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**Short communication**

# Anti-inflammatory, analgesic and antipyretic N-acetyl-$\Delta^2$-pyrazolines and dihydrothienocoumarines

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**Summary** — 1-Acetyl-3-(2-hydroxyphenyl)-5-(R,R'-aryl)-4,5-dihydro-(1H)pyrazoles (**2a–o**) were synthesized and showed anti-inflammatory and analgesic activity. The substituents on the 5-aryl group were necessary for biological activity. R-R'-aryl-2-dihydro-1,2(4H)thieno(2,3-c)benzo(e)pyranone-4 derivatives (**3a–f**) also showed analgesic and anti-inflammatory activity. The position and the number of the substituents caused a modulation of analgesic or anti-inflammatory activity of the N-acetyl-$\Delta^2$-pyrazoline **2** and dihydrothienocoumarines **3**. All compounds showed low antipyretic activity.

**anti-inflammatory (activity) / analgesic (activity) / antipyretic (activity) / N-acetyl-3,5-diaryl-$\Delta^2$-pyrazolines (synthesis) / 2-aryl-dihydrothienocoumarines (synthesis)**

## Introduction

The reported bactericidal and fungicidal activities [1–3] and the anticonvulsant and monoamine oxidase (MAO) inhibitory properties [4, 5] of N-substituted 4,5-dihydropyrazoles together with the anti-inflammatory activity of pyrazoleacetic acids [6] stimulated the search for the synthesis of newer pyrazole derivatives by Michael condensation This method was also useful in the synthesis of dihydrothienocoumarines which showed analgesic, antipyretic and anti-inflammatory properties [7–12].

We were particularly interested in studying whether N-acetyl-4,5-dihydropyrazole derivatives showed anti-inflammatory and analgesic properties, as well as pyrazoleacetic acids, and if the substituents were able to affect these activities. Furthermore, it was interesting to verify whether the introduction of two substituents in the dihydrothienocoumarine derivatives was able to modulate analgesic or anti-inflammatory activity, as reported by Xicluna [7] for the mono-substituted compounds.

### *Chemistry*

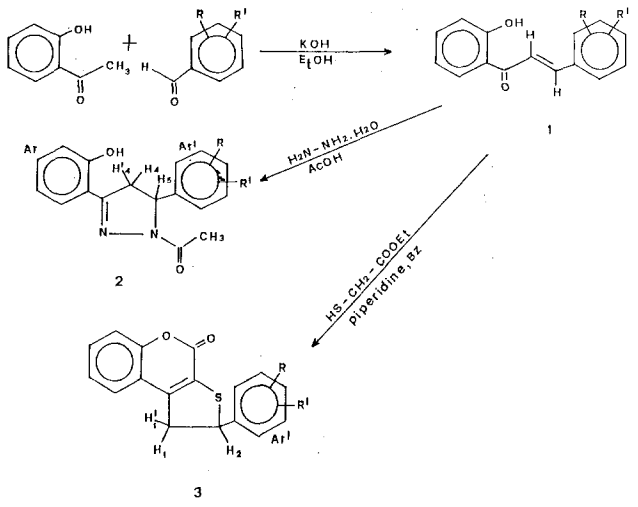
Synthesis of N-acetyl-$\Delta^2$-pyrazolines have been reported in some publications dealing with condensation of N-arylhydrazonaldehydes with methyl propionate [13], with thermal rearrangement of flavinio salts in the presence of hydrazine [14], or with reactions of azachalcones with hydrazine under suitable conditions [3, 15].

The dihydrothienocoumarines, synthesized by Xicluna [7], were obtained by reaction of the α, β-unsatured ketones with ethylthioglycolate in the presence of piperidine.

1-Acetyl-3-(2-hydroxyphenyl)-5-(R,R'-aryl)-4,5-dihydro-(1H)pyrazoles (**2a–o**) were synthesized by the reaction of suitable substituted chalcones (**1**) with hydrazine in acetic acid, while R,R'-aryl-2-dihydro-1,2(4H)thieno(2,3-c)benzo(e)pyranone-4 (**3a–f**) were obtained according to the method of Xicluna [7] (scheme l) (table I).

1,3-Diarylpropen-1-ones (**1**) were synthesized by condensation of o-hydroxyacethophenone with substituted benzaldehydes [4, 7, 14, 16–20].

The structure of the N-acetyl-$\Delta^2$-pyrazolines and dihydrothienocoumarines were unequivocally assigned by the use of the physical methods. The IR spectra of the **2a–o** compounds showed bands around 2850 $cm^{-1}$ (OH), 1690 $cm^{-1}$ (C=O), 1610 $cm^{-1}$ (C=N) and 1390 $cm^{-1}$ of medium or low intensity attributed to the $CH_2$ deforming vibrations of the 2-pyrazoline ring.



