%) solution. 50 ml of ice-cold water was then added and the solution was filtered off after 30 minutes and rinsed with iced water. After crystallization from ethanol, 315 mg of compound **8** was obtained as brown powder; mp: 271°C, Yield 67%; ESI-MS: 494.22 (M + Na, 100%). UV-Vis: λ_{max} (DMSO) = 385 nm; IR (potassium bromide): 3367 cm^{-1} (OH), 3060 (CH), 1696 (C = O), 1598 (C_{Ar}=C_{Ar}), 1465 (-N = N-), 1274 (C-N), 1202 (C-O), 764 (= C_{Ar}H) cm^{-1}; ^{1}H-NMR($CDCl_3$) δ ppm : 7.40 (dd, 2H, J = 5.3 and 3.2Hz, H-3, H-7), 7.32 (dd, 2H, J = 5.3 and 3.3Hz, H-2, H-6), 7.19 (m, 4H, H-1, H-4, H-5, H-8), 4.75 (s, 2H, H-9, H-10), 3.25 (s, 2H, H-11, H-15), 6.98 (s, 1H, H-6'), 6.68 (d, 1H, J = 8.1, H-2'), 6.18 (d, 1H, J = 8.2, H-3'), 7.45–7.35 (m, 5H, H-2", H-3", H-4",H-5", H-6"). NMR ^{13}C ($CDCl_3$) δ ppm: 173.9, 160.7, 141.4, 138.8, 130.8, 128.8, 127.8, 127.2, 126.9, 125.2, 124, 122.9, 116.0, 47.0 and 46.1. Anal. Calcd. for $C_{30}H_{21}N_3O_3$ (471.16): C, 76.42; H, 4.49; N, 8.91; found: C, 76.12; H, 4.68; N, 8.68.

Antimicrobial Evaluation

Tested microorganisms

The antimicrobial activity was performed against four bacterial and three fungal species. The selected microorganisms were one Gram-positive *Staphylococcus aureus*ATCC25923, three Gram-negative *Vibrio cholerae*NB2, *V. cholerae*SG24 and *V. cholerae*CO6 and three yeast strains *Candida albicans* ATCC10231, *Candida tropicalis*PK233 and *Cryptococcus neoformans* H99. These microorganisms were taken from our

laboratory collection. The fungal and bacterial strains were grown at 37°C and maintained on Sabouraud Dextrose Agar (SDA, Conda, Madrid, Spain) and nutrient agar (NA, Conda) slants respectively.

Determination of Minimum Inhibitory Concentration (MIC) and Minimum Microbicidal Concentration (MMC)

The antibacterial and antifungal activity was evaluated by determining the MICs and MMCs as previously described [27]. MICs of synthesized compounds were determined by broth micro dilution. Each test sample was dissolved in dimethylsulfoxide (DMSO) to give a stock solution. This was serially diluted two-fold in Mueller-Hinton Broth (MHB) for bacteria and Sabouraud Dextrose Broth (SDB) for fungi to obtain concentration ranges of 512 to 0.25 µg/mL. Then, 100 µL of each sample concentration was added to respective wells (96-well micro plate) containing 90 µL of SDB/MHB and 10 µL of inoculum to give final concentration ranges of 256 to 0.125 µg/mL. The final concentrations of microbial suspensions were $2.5x10^5$ cells/mL for yeasts and 10^6 CFU/mL for bacteria. Dilutions of nystatin (Sigma-Aldrich, Steinheim, Germany) and ciprofloxacin (Sigma-Aldrich, Steinheim, Germany) were used as positive controls for yeasts and bacteria respectively. Broth with 10 µL of DMSO was used as negative control. MICs were assessed visually and were taken as the lowest sample concentration at which there was no growth or virtually no growth. The lowest concentration that yielded no growth after the sub-culturing was considered as the MMCs. All the tests were performed in triplicate [27].

Abbreviations

UV: ultra-violet; IR: infra-red; FTIR: Fourier-transform infrared spectroscopy; HRMS: High resolution mass spectroscopy; ^{1}H NMR: Proton nuclear magnetic resonance; ^{13}C NMR: Carbon nuclear magnetic resonance; µg: Microgram; °C: Degree centigrade; h: Hour; g: Gram; mg: Milligram; L: Liter; mL: Milliliter; µL: Microliter; MIC: Minimum Inhibitory Concentration; MMC Minimum Microbicidal Concentration; DMSO: Dimethylsulfoxide.

Declarations

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Authors' contributions

All authors equally contributed to the paper and have given approval to the final version of the paper. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

Availability of data and materials

All data generated or analyzed during this study are included in this published article and its supplementary material

Consent for publication

Not applicable.

Ethics approval and consent to participate

Not applicable.

