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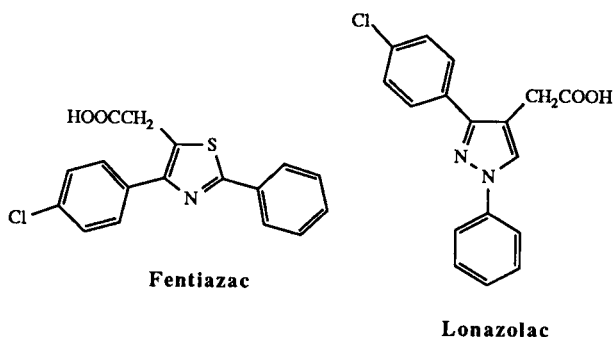
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A series of antiinflammatory agents, based on the structural integration of fentiazac and lonazolac, was synthesized.

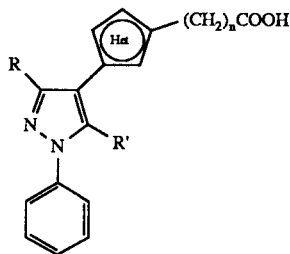
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### Introduction.

The historical role played by aryl and heteroaryl acetic acids as inflammation-remittive agents is well documented. Compounds such as diclofenac, sulindac and tolmetin have all enjoyed a high level of clinical interest while indomethacin has remained a mainstay in traditional NSAID therapy since its initial appearance over twenty-eight years ago [1]. Acetic acid derivatives incorporating thiazolyl and pyrazolyl residues, exemplified by fentiazac [2] and lonazolac [3], have also been recognized for their antiinflammatory activity although both are less efficacious than indomethacin.



As a compliment to our efforts in the inflammation area we became involved in the synthesis and identification of proprietary molecules of the acetic and carboxylic acid classes. Among several possible choices envisioned for synthesis was a short series of prototypes which would result from the structural hybridization of fentiazac and lonazolac.



While searches of the chemical literature indicated that combinations of this nature were essentially unprecedented some anecdotal evidence was uncovered which implied that such modifications do not necessarily provide active

agents [4]. This particular case documents the insertion of a tetrazole spacer between the indole and acetic acid subunits of indomethacin. None of the compounds modified in this fashion expressed significant antiinflammatory effects as measured in the rat foot edema model. Our proposed series however would combine pyrazole and slightly basic thiazole nuclei perhaps providing molecules with differing  $pK_a$  profiles. Of significant importance in evaluating the SAR around our series was the inclusion of key structural components such as the placement of steric bulk in positions flanking the thiazole and pyrazole rings to determine the effects of modifying molecular coplanarity. Alteration of the acid chain length was also considered vital in determining the relationship, if any, between  $pK_a$  and antiinflammatory activity.

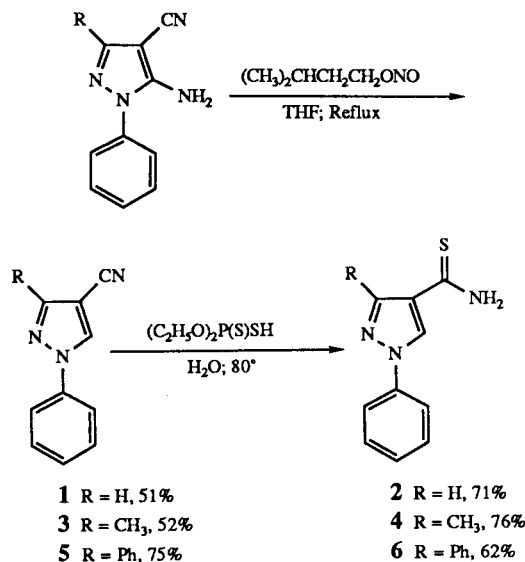
In view of the apparent lack of prior art in this area the synthesis of a probe series of compounds was initiated.

### Chemistry.

Synthesis of the regioisomeric thiazolyl acids shown in Schemes 2 and 3 was based on variations of the Hantzsch synthesis [5].