**Scheme 1.**

The NMR data of the **2a–o** compounds are shown in table II; the signals for the pyrazole ring showed $H'_4$, $H_4$ and $H_5$ protons as double doublets centered at ppm 3.20–3.30, 3.80–3.90 and 5.50–5.80, respectively, with $J_{H'_4H_4}$ = 18.00 Hz, $J_{H'_4H_5}$ = 15.00 Hz, $J_{H_4H_5}$ = 12.00 Hz.

The IR spectra of the **3a–f** compounds showed bands at 1720 $cm^{-1}$ (C=O), 1600 $cm^{-1}$ (C=C), 1000 $cm^{-1}$ (C-O) and 750 $cm^{-1}$ (C-S).

The NMR spectra of the **3a–f** compounds, shown in table III, showed an ABX system due to three protons of dihydrothienyl ring: the $H_1$, $H'_1$ and $H_2$ protons showed signals as double doublets centered at ppm 3.72–3.76, 4.15–4.20 and 5.50–5.65 respectively, with $J_{H_1H_2}$ = 6.5–7.0 Hz, $J_{H'_1H_2}$ = 6.5–7.0 Hz, $J_{H'_1H_1}$ = 18.5 Hz.

## Pharmacology

The compounds **2** and **3** were tested at a dose of 50 mg/kg corresponding to their $ED_{50}$ value and showed good anti-inflammatory and analgesic activity, except for **2e**, **2m** and **3c**. The activity of compounds **2e**, **2m** and **3c** was generally ten times below the indomethacin value, but higher than that showed by the acetylsalicylic acid and the phenylbutazone, whose values were reported by Xicluna [7] (tables IV, V). The antipyretic activity of compounds **2** and **3**, on the contrary, was very low (table VI).

The presence of substituents on the 5-aryl group of the N-acetyl-$\Delta^2$-pyrazoline derivatives (**2a–o**) was necessary for anti-inflammatory and analgesic activity. With regard to the anti-inflammatory properties, the most active compound was the 2'-methoxy derivative **2h**, followed by the 2',4'-dimethoxy **2n** and by the 2'- and 3'-chloro derivatives **2b**, **2c**; these last two also displayed the most analgesic power. Bromine caused a marked drop in all types of activity.

Moreover, the position and the number of the substituents might modulate analgesic or anti-inflammatory activity, but the prevalence of one of these properties was less clear than that showed by the dihydrothienocoumarines **3**.

The presence of a chloro substituent in the para position (**2d**) caused a decrease in all activities, while in the ortho or meta position (**2b**, **2c**) it gave rise to an increase in analgesic activity; the dichloro substitution (**2m**) modulated only the analgesic and antipyretic properties. The less active 4'-methyl compound (**2i**) showed a slight prevalence of the anti-inflammatory activity. In the methoxylated compounds, disubstitution (**2m**, **2o**) led to the presence of the analgesic activity which is absent in the mono derivative (**2h**).

All the compounds **3** showed anti-inflammatory, analgesic and antipyretic activity, except the **3c** derivative that was inclined to produce an edematous reaction.

In this case, the position and the number of the substituents also modulated anti-inflammatory or analgesic activity, but the distinction between these two activities was less clear than that observed with Xicluna's analgesic compounds [7], which generally caused an edematous reaction.

The displacement of the bromo substituent in the meta or para position caused a greater increase of the analgesic activity. The disubstitution seemed to be a less active modulator of the biological properties; in fact, only the **3f** compound, showed low anti-inflammatory activity, while the **3d** and **3e** compounds were very active.

## Conclusion

The results of our research showed that N-acetyl-$\Delta^2$-pyrazolines (**2a–2o**) were good anti-inflammatory and analgesic compounds, but the number and the position of the substituents were not able to modulate their activity. The same behaviour was verified for the dihydrothienocoumarines (**3a–3f**). Only the **2e, 2m** and **3c** derivatives were analgesic, non-narcotic compounds without anti-inflammatory activity.

The new anti-inflammatory activity shown by N-acetyl-$\Delta^2$-pyrazolines **2a–o** makes further studies dealing with the synthesis of other related structures carrying different substituents very interesting. The determination of their anti-inflammatory, analgesic and antipyretic activities may possibly give new information on the structure/activity relationship.

