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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



**No. 08-007227- -00006-0000**

Fecha: 2012-03-29 11:35:12 Dep. 2020 DIR.NUEVASCR  
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Act. 523 RESPUESTA Folios: 5

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Señor  
**JEFE DIVISIÓN DE NUEVAS CREACIONES**  
**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO**  
E. S. D.

**REF: EXPEDIENTE: 08-007227**

**TITULO: "MODULADORES DE LXR BASADOS EN  
IMIDAZOL"**

**ACTUACIÓN: RESPUESTA A SOLICITUD DE DOCUMENTOS**

**CARLOS ORLANDO MAYA RODRÍGUEZ**, mayor de edad, vecino de esta ciudad, identificado con la Cédula de Ciudadanía No.17.117.818 expedida en Bogotá, Abogado titulado en ejercicio y portador de la Tarjeta Profesional No. 17.402 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad EXELIXIS INC, Según poder debidamente conferido y legalizado, adjunto al expediente de la referencia.

Encontrándome dentro del término legal comparezco para responder el oficio de Requerimiento sobre SOLICITUD DE SUMINISTRO DE INFORMACIÓN, emanado de esa Oficina, con fundamento en el Artículo 46 de la Decisión 486 de 2.000 de C.A.N, damos respuesta en los siguientes términos.

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1.- Aportamos copia del documento solicitado en su petición de <sup>2</sup>  
Solicitud de Suministro de Información de "YANBORISOV ET AL...",  
asi:

- ("LV1-#1579620-v1-Yanborisov\_\_Pharmaceutical\_Chemistry\_ Journal\_ 1998\_  
32(9)\_480-482.pdf"

Por lo tanto, ruego a usted dar por subsanado dicho requerimiento, según el artículo 46 de la decisión 486 de la Comunidad Andina de Naciones y ordenar lo pertinente para que la solicitud pueda seguir su curso normal.

### NOTIFICACIONES

Mi poderdante y yo recibiremos notificaciones en la Secretaría de su Despacho o en mi Oficina de Abogado ubicada en la Carrera 13A No. 28-38 Ofc. 246 MZ. 2 Parque Central Bavaria de la ciudad de Bogotá D.C.

Del señor Jefe,

CARLOS ORLANDO MAYA RODRIGUEZ

No.17.117.818 expedida en Bogotá,

T.P No. 17.402 del C.S.J.

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in position 5 of the heterocycle (5.08 ppm), doublets of the enantiotopic protons of a methylene group in position 1 of the heterocycle (3.18 and 4.05 ppm, spin-spin coupling constant 18 Hz), and signals of aromatic protons in position 5 of the heterocycle, centered at 7.25 ppm.

## EXPERIMENTAL CHEMICAL PART

The IR absorption spectra of the synthesized compounds were recorded on a UR-20 spectrophotometer using samples prepared as nujol mulls. The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were measured on an RS-60 spectrometer operated at a working frequency of 60 MHz, using  $\text{DMSO}-d_6$  as the solvent and hexamethyldisiloxane as the internal standard.

The course of the reactions was monitored and the purity of the synthesized compounds was checked by TLC on Silufol UV-254 plates eluted in the ether-benzene-acetone (10:9:1) system. The spots of 5-aryl-4-acetyl-1-carboxyalkyltetrahydropyrrole-2,3-diones were developed in iodine vapors.

The data of elemental analyses agree with the results of analytical calculations according to the empirical formulas.

**General method of obtaining 1-substituted 5-aryl-4-acetyl-3-hydroxy-3-pyrrolin-2-ones (I-X).** To a mixture of 0.01 mole methyl ester of acylpyruvic acid and 0.01 mole aromatic aldehyde in 10 ml of ethyl alcohol was added 0.01 mole carboxy- or hydroxyalkylamine in 5 ml water. The mixture was heated until dissolution of the reagents and then allowed to stand for 12 h at room temperature. The precipitate was filtered and crystallized from ethyl alcohol. Reaction mixtures for the synthesis of compounds IV, V, and VIII contained additionally 0.01 mole of sodium bicarbonate in 5 ml water.

