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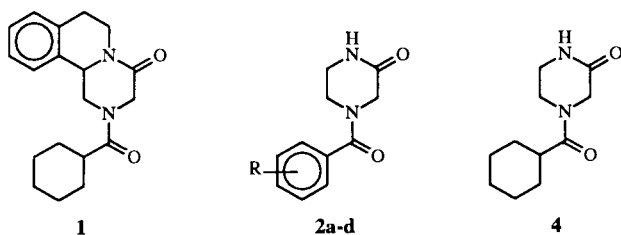
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The title compounds have been synthesized in a one step reaction by condensation between 2-piperazinone with substituted benzoic acids.

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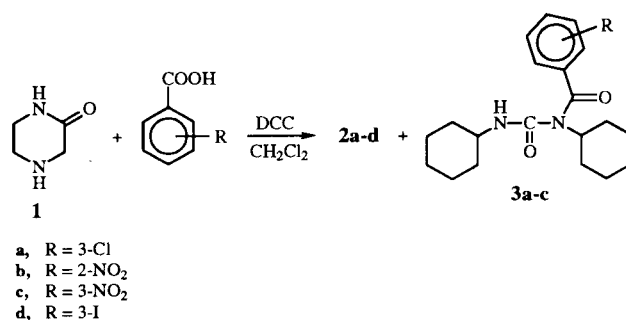
The antihelmintic compound called Praziquantel **1** has become the most successful drug for the treatment against cestodiasis disease caused by *Cysticercus cellulosae* [3]. Such a compound has provided great effectiveness as well as excellent tolerance under long-period treatments. Since its first total synthesis [4], improved approaches have been carried out for scale production [5]. This antihelmintic agent is introduced as a drug in the racemic form, however recent theoretical studies established evidence that the isomer presenting syn carbonyl configuration was responsible for the interaction with the active site of the parasite and therefore for the pharmacological effect [6]. Such evidence prompted us to prepare the praziquantel analogs 4-(2-,3- and 4-*R*)-Carboxyphenyl-1,4-pyrazin-2-ones **2a-d**.



Our synthetic approach consists in the condensation between 2-piperazinone **1** [7] with substituted benzoic acids with the aid of DCC as a condensing agent (Scheme I). The proposed mechanism involves nucleophilic attack of the carboxylic group of the substituted benzoic acids to the electrophilic carbon of DCC giving place to the intermediate *O*-acylisourea. Further reaction of this intermediate with 2-piperazinone **1** afforded acylation products **2a-d** or simultaneous *O*-acyl migration to the nitrogen to generate compounds **3a-c** [8].

Characterization of compounds **2a-d** by ^1H nmr in all cases showed proton signals both in aliphatic and aromatic regions indicating the fusion between the 2-piperazinone and the carboxyphenyl moiety. In addition in spectra showed characteristic absorption bands at 3048 cm^{-1} for amino and at 1681 and 1643 cm^{-1} for the two carbonyl

Scheme 1



present in the molecule one of which provines from 2-piperazinone and the other from the new amide linkage.

The unambiguous elucidation of the tridimensional structure and carbonyl syn configuration of this set of compounds was provided by X-ray diffraction resolution of derivative **2d**. Thus the crystal resolution showed the piperazinone rings adopting sofa conformation with C(5) 0.67 (1) Å, out of the plane formed by the rest of the ring (Figure 1). The carbonyl of the *m*-iodobenzoyl group forms an angle of 21.7° with the plane, while it is almost

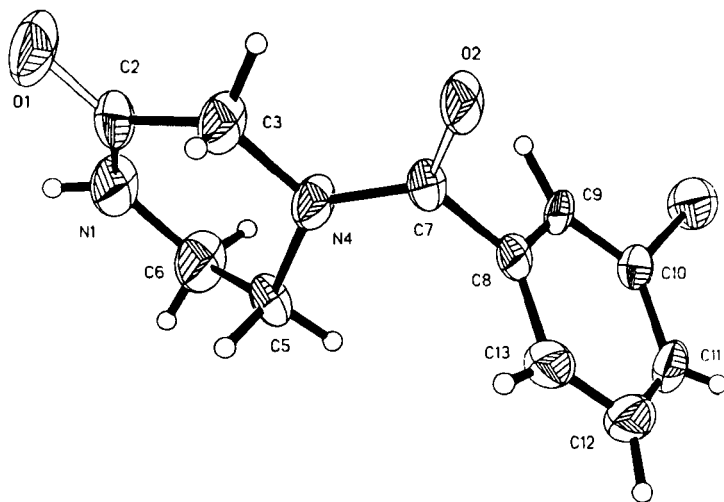


Figure 1. Tridimensional structure of derivative **2d**.