**Table I.** N-acetyl-3,5-diaryl-$\Delta^2$-pyrazolines **2a–o** and 2-aryl dihydrothienocoumarines.

| *Compound* | *R* | *R'* | *MP °C* | *Yield %* | *Formula* |
|---|---|---|---|---|---|
| **2a** | H | H | 135 | 90 | $C_{17}H_{16}N_2O_2$ |
| **2b** | H | 2-Cl | 175 | 66.8 | $C_{17}H_{15}N_2O_2Cl$ |
| **2c** | H | 3-Cl | 183 | 66.8 | $C_{17}H_{15}N_2O_2Cl$ |
| **2d** | H | 4-Cl | 140 | 71 | $C_{17}H_{15}N_2O_2Cl$ |
| **2e** | H | 2-Br | 176 | 67 | $C_{17}H_{15}N_2O_2Br$ |
| **2f** | H | 3-Br | 205 | 72 | $C_{17}H_{15}N_2O_2Br$ |
| **2g** | H | 4-Br | 150 | 75 | $C_{17}H_{15}N_2O_2Br$ |
| **2h** | H | 2-$OCH_3$ | 180 | 62 | $C_{18}H_{18}N_2O_3$ |
| **2i** | H | 4-$CH_3$ | 145 | 54.5 | $C_{18}H_{18}N_2O_2$ |
| **2l** | H | 4-$N(CH_3)_2$ | 190 | 46.4 | $C_{19}H_{21}N_3O_2$ |
| **2m** | 2-Cl | 4-Cl | 180 | 81 | $C_{17}H_{14}N_2O_2Cl_2$ |
| **2n** | 2-$OCH_3$ | 4-$OCH_3$ | 170 | 90 | $C_{19}H_{20}N_2O_4$ |
| **2o** | 2-$OCH_3$ | 5-$OCH_3$ | 170 | 90 | $C_{19}H_{20}N_2O_4$ |
| **3a** | H | 2-Br | 165 | 49 | $C_{17}H_{11}SO_2Br$ |
| **3b** | H | 3-Br | 176 | 39 | $C_{17}H_{11}SO_2Br$ |
| **3c** | H | 4-Br | 180 | 69 | $C_{17}H_{11}SO_2Br$ |
| **3d** | 2-Cl | 4-Cl | 205 | 28 | $C_{17}H_{10}SO_2Cl_2$ |
| **3e** | 2-$OCH_3$ | 4-$OCH_3$ | 125 | 29 | $C_{19}H_{16}SO_4$ |
| **3f** | 2-$OCH_3$ | 5-$OCH_3$ | 140 | 48 | $C_{19}H_{16}SO_4$ |

**Table II.** NMR data of N-acetyl-3,5-diaryl-$\Delta^2$-pyrazolines **2a–o**.

| | *OH* | *Ar, Ar'* | $H_5$ | $H_4$ | $H'_4$ | $J_{H'_4H_5}$ | $J_{H'_4H_4}$ | $J_{H_4H_5}$ | $OCH_3$ |
|---|---|---|---|---|---|---|---|---|---|
| **2a** | s 10.35 (1H) | m 7.50–6.80 (9H) | dd 5.50 | dd 3.80 | dd 3.25 | 18.00 | 18.00 | 12.00 | s 2.45 (3H) |
| **2b** | s 10.40 (1H) | m 7.50–6.80 (8H) | dd 5.80 | dd 3.85 | dd 3.20 | 15.00 | 18.00 | 12.00 | s 2.40 (3H) |
| **2c** | s 10.20 (1H) | m 7.80–6.90 (8H) | dd 5.55 | dd 3.90 | dd 3.35 | 15.00 | 18.00 | 12.00 | s 2.35 (3H) |
| **2d** | s 10.20 (1H) | m 7.50–6.80 (8H) | dd 5.55 | dd 3.80 | dd 3.35 | 15.00 | 18.00 | 12.00 | s 2.40 (3H) |
| **2e** | s 10.40 (1H) | m 7.55–6.80 (8H) | dd 5.80 | dd 3.85 | dd 3.20 | 15.00 | 18.00 | 12.00 | s 2.40 (3H) |
| **2f** | s 10.20 (1H) | m 7.80–6.90 (8H) | dd 5.50 | dd 3.90 | dd 3.30 | 15.00 | 18.00 | 12.00 | s 2.35 (3H) |
| **2g** | s 10.25 (1H) | m 7.60–6.85 (8H) | dd 5.50 | dd 3.90 | dd 3.25 | 15.00 | 18.00 | 12.00 | s 2.40 (3H) |
| **2h** | s 10.40 (1H) | m 7.50–6.80 (8H) | dd 5.80 | m 4.00–3.60 (4H) ($H_4$, $OCH_3$) | dd 3.20 | | 18.00 | 12.00 | s 2.40 (3H) |
| **2i** | s 10.30 (1H) | m 7.50–6.80 (8H) | dd 5.50 | dd 3.80 | dd 3.25 | 15.00 | 18.00 | 12.00 | s 2.40 (3H) |
| **2l** | s 10.35 (1H) | m 7.50–6.60 (8H) | dd 5.50 | dd 3.80 | dd 3.30 | 15.00 | 18.00 | 12.00 | s 2.90 (6H) $N(CH_3)_2$ |
| **2m** | s 10.20 (1H) | m 7.55–6.80 (7H) | dd 5.85 | dd 3.90 | dd 3.20 | 15.00 | 18.00 | 12.00 | s 2.40 (3H) |
| **2n** | s 10.40 (1H) | m 7.50–6.80 (7H) | dd 5.80 | m 4.20–3.70 (7H) ($H_4$, $20CH_3$) | dd 3.20 | | 18.00 | 12.00 | s 2.40 (3H) |
| **2o** | s 10.40 (1H) | m 7.50–6.80 (7H) | dd 5.80 | m 4.10–3.75 (7H) ($H_4$, $20CH_3$) | dd 3.20 | | 18.00 | 12.00 | s 2.40 (3H) |