**5-(*p*-Bromophenyl)-4-(1-aminothiocabonylhydrazineoethylidene)-1-(2-aminocarbonylmethyl)-tetrahydropyrrole-2,3-dione (XI).** A mixture of 1 g 5-(*p*-bromophenyl)-4-acetyl-3-hydroxy-1-(2-aminocarbonylmethyl)-3-pyrrolin-2-

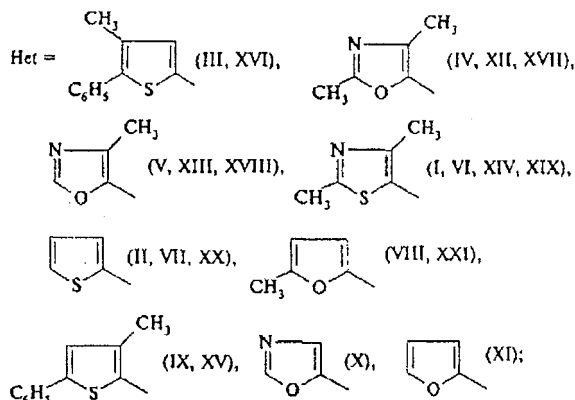
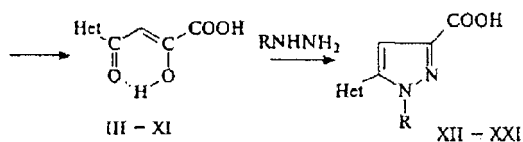
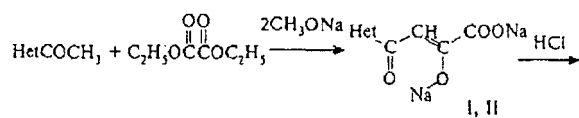
## CHARACTERIZATION OF DERIVATIVES

V. Milyutin,<sup>2</sup>

9, pp. 26-28, September, 1998.

um salts (I, II) of heteroarylpyruvic acids as well proper (III-XI) were obtained by the Claisen of the acetyl derivatives of five-membered hetero diethyloxalate in the presence of sodium salt 1). The products appear as crystalline substances soluble in ordinary organic solvents. In compounds, salts I and II are well soluble in hot water. Spectra of heteroarylpyruvic acids III-XI contain bands due to the stretching vibrations of carboxyl group in the region of 1695-1710  $\text{cm}^{-1}$  and a broad band due to the superimposition of the stretching vibrations of the heteroaryl group (involved in the intermolecular hydrogen bonding [4]) and the vibrations of C=N and C=C bonds (1600-1650  $\text{cm}^{-1}$ ). The  $^1\text{H}$  NMR spectra contain, besides the protons of substituents in the heterocycle, a methine protons (8.95-7.05 ppm) and a broad band of carboxyl protons (8.95-11.10). No signals from heteroaryls were detected, probably because of their exchange caused by exchange processes. The IR and NMR spectra are indicative of the complete enolization of I show evidence that acids III-XI exist in the solid state as well as in solution, in a form with intramolecular hydrogen bond (similarly to their aryl analogs) [5]. Heteroarylpyruvic acids with hydrazine hydrate or hydrazine in dioxane or isopropanol leads, at a good corresponding 5-heteroaryl-1-R-pyrazolo-3-carboxylic acids -XXI. These are colorless or slightly colored substances soluble in DMF and acetic acid and insoluble in water. The IR spectra of compounds XII-XXI contain strong absorption bands in the region of 1700-1710  $\text{cm}^{-1}$ , carboxyl group, and a broad weak band in the region of 3200-3340  $\text{cm}^{-1}$ , attributed to stretching vibrations of the N-H bond in the spectra of compounds XII-XXI served in the region of 3200-3340  $\text{cm}^{-1}$ . The IR spectra of compounds XII-XV, XVII, and besides the signals from protons of the substituents in position 5, a distinct singlet from the methine proton of the heterocycle fragment (6.88-7.13 ppm).

| $^1\text{H}$ NMR chemical shift $\delta$ , ppm |                          |                     |                                            |
|------------------------------------------------|--------------------------|---------------------|--------------------------------------------|
| 5-CH, s                                        | CH <sub>2</sub> (J, Hz)  | CH <sub>3</sub> , s | Other protons                              |
| 5.15                                           | 2.95 d (18), 4.05 d (18) | 2.25                |                                            |
| 5.21                                           | 3.41 m                   | 2.18                |                                            |
| 5.18                                           | 3.18 d (18), 4.21 d (18) | 2.35                |                                            |
| 5.15                                           | 3.31 d (18), 4.33 d (18) | 2.23                | 1.05 t, 3.78 q ( $\text{OC}_2\text{H}_5$ ) |
| 5.21                                           | 3.45 d (18), 4.43 d (18) | 2.25                | 1.08 t, 3.90 q ( $\text{OC}_2\text{H}_5$ ) |
| 5.15                                           |                          | 2.21                | 1.18-3.38 m ( $(\text{CH}_2)_3$ )          |
| 4.98                                           | 3.06 d (18), 4.15 d (18) |                     |                                            |
| 5.10                                           | 3.65-3.71 m              | 2.15                | 4.45 m (CHPh), 7.31 m (Ph)                 |
| 5.26                                           | 3.36 d (18), 4.26 d      | 2.36                |                                            |
| 5.65                                           | 3.55 d (18), 4.15 d (18) |                     |                                            |
| 5.35                                           | 3.18 d (18), 4.15 d (18) | 1.73                | 3.71 s ( $\text{OCH}_3$ ), 12.55 s (NH)    |
| 5.08                                           | 3.18 d (18), 4.05 d (18) | 2.11                |                                            |



R = H (XII - XV), C<sub>6</sub>H<sub>5</sub> (XVI - XXI).