Table 1
Yields and Analytical Characterization of Compounds **2a-d** and **4**

No.	R	Mp (°C)	Yield (%)	Analysis (%)			IR (cm ⁻¹)	¹ H NMR (δ in ppm)	MS (EI 70 eV) m/z (%)
				Calcd./Found	C	H			
2a	3-Cl-	182-184	13	55.45	4.66	11.76	3408 (NH)	7.6 (N-H), 7.4-7.5 (4 H), 4.1 (2 H), 3.7 (2 H), 3.4 (2 H)	238, 139 (100)
				55.60	4.60	12.00	1681 (C=O) 1643 (C=O)		
2b	2-NO ₂ -	156-157	8	53.00	4.45	16.87	3409 (NH)	7.4-8.2 (4H), 7.8 (N-H), 3.5 (2 H), 3.4 (2 H), 3.3 (2 H).	249, 150 (100)
				53.31	4.41	16.52	1681 (C=O) 1653 (C=O)		
2c	3-NO ₂ -	170-171	29	53.00	4.45	16.87	3432 (NH)	7.6-8.4 (4 H), 7.7 (N-H), 3.6 (2 H), 3.4 (2 H), 3.3 (2 H)	249, 150 (100)
				53.31	4.41	16.52	1704 (C=O) 1649 (C=O)		
2d	3-I-	175-178	21	40.00	3.36	8.49	3408 (NH)	7.15-7.8 (4 H), 7.6 (N-H), 4.2 (2 H), 3.7 (2 H), 3.4 (2 H)	330, 231 (100)
				40.24	3.30	8.78	1680 (C=O) 1641 (C=O)		
4	-	193	30	62.82	8.63	13.33	3434 (NH)	6.6 (N-H), 3.3-4.5 (6 H), 1.0-2.5 (11 H)	210, 83 (100).
				63.01	8.59	13.81	1688 (C=O) 1650 (C=O)		

Table 2
Yields and Analytical Characterization of Compounds **3 a-c**

No.	R	Mp (°C)	Yield (%)	Analysis (%)			IR (cm ⁻¹)	MS (EI 70 eV) m/z
				Calcd./Found	C	H		
3a	3-Cl	175-177	31	66.19	7.50	7.72	3409 (NH)	362, 139 (100)
				66.31	7.45	7.91	1694 (C=O) 1643 (C=O)	
3b	2-NO ₂	147-148	11	64.32	7.29	11.25	3395 (NH)	373, 150 (100)
				64.52	7.25	11.72	1707 (C=O) 1654 (C=O)	
3c	4-NH ₂	175-177	69	64.32	7.29	11.25	3435 (NH)	343, 120 (100)
				64.52	7.25	11.72	1692 (C=O) 1622 (C=O)	

Table 3
Bond Lengths (Å)

I-C(10)	2.097(7)	N(1)-C(2)	1.33(1)
N(1)-C(6)	1.45(2)	C(2)-O(1)	1.23(1)
C(2)-C(3)	1.52(1)	C(3)-N(4)	1.47(1)
N(4)-C(5)	1.44(1)	N(4)-C(7)	1.335(9)
C(5)-C(6)	1.51(1)	C(7)-O(2)	1.22(1)
C(7)-C(8)	1.52(1)	C(8)-C(9)	1.390(9)
C(8)-C(13)	1.40(1)	C(9)-C(10)	1.38(1)
C(10)-C(11)	1.39(1)	C(11)-C(12)	1.38(1)
C(12)-C(13)	1.38(1)		

Bond Angles (degrees)