Solvent: $CDCl_3$

## Experimental protocols

*Chemical synthesis*

Melting points were determined in open capillaries with a Büchi SMP-20 apparatus and are uncorrected. IR spectra were recorded with a Perkin-Elmer 281 B instrument, NMR spectra on a Varian EM-390 instrument, using TMS as an internal standard. Elemental analyses were within ± 0.4% of the theoretical values.

*1-(2-Hydroxyphenyl)-3-(R,R'-aryl)-2-propen-1-ones (**1a–o**)*

0.08 mol of aldehyde in 15–20 ml of absolute EtOH were added to a solution of 0.08 mol of o-hydroxy-acetophenone in 10 ml of KOH (50%) in anhydrous EtOH and were allowed to stand for 24 h at room temperature under $N_2$ with stirring. The reaction mixture was poured into ice and neutralized with diluted acetic acid; the solid was filtered and crystallized from MeOH.

Physical and spectroscopic characteristics of these compounds were respondent to known data [4, 7, 14, 16–20].

**Table III.** NMR data of 2-aryl-dihydrothienocoumarines **3a–f**.

| | *Ar, Ar'* | $H_2$ | $H'_1$ | $H_1$ | $J_{H'_1H_1}$ | $J_{H_1H_2}$ | $J_{H'_1H_2}$ | $CH_3$ |
|---|---|---|---|---|---|---|---|---|
| **3a** | m 7.80–7.35 (8H) | dd 5.55 | dd 4.18 | dd 3.72 | 18.50 | 6.50 | 6.50 | – |
| **3b** | m 8.00–7.40 (8H) | dd 5.50 | dd 4.16 | dd 3.76 | 18.00 | 6.50 | 6.50 | – |
| **3c** | m 7.80–7.40 (8H) | dd 5.50 | dd 4.15 | dd 3.75 | 18.50 | 7.00 | 7.00 | – |
| **3d** | m 8.10–7.30 (7H) | t 5.65 | t 4.20* | – | – | – | – | – |
| **3e** | m 7.90–7.40 (4H, Ar)<br>m 7.20–6.90 (3H, Ar') | t 5.60 | – | – | – | – | – | m 4.10–3.70<br>(8H, $H_1$, $H'_1$, $2CH_3$) |
| **3f** | m 7.90–7.40 (4H, Ar)<br>m 7.10–6.90 (3H, Ar') | t 5.60 | – | – | – | – | – | m 4.10–3.60<br>(8H, $H_1$, $H'_1$, $2CH_3$) |

*(2H)$H_1$, $H'_1$. $J_{H_1H_2}$ = 6.00. Solvent: DMF—$d_7$.

**Table IV.** Anti-inflammatory activity of N-acetyl-3,5-diaryl-$\Delta^2$-pyrazolines **2a–o** and 2-aryl-dihydrothienocoumarines **3a–f**.