Nitriles **1**, **3** and **5** in Scheme 1 were synthesized by the non-aqueous diazotization of their corresponding 4-

Scheme 1



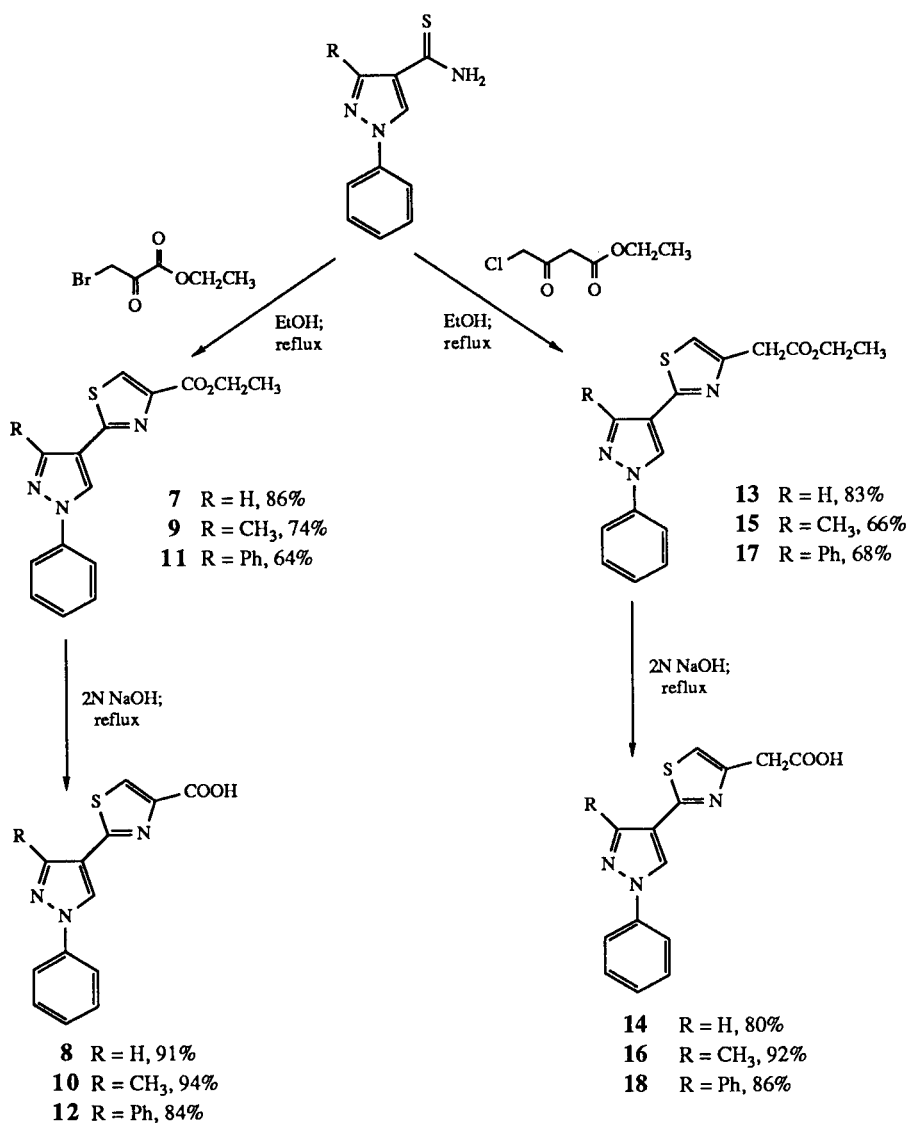
cyano-5-amino precursors with isopentylnitrite in refluxing tetrahydrofuran. This methodology, developed previously for the conversion of ethyl 1-phenyl-5-amino-4-pyrazolecarboxylates into their desamino analogs [6], was found to be equally applicable to their 4-cyano congeners. Subsequent thiolysis with aqueous *O,O*-diethyldithiophosphoric acid [7] gave thioamides **2** [8], **4** and **6** in good to moderate overall yield.