C(2)-N(1)-C(6)	124.0(8)	N(1)-C(2)-O(1)	123.0(8)
N(1)-C(2)-C(3)	119.9(9)	O(1)-C(2)-C(3)	117.2(8)
C(2)-C(3)-N(4)	112.6(8)	C(3)-N(4)-C(5)	116.0(7)
C(3)-N(4)-C(7)	118.0(7)	C(5)-N(4)-C(7)	124.7(8)
N(4)-C(5)-C(6)	107.9(9)	N(1)-C(6)-C(5)	112.0(10)
N(4)-C(7)-O(2)	122.0(8)	N(4)-C(7)-C(8)	118.9(7)
O(2)-C(7)-C(8)	119.0(6)	C(7)-C(8)-C(9)	116.9(6)
C(7)-C(8)-C(13)	122.0(6)	C(9)-C(8)-C(13)	121.0(8)
C(8)-C(9)-C(10)	118.2(7)	I-C(10)-C(9)	118.6(5)
I-C(10)-C(11)	119.7(6)	C(9)-C(10)-C(11)	121.6(7)
C(10)-C(11)-C(12)	119.3(9)	C(11)-C(12)-C(13)	120.5(8)
C(8)-C(13)-C(12)	119.3(7)		

perpendicular (87.4°) to the aromatic ring of the 3-iodo-phenyl group. As a result of this, both carbonyl groups retain a syn relation. These observations were in agreement with the data obtained for the crystal resolution of another praziquantel analog reported previously [9].

The side reaction products **3a-c** which were obtained according to the present methodology were characterized by ir and mass spectra (Table 2). Also by following the same synthetic pathway we were able to prepare 4-cyclohexyl-1,4-pyrazin-2-one **4** by condensation between 2-piperazinone **1** with cyclohexanecarboxylic acid. Pharmacological studies of praziquantel analogs **2a-d** and **4** are still in progress and will be published elsewhere.

EXPERIMENTAL

Melting points were determined in Fisher-Jones melting point apparatus and are uncorrected. The ir spectra were determined in Perkin-Elmer 283-B and Nicolet FT-5SX spectrometers. The ¹H nmr and ¹³C nmr were determined on Varian Gemini 200 and Varian VXR-300S spectrometers using tetramethylsilane as an internal standard, chemical shifts are expressed as δ (ppm values).

Column chromatography was carried out on a Merck silica gel 60F-254. Thin layer chromatography was taken on a Merck silica gel F254. X-ray diffraction of monocrystal was determined in a Nicolet R3m diffractometer. All the new compounds gave satisfactory elemental analysis.

Crystallography.

X-Ray Analysis Data for 4-(3-Iodo)carboxyphenyl-1,4-pyrazin-2-one **2d**.

Crystals were grown from hexane-dichloromethane, crystal size 0.14 x 0.18 x 0.24 mm, monoclinic, space group $P2_1/n$, $Z = 4$, $a = 12.555(2)$, $b = 7.650(1)$, $c = 12.771(1)$ Å, $\beta = 107.50(1)^\circ$, $D_x = 1.874$ g/cm³, $F(000) = 564$, μ (MoK α) = 26.93 cm⁻¹, Siemens R3m 4 circle diffractometer with MoK α radiation (graphite), $\theta/2\theta$ step scan mode, 2426 reflections measured [$I_o > 4\sigma(I)$]. The structure was solved by direct methods and refined with SHELXTL program [10]. Final R factors: ($R = \Sigma(|F_o| - |F_c|)/\Sigma|F_o|$) $R = 0.067$, ($R_w = \{\Sigma w(|F_o| - |F_c|)^2/\Sigma w|F_o|^2\}^{1/2}$) $R_w = 0.079$.

Reaction of 2-piperazinone with substituted benzoic acids.

General Method (R = 3-Cl).

Equimolar amounts of 3-chlorobenzoic acid (1 x 10⁻³ mole, 0.156 g) and 2-piperazinone **1** (1 x 10⁻³ mole, 0.1 g) were dissolved in 10 ml of methylene chloride at 0° with vigorous stirring. Addition of an equimolar amount of 1,3-dicyclohexylcarbodiimide (1 x 10⁻³ mole, 0.206 g) was accomplished and after 30 minutes the reaction was allowed to reach room temperature during 2-4 hours. Dicyclohexylurea was removed by filtration and the organic layer washed with water, dried over anhydrous sodium sulfate, filtered and concentrated under *vacuum* to afford a solid which was purified by column chromatography, using as eluents methylene chloride, increasing polarity with ethanol. Compound **3a** appears in the first

fractions mp 175-177°, 0.075 g (31%), while in the more polar fractions compound **2a** was obtained, mp 182-184°, 0.030 g, (13%). Analytical characterization is given in Tables 1 and 2.

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