| *Compound* | *mg/kg po* | *Volume of edema (ml ± SE)* | | |
|---|---|---|---|---|
| | | *0* | *1 h** | *2 h* |
| Controls | | 0.7 ± 0.1 | 1.2 ± 0.1 (+ 71.4) | 1.4 ± 0.1 (+ 100.0) |
| Indomethacin | 5 | 1.2 ± 0.07 | 1.3 ± 0.2 (63.1) | 1.5 ± 0.2 (75.0) |
| **2a** | 50 | 0.6 ± 0.1 | 0.9 ± 0.1 (21.4) | 1.1 ± 0.1 (16.7) |
| **2b** | 50 | 0.9 ± 0.03 | 1.1 ± 0.3 (49.2) | 1.3 ± 0.4 (55.6) |
| **2c** | 50 | 1.1 ± 0.1 | 1.4 ± 0.3 (44.1) | 1.6 ± 0.3 (54.5) |
| **2d** | 50 | 0.7 ± 0.1 | 1.0 ± 0.1 (28.5) | 1.1 ± 0.1 (42.9) |
| **2e** | 50 | 0.6 ± 0.1 | 0.9 ± 0.1 (21.4) | 1.2 ± 0.1 (0) |
| **2f** | 50 | 0.7 ± 0.1 | 0.9 ± 0.1 (42.8) | 1.2 ± 0.1 (28.6) |
| **2g** | 50 | 0.6 ± 0.1 | 0.9 ± 0.1 (21.4) | 1.1 ± 0.1 (16.7) |
| **2h** | 50 | 0.8 ± 0.1 | 1.2 ± 0.1 (21.4) | 1.0 ± 0.1 (75.0) |
| **2i** | 50 | 0.7 ± 0.1 | 0.9 ± 0.1 (42.8) | 1.1 ± 0.1 (42.9) |
| **2l** | 50 | 0.6 ± 0.1 | 1.0 ± 0.1 (4.7) | 1.1 ± 0.1 (16.7) |
| **2m** | 50 | 0.6 ± 0.1 | 0.9 ± 0.1 (21.4) | 1.2 ± 0.1 (0) |
| **2n** | 50 | 0.9 ± 0.1 | 1.1 ± 0.1 (49.2) | 1.2 ± 0.1 (66.7) |
| **2o** | 50 | 0.9 ± 0.3 | 1.1 ± 0.1 (49.2) | 1.3 ± 0.2 (55.6) |
| **3a** | 50 | 0.8 ± 0.1 | 1.1 ± 0.1 (33.9) | 1.1 ± 0.1 (62.5) |
| **3b** | 50 | 0.6 ± 0.1 | 0.8 ± 0.1 (38.1) | 0.9 ± 0.1 (21.4) |
| **3c** | 50 | 0.6 ± 0.1 | 1.1 ± 0.1 (+11.9) | 1.2 ± 0.1 (0) |
| **3d** | 50 | 0.9 ± 0.1 | 1.1 ± 0.1 (49.2) | 1.1 ± 0.1 (77.8) |
| **3e** | 50 | 0.7 ± 0.1 | 0.9 ± 0.1 (42.8) | 1.3 ± 0.1 (14.3) |
| **3f** | 50 | 0.6 ± 0.1 | 0.9 ± 0.1 (21.4) | 1.1 ± 0.1 (16.7) |
| Phenylbutazone** | 125 | | | (60.0) |

*Times from the administration. **Ref [7]. In parentheses percentage decrease of edema calculated in comparison with control values.

**Table V.** Analgesic activity of N-acetyl-3,5-diaryl-$\Delta^2$-pyrazolines **2a–o** and 2-aryl-dihydrothienocoumarines **3a–f**.