Ring closure with ethyl bromopyruvate or ethyl 4-chloroacetoacetate in refluxing ethanol as outlined in Scheme 2 gave esters **7**, **9**, **11** and **13**, **15** and **17** respectively. It is of interest to note that the ultimate salt formulation of these esters depends to a large extent on the workup conditions employed. With the exception of compounds **7** and **15** which precipitated as free base and hydrochloride salt directly from solution it was observed that the ethanolic

mother liquor frequently did not deposit a cyclization product on cooling. In these cases removal of the solvent and trituration of the residue with ethyl acetate/hexane mixtures provided the pure hydrobromide or hydrochloride salt. That these compounds form relatively weak salts is best exemplified by the facile conversion of hydrochlorides **13** and **17** into their complete and partial free bases by simple warming under vacuum. Saponification with aqueous base furnished the indicated target acids.

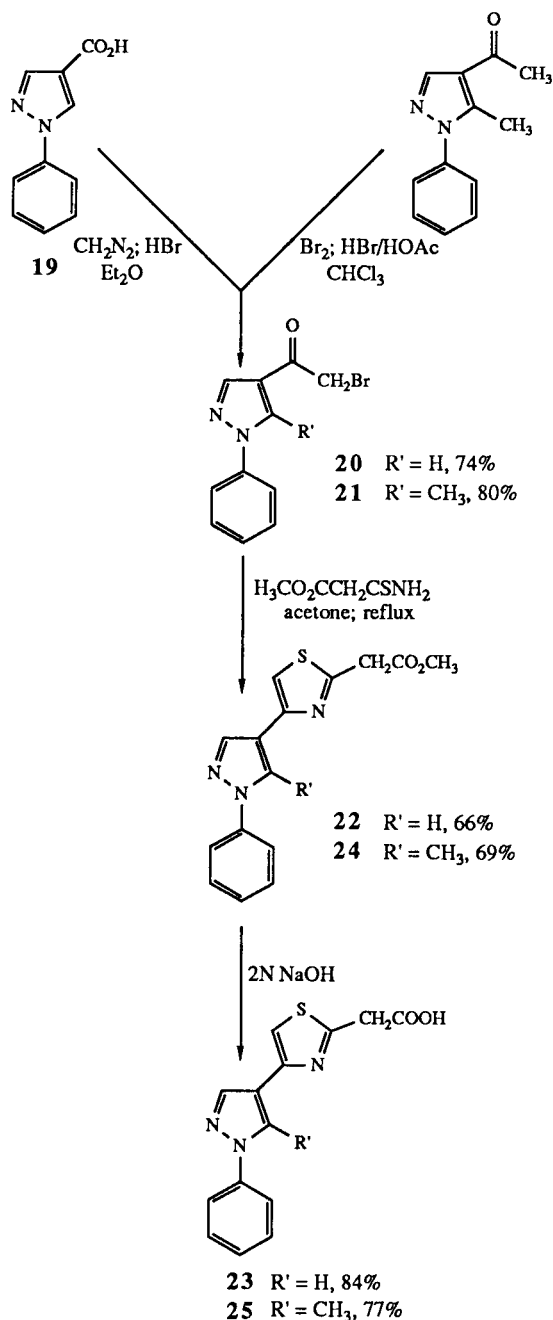
In Scheme 3 the requisite  $\alpha$ -bromoketones **20** and **21** were synthesized by two different methods. Cleavage of ethyl 1-phenyl-4-pyrazolecarboxylate [6] to acid **19** [9] followed by homologation with diazomethane/hydrogen bromide [10] gave **20** in good overall yield. This bromoketone had been synthesized previously in 39% yield by the direct bromination of 1-phenyl-4-acetylpyrazole [11]. A

Scheme 2



commercial sample of 1-phenyl-4-acetyl-5-methylpyrazole was converted into **21** by treatment with bromine in an acetic acid/chloroform mixture containing catalytic hydrogen bromide. Ring closure of bromoketones **20** and **21** with methyl 2-thiocarbamoylacetate [7] in refluxing acetone gave analytically pure hydrobromide salts **22** and **24**. Early investigations had indicated these salts to be rather insoluble in acetone therefore a cyclization solvent change was implemented in order to facilitate their isolation in pure form. Hydrolytic cleavage as before gave final acids **23** and **25** as indicated.