In the other cases, this signal superimposes on the group of signals from aromatic and heteroaromatic protons. The spectra of compounds XII, XIII, and XXI show a broad signal of carboxyl protons at 9.85 - 10.45 ppm. The latter signal (as well as the signal of the NH group of pyrazole fragments in the spectra of compounds XII - XV) is not observed in the

spectra of other compounds, probably as a result of strong broadening caused by exchange processes (Table 2).

## EXPERIMENTAL CHEMICAL PART

The IR spectra of the synthesized compounds were measured on a UR-20 spectrophotometer (Germany); the <sup>1</sup>H NMR spectra were recorded using an RYa-2310 spectrometer (Russia) operated at 60 MHz.

**Heteroarylpyruvic acids (III - XI) and their sodium salts (I, II).** To a warm solution of sodium methylate, obtained upon dissolving 2.30 g (0.1 mole) of sodium in 20.0 ml of methanol, was added by portions with stirring a warm solution of 0.05 mole of an acetylheteroaromatic compound and 0.05 mole of diethyl oxalate in 10 ml of methanol and the mixture was allowed to stand for 24 h. Then the solidified mass was treated with hot acetic acid until dissolution. To this solution was added concentrated HCl. Upon cooling, the precipitate was filtered, dried, and recrystallized (Table 1). To obtain the sodium salts (I, the solidified mass was treated with ether and the precipitate was recrystallized from an ethanol - water mixture.

**Pyrazolocarboxylic acids XII - XXI.** A mixture of 0.01 mole of the corresponding heteroarylpyruvic acid and 0.01 mole hydrazine was boiled for 1 h in 25 - 30 ml of a solvent. The solvents were represented by dioxane (for compounds XII, XIV, XVII, XVIII, XXI), ethanol (XV), or isopropyl alcohol (XVI, XIX, XX). The solution was cooled and allowed to stand at room temperature for 12 - 13 h. Compounds XII, XIII, XV, XVIII, XX, and XXI precipitate; compounds XIV and XIX were obtained by evaporating the solu-

TABLE 2. Spectroscopic Characteristics of the Synthesized Compounds

| Compound | IR spectrum $\nu_{\text{max}}$ , cm <sup>-1</sup> | <sup>1</sup> H NMR spectrum (DMSO) $\delta$ , ppm                                                                                |
|----------|---------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------|
| III      | 1705, 1625, 1575 (w)                              | 2.48 (CH <sub>3</sub> ), 7.07 (=CH-), 7.36 (C <sub>6</sub> H <sub>5</sub> ), 8.16 (*), 11.10 broad (OH)                          |
| IV       | 3120, 1720, 1610, 1625                            | 2.35 (3-CH <sub>3</sub> ), 2.48 (5-CH <sub>3</sub> ), 6.58 (=CH-), 10.25 broad (OH)                                              |
| V        | 3150, 1720, 1600                                  | 2.38 (CH <sub>3</sub> ), 6.61 (=CH-), 8.51 (**), 9.31 broad (OH)                                                                 |
| VI       | 1705, 1620, 1600                                  | 2.60 (2-CH <sub>3</sub> ), 2.65 (4-CH <sub>3</sub> ), 6.52 (=CH-)                                                                |
| VII      | 3110, 1615, 1720                                  | 7.01 (=CH-), 7.23, 8.15 (3-H, 4-H, 5-H — group of lines), 8.95 broad (OH)                                                        |
| VIII     | 3100, 1725, 1610                                  | 7.10 (=CH-), 2.50 (CH <sub>3</sub> ), 7.95 (3-H, 4-H — group of lines), 10.15 broad (OH)                                         |
| XI       | 3130, 1710, 1605                                  | 6.93 (=CH-), 8.00 (3-H, 4-H, 5-H — group of lines), 10.25 broad (OH)                                                             |
| XII      | 3200, 3060, 1710, 1650                            | 2.25 (4-CH <sub>3</sub> ), 2.35 (2-CH <sub>3</sub> ), 6.85 (4-H), 10.45 broad (OH)                                               |
| XIII     | 3200 (NH), 3080 (w), 1710, 1650, 1570             | 2.26 (4-CH <sub>3</sub> ), 6.95 (4-H <sub>pyrazole</sub> ), 8.28 (2-H <sub>oxazole</sub> )                                       |
| XIV      | 3064, 1715, 3184, 1580                            | 2.55 (2-CH <sub>3</sub> ), 2.41 (4-CH <sub>3</sub> ), 6.88 (=CH-), 9.85 broad (OH)                                               |
| XV       | 3180, 3340, 1715, 1590                            | 2.35 (3-CH <sub>3</sub> ), 6.75 (4-H <sub>pyrazole</sub> ), 7.36 (group of lines), 8.05 broad (OH + NH)                          |
| XVI      | 3090, 1715, 1610                                  | 2.25 (4-CH <sub>3</sub> ), 7.48 (group of lines)                                                                                 |
| XVII     | 3100, 1700, 1615                                  | 2.21 (4-CH <sub>3</sub> ), 2.35 (2-CH <sub>3</sub> ), 7.08 (4-H <sub>pyrazole</sub> ), 7.41 (C <sub>6</sub> H <sub>5</sub> )     |
| XVIII    | 3100 (OH), 1710, 1650 (w), 1610                   | 2.35 (CH <sub>3</sub> ), 7.13 (4-H <sub>pyrazole</sub> ), 7.45 (C <sub>6</sub> H <sub>5</sub> ), 8.26 (2-H <sub>oxazole</sub> )  |
| XX       | 3110, 1615                                        | 7.21 (group of lines)                                                                                                            |
| XXI      | 3100, 1725, 1610                                  | 2.36 (CH <sub>3</sub> ), 7.08 (C <sub>6</sub> H <sub>5</sub> + 3-H, 4-H <sub>furan</sub> + 4-H <sub>pyrazole</sub> ), 10.31 (OH) |