| *Compound* | *mg/kg po* | *Reaction times (s)* 0′ | 30′* | 1 h | 2 h | 4 h |
|---|---|---|---|---|---|---|
| Controls | | 6.6 ± 0.2 | 7.0 ± 0.4 | 6.1 ± 0.5 | 6.6 ± 0.4 | 7.2 ± 0.5 |
| Indomethacin | 5 | 6.5 ± 0.4 | 10.6 ± 0.7 | 12.2 ± 0.9 | 11.0 ± 0.9 | 10.0 ± 0.8 |
| | | | (63.1) | (87.7) | (69.2) | (53.8) |
| **2a** | 50 | 6.9 ± 0.1 | 7.6 ± 0.2 | 8.4 ± 0.4 | 8.3 ± 0.4 | 7.4 ± 0.4 |
| | | | (10.1) | (21.7) | (20.2) | (7.2) |
| **2b** | 50 | 6.6 ± 0.1 | 8.4 ± 0.6 | 11.3 ± 0.8 | 9.9 ± 0.5 | 8.4 ± 0.5 |
| | | | (27.3) | (71.2) | (50.0) | (27.3) |
| **2c** | 50 | 6.4 ± 0.4 | 9.0 ± 0.4 | 11.5 ± 0.5 | 9.9 ± 0.2 | 8.7 ± 0.9 |
| | | | (40.6) | (79.6) | (54.6) | (35.9) |
| **2d** | 50 | 6.9 ± 0.3 | 8.4 ± 0.8 | 10.6 ± 0.6 | 9.1 ± 0.6 ? | 7.6 ± 0.5 |
| | | | (21.7) | (53.6) | (31.9) | (10.1) |
| **2e** | 50 | 7.1 ± 0.2 | 9.3 ± 0.5 | 10.4 ± 0.5 | 9.2 ± 0.3 | 6.7 ± 0.2 |
| | | | (30.9) | (46.4) | (29.5) | (5.6) |
| **2f** | 50 | 6.6 ± 0.3 | 7.8 ± 0.6 | 8.7 ± 0.5 | 8.0 ± 0.4 | 7.7 ± 0.3 |
| | | | (18.2) | (31.8) | (21.2) | (16.6) |
| **2g** | 50 | 6.5 ± 0.2 | 8.8 ± 0.1 | 8.6 ± 0.2 | 8.5 ± 0.2 | 7.5 ± 0.3 |
| | | | (32.8) | (39.1) | (30.7) | (13.3) |
| **2h** | 50 | 6.8 ± 0.3 | 8.6 ± 0.2 | 10.0 ± 0.3 | 8.6 ± 0.4 | 7.7 ± 0.3 |
| | | | (26.4) | (47.0) | (26.4) | (13.2) |
| **2i** | 50 | 6.7 ± 0.3 | 8.3 ± 0.4 | 10.3 ± 0.7 | 8.7 ± 0.9 | 8.0 ± 0.4 |
| | | | (23.8) | (53.7) | (29.8) | (19.4) |
| **2l** | 50 | 6.6 ± 0.5 | 8.9 ± 1.0 | 10.2 ± 1.0 | 8.9 ± 0.9 | 7.7 ± 1.0 |
| | | | (34.8) | (54.5) | (34.8) | (16.7) |
| **2m** | 50 | 6.4 ± 0.4 | 8.1 ± 0.6 | 10.3 ± 1.0 | 9.2 ± 1.0 | 8.8 ± 0.4 |
| | | | (26.6) | (60.9) | (45.8) | (37.5) |
| **2n** | 50 | 6.6 ± 0.3 | 8.7 ± 0.5 | 10.8 ± 0.5 | 9.8 ± 0.4 | 7.8 ± 0.6 |
| | | | (31.8) | (63.6) | (48.4) | (18.2) |
| **2o** | 50 | 6.5 ± 0.3 | 8.6 ± 0.8 | 10.8 ± 0.4 | 8.9 ± 0.4 | 8.6 ± 0.7 |
| | | | (32.3) | (66.2) | (36.9) | (32.3) |
| **3a** | 50 | 6.6 ± 0.2 | 8.5 ± 0.3 | 9.9 ± 0.3 | 8.3 ± 0.3 | 7.2 ± 0.4 |
| | | | (28.8) | (50.0) | (25.7) | (9.1) |
| **3b** | 50 | 6.8 ± 0.3 | 8.6 ± 0.4 | 9.9 ± 0.8 | 8.5 ± 0.6 | 7.6 ± 0.5 |
| | | | (26.4) | (45.6) | (25.0) | (9.0) |
| **3c** | 50 | 6.1 ± 0.4 | 7.7 ± 0.9 | 9.8 ± 0.1 | 8.4 ± 0.8 | 7.5 ± 0.7 |
| | | | (26.2) | (60.6) | (37.7) | (23.0) |
| **3d** | 50 | 6.0 ± 0.1 | 7.8 ± 0.6 | 9.9 ± 0.7 | 8.7 ± 0.9 | 7.6 ± 0.7 |
| | | | (35.4) | (53.8) | (32.3) | (13.8) |
| **3e** | 50 | 6.5 ± 0.2 | 8.8 ± 0.1 | 10.0 ± 0.5 | 8.6 ± 0.1 | 7.4 ± 0.9 |
| | | | (32.8) | (53.1) | (39.1) | (23.4) |
| **3f** | 50 | 6.4 ± 0.2 | 8.5 ± 0.8 | 9.8 ± 0.2 | 8.9 ± 0.2 | 7.9 ± 0.3 |
| | | | (30.0) | (55.0) | (45.0) | (26.7) |
| Phenylbutazone** | 50 | | (50.0) | | | |
| Aspirine** | 50 | | (50.0) | | | |

*Times from the administration. **$ED_{50}$ determined by ip injection of $CH_3COOH$ (7). In parentheses percentage increase of the reaction times calculated in comparison with basal values

**Table VI.** Antipiretic activity of N-acetyl-3,5-diaryl-$\Delta^2$-pyrazolines **2a–o** and 2-aryl-dihydrothienocoumarines **3a–f**.