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Figures

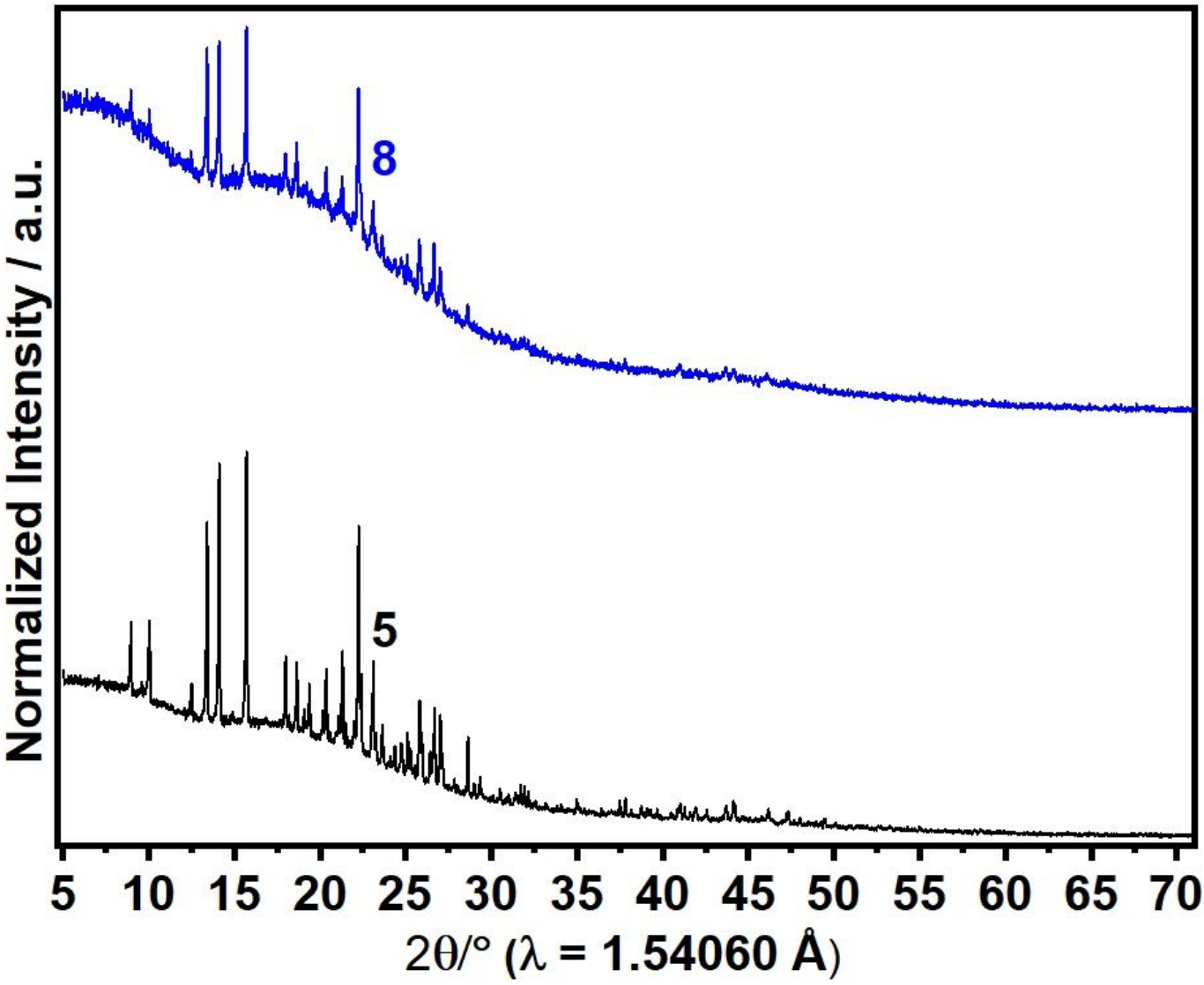

Figure 1

Ex situ PXRD pattern (Cu Kα1 radiation) of XRD of compound 5 and 8.

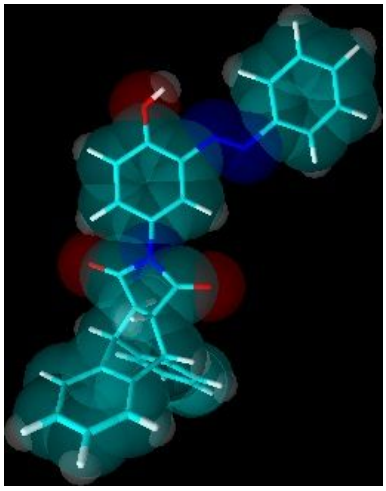

Figure 2

Optimized 3D view of compound 8. The structure was drawn with the program ACD/3D viewer (freeware) of ACD/Labs.

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