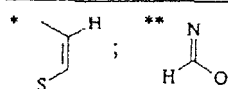


TABLE 3. Antibacterial Activity of Compounds III – XI, XVI, XIX, and XX

| Compound             | MIC, $\mu\text{g/ml}$   |                                |
|----------------------|-------------------------|--------------------------------|
|                      | <i>St. aureus</i> P-209 | <i>E. coli</i> M <sub>17</sub> |
| III                  | 500                     | 500                            |
| IV                   | 500                     | 500                            |
| V                    | 500                     | 500                            |
| VI                   | 500                     | 250                            |
| VII                  | 500                     | 250                            |
| VIII                 | 1000                    | 1000                           |
| IX                   | 500                     | 500                            |
| X                    | 500                     | 500                            |
| XI                   | 500                     | 500                            |
| XVI                  | 500                     | 500                            |
| XIX                  | 500                     | 500                            |
| XX                   | 500                     | 500                            |
| Mercury dichloride   | 1000                    | 1000                           |
| Aethacridine lactate | 2000                    | 500                            |

tion and recrystallizing the residue from the corresponding solvent (Table 1).

#### EXPERIMENTAL BIOLOGICAL PART

The antiaggregant activity of compounds I and II was studied photometrically using the Born method [6]. The tests were performed on thrombocytes in a dog plasma and evaluated as percentage decrease in the optical density of samples. The thrombocyte aggregation was induced by ADP (0.05 mg per ml plasma). The reference drug was papaverine hydrochloride.

The antibacterial activity of compounds III – XI, XVI, XIX, and XX with respect to the standard strains of *Escherichia coli* M<sub>17</sub> and *Staphylococcus aureus* P-209 were studied by the method of double serial dilutions in a beef-in-fusion broth using a bacterial load of  $250 \times 10^3$  microbial

cells per ml solution [4]. The acting dose was determined as a minimum inhibiting concentration of the compound (MIC,  $\mu\text{g/ml}$ ) suppressing the growth of test microbes. The reference drugs were mercury dichloride and aethacridine lactate.

The antiinflammatory activity of compounds XII and XVII was assessed on the model of inflammation in white rats (weighing 160 – 200 g), induced by subplantar injections of a 1% carrageenan solution (0.1 ml) into a hind paw.

The results of experiments showed that compounds I and II exhibit an antiaggregant activity at a concentration of 0.625 mg/ml, suppressing the thrombocyte aggregation by 50.4 and 36.6%, respectively (against 27.3% for papaverine hydrochloride at a concentration of 0.08 mg/ml).

Compounds XII and XVII tested at 50 mg/kg (p.o.) showed no evidence of antiinflammatory activity.

Compounds III – XI, XVI, XIX, and XX exhibited a weak antiinflammatory effect (Table 3).

The LD<sub>50</sub> values of compounds I and II are 150 and 250 mg/kg, respectively (cf. 31 mg/kg for papaverine).

#### REFERENCES

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6. *Evaluation of the Antiinflammatory Activity of Medicinal Preparations* [in Russian], Moscow (1981), pp. 9 – 10.