| *Compound* | *mg/kg po* | *Body temperatures (°C ± SE)* 0' | 30'* | 1 h | 2 h | 4 h | 6 h |
|---|---|---|---|---|---|---|---|
| Controls | | 38.6 ± 0.1 | 38.4 ± 0.2 | 38.6 ± 0.3 | 38.5 ± 0.1 | 38.5 ± 0.2 | 38.4 ± 0.1 |
| Indomethacin | 5 | 38.7 ± 0.1 | 38.3 ± 0.1 (1.0) | 37.9 ± 0.1 (2.1) | 37.2 ± 0.4 (3.8) | 36.7 ± 0.3 (5.2) | 36.2 ± 0.1 (6.4) |
| **2a** | 50 | 38.5 ± 0.1 | 38.5 ± 0.1 (0.0) | 38.4 ± 0.2 (0.3) | 38.3 ± 0.1 (0.5) | 38.0 ± 0.1 (1.3) | 37.9 ± 0.2 (1.5) |
| **2b** | 50 | 38.6 ± 0.1 | 38.6 ± 0.1 (0.0) | 38.0 ± 0.4 (1.5) | 37.7 ± 0.2 (2.3) | 37.0 ± 0.6 (4.1) | 37.0 ± 0.2 (4.1) |
| **2c** | 50 | 38.3 ± 0.3 | 38.3 ± 0.1 (0.0) | 38.2 ± 0.2 (0.2) | 38.2 ± 0.2 (0.2) | 37.5 ± 0.1 (2.1) | 37.5 ± 0.2 (2.1) |
| **2d** | 50 | 38.3 ± 0.2 | 38.2 ± 0.2 (0.3) | 38.0 ± 0.2 (0.8) | 37.7 ± 0.1 (1.5) | 37.3 ± 0.2 (2.6) | 37.3 ± 0.2 (2.6) |
| **2e** | 50 | 38.6 ± 0.1 | 38.3 ± 0.1 (0.7) | 38.3 ± 0.1 (0.7) | 38.1 ± 0.1 (1.3) | 37.9 ± 0.3 (1.8) | 37.9 ± 0 3 (1.8) |
| **2f** | 50 | 38.6 ± 0.1 | 38.4 ± 0.2 (0.5) | 38.3 ± 0.2 (0.7) | 38.3 ± 0.1 (0.7) | 38.1 ± 0.1 (1.3) | 38.0 ± 0.2 (1.5) |
| **2g** | 50 | 38.7 ± 0.1 | 38.4 ± 0.2 (0.8) | 38.4 ± 0.2 (0.8) | 38.1 ± 0.1 (1.5) | 38.0 ± 0.1 (1.8) | 38.0 ± 0.2 (1.8) |
| **2h** | 50 | 38.3 ± 0.1 | 38.0 ± 0.3 (0.8) | 37.7 ± 0.2 (1.5) | 37.6 ± 0.1 (1.8) | 37.2 ± 0.1 (2.8) | 37.1 ± 0.1 (3.1) |
| **2i** | 50 | 38.7 ± 0.1 | 38.4 ± 0.1 (0.8) | 37.7 ± 0.1 (2.6) | 37.5 ± 0.1 (3.1) | 37.4 ± 0.1 (3.3) | 37.4 ± 0.1 (3.3) |
| **2l** | 50 | 38.4 ± 0.3 | 38.3 ± 0.2 (0.2) | 38.2 ± 0.2 (0.5) | 38.1 ± 0.2 (0.8) | 37.9 ± 0.1 (1.3) | 37.9 ± 0.1 (1.3) |
| **2m** | 50 | 38.5 ± 0.2 | 38.4 ± 0.1 (0.3) | 37.7 ± 0.2 (2.1) | 37.6 ± 0.2 (2.3) | 37.2 ± 0.8 (3.3) | 37.2 ± 0.1 (3.3) |
| **2n** | 50 | 38.3 ± 0.2 | 38.2 ± 0.1 (0.2) | 37.7 ± 0.1 (1.5) | 37.6 ± 0.1 (1.8) | 37.5 ± 0.2 (2.1) | 37.5 ± 0.1 (2.1) |
| **2o** | 50 | 38.6 ± 0.2 | 38.3 ± 0.1 (0.7) | 37.6 ± 0.1 (2.6) | 37.6 ± 0.2 (3.1) | 37.3 ± 0.1 (3.3) | 37.3 ± 0.2 (3.3) |
| **3a** | 50 | 38.3 ± 0.1 | 38.1 ± 0.1 (0.5) | 37.7 ± 0.3 (1.5) | 37.6 ± 0.1 (1.8) | 37.2 ± 0.2 (2.8) | 37.1 ± 0.2 (3.1) |
| **3b** | 50 | 38.2 ± 0.1 | 38.0 ± 0.2 (0.5) | 37.5 ± 0.3 (1.8) | 37.4 ± 0.1 (2.1) | 37.3 ± 0.3 (2.4) | 37.0 ± 0.3 (3.1) |
| **3c** | 50 | 38.1 ± 0.2 | 37.6 ± 0.1 (1.3) | 37.6 ± 0.3 (1.3) | 37.5 ± 0.3 (1.5) | 37.4 ± 0.2 (1.8) | 37.4 ± 0.2 (1.8) |
| **3d** | 50 | 38.2 ± 0.1 | 37.9 ± 0.3 (0.8) | 37.7 ± 0.2 (1.3) | 37.6 ± 0.2 (1.6) | 37.5 ± 0.3 (1.8) | 37.4 ± 0.2 (2.1) |
| **3e** | 50 | 38.5 ± 0.3 | 38.1 ± 0.2 (1.0) | 38.0 ± 0.1 (1.3) | 37.6 ± 0.2 (2.3) | 37.5 ± 0.2 (2.5) | 37.2 ± 0.3 (3.4) |
| **3f** | 50 | 38.7 ± 0.2 | 38.1 ± 0.1 (1.5) | 37.8 ± 0.1 (2.3) | 37.6 ± 0.2 (2.8) | 37.4 ± 0.2 (3.3) | 37.4 ± 0.4 (3.3) |

*Times from the administration. In parentheses percentage decrease of the body temperature calculated in comparison with basal values.

*1-Acetyl-3-(2-hydroxyphenyl)-5-(R,R'-aryl)-4,5-dihydro-(1H) pyrazoles (**2a–o**)*

2-Hydroxychalcone **1** (0.01 mol) was added to a solution of hydrazine hydrate (0.02 mol) in 20 ml of acetic acid. The mixture was then refluxed for 24 h on stirring and poured onto ice; the solid was filtered and crystallized from MeOH.

IR, KBr, spectra showed bands around $cm^{-1}$: 2850 (OH), 1690 (C=O), 1610 (C=N), 1390 ($CH_2$).

NMR data of the compounds **2a–o** are shown in table II.

*R,R'-aryl-2-dihydro-1,2(4H)thieno(2,3-c)benzo(e)pyranone-4 (**3a–f**)*

0.01 mole of 2-hydroxychalcone 1, 1 ml of piperidine and 0.01 mole (1.1 ml) of ethyl-thioglycolate in 50 ml of benzene were refluxed for 24 h on stirring. The solution was washed with 100 ml HCl (1:1) and water. The organic layer was collected, dried on anhydrous sulphate, filtered and evaporated to dryness under reduced pressure. The oily residue was solidified with methanol, filtered and crystallized from MeOH.

IR, KBr, spectra showed bands around $cm^{-1}$: 1720 (C=O), 1600 (C=C), 1000 (C-O), 750 (C-S).

NMR data of the compounds **3a–f** are shown in table III.

### Pharmacological evaluation

*Anti-inflammatory activity*

Anti-inflammatory activity was evaluated by the paw edema test using carrageenin (1%) on albino rats of both sexes (pregnant animals excluded) weighing 200–220 g; each group comprised five animals. The drugs were administered by oral route 30' before the carrageenin, at a dose of 50 mg/kg.

The volume of the rat's paw was measured 1, 2 and 4 h after administration of carrageenin, and indomethacin was used as a reference compound (5 mg/kg).

The reported values were the average of five determinations ± es and the percentage of activity was calculated in comparison with controls. Significance was calculated using Student's *t*-test for coupled values.

*Analgesic activity*

Analgesic activity was determined by means of the hot plate test (60°C) in *Mus musculus* of both sexes (pregnant animals excluded). Each group comprised five animals.

The reported values were the average of five determinations ± SE and the percentage of activity was calculated in comparison with basal values. Significance was calculated using Student's *t*-test for coupled values.

The drugs were administered by the oral route at a dose of 50 mg/kg and indomethacin was used as a reference compound (5 mg/kg).

*Antipyretic activity*

Antipyretic activity was determined by measuring the variation in body temperature in albino rats of both sexes (pregnant animals excluded) weighing 180–200 g. Fever was induced by a 10% solution of brewer's yeast (10 ml/kg) subcutaneously administered. Each group comprised five animals.

The reported values were the average of five determinations ± SE and the percentage of activity was calculated in comparison with basal values. Significance was calculated using Student's *t*-test for coupled values.

The compounds tested were administered by the oral route at a dose of 50 mg/kg and indomethacin was used as a reference compound (5 mg/kg).

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