Scheme 3



## Summary.

In the present study a total of eight prototypical thiazolylcarboxylic and acetic acids were prepared by the hybridization of known antiinflammatory agents fentiazac and lonazolac. The biological screening data of these derivatives will be the subject of a future report.

## EXPERIMENTAL

Melting points, furnished in degrees Celsius, were determined with a Thomas-Hoover apparatus and are uncorrected. Elemental analyses were performed by John W. Greene of the Pfizer Central Research Analytical Department. The  $^1\text{H}$  nmr spectra were obtained on Bruker AM-300 and Varian XL-300 instruments in deuteriodimethyl sulfoxide unless otherwise noted. Electron impact mass spectral measurements were made on a Finnegan 4510 (70 eV) spectrometer. Fourier-Transform infrared spectra were recorded in potassium bromide on a Nicolet 510 instrument using the DRIFTS technique [12].

Unless noted, all reagents employed were purchased commercially and used without further purification.

### 1-Phenyl-4-cyanopyrazole (**1**).

A stirred solution of 1-phenyl-4-cyano-5-aminopyrazole (5.00 g, 27.14 mmoles) in 60 ml of tetrahydrofuran was treated with 6.36 g (54.29 mmoles) of isopentyl nitrite and the solution was refluxed overnight. The solvent was evaporated and the residual oil scratched until solidification began. The residue was kept on high vacuum for several hours, triturated with a little methanol and the insoluble product was collected by filtration. The methanol filtrate was evaporated and this trituration and filtration process was repeated until a total of 2.34 g (51% yield) of tan solid had been collected, mp 91-93°; lit [13] mp 95°;  $^1\text{H}$  nmr:  $\delta$  9.33 (s, 1H), 8.35 (s, 1H), 7.85 (m, 2H), 7.56 (m, 2H), 7.43 (m, 1H); ms:  $m/z$  (relative intensity) 169 ( $\text{M}^+$ , 80), 78 (100).

### 1-Phenyl-4-pyrazolethiocarboxamide (**2**).

A stirred mixture of **1** (2.00 g, 11.82 mmoles) in 2.20 g (11.82 mmoles) of *O,O*-diethyldithiophosphoric acid and 213 mg (11.82 mmoles) of water was heated at 80° until the initially formed clear yellow melt had resolidified (~5 minutes). The solid was pulverized, diluted with an additional 5 ml of water and stirred at 80° for another forty-five minutes. The mixture was poured into 30 ml of 5% sodium bicarbonate and washed with ethyl acetate until all of the product had been extracted. The extracts were dried over magnesium sulfate and evaporated to a yellow solid. Trituration with a little ether and filtration gave the pure title compound as an off-white, microcrystalline solid (1.71 g, 71% yield), mp 178-180°;  $^1\text{H}$  nmr:  $\delta$  9.50 (br s, 1H), 9.25 (br s, 1H), 8.89 (s, 1H), 8.18 (s, 1H), 7.82 (m, 2H), 7.53 (m, 2H), 7.39 (m, 1H); ms:  $m/z$  (relative intensity) 203 ( $\text{M}^+$ , 100), 187 (43), 170 (49), 143 (27); ir: 3355, 3162, 1621, 1396, 701  $\text{cm}^{-1}$ .

*Anal.* Calcd. for  $\text{C}_{10}\text{H}_9\text{N}_3\text{S}$ : C, 59.09; H, 4.46; N, 20.67. Found: C, 58.81; H, 4.40; N, 20.71.

### 1-Phenyl-3-methyl-4-cyanopyrazole (**3**).

The title compound was obtained in 52% yield by the reaction of 1-phenyl-3-methyl-4-cyano-5-aminopyrazole [14] (5.00 g, 25.22 mmoles) and isopentyl nitrite (5.91 g, 50.45 mmoles) in tetrahydrofuran as described above, mp 94-96°; lit [9] mp 93-95°;  $^1\text{H}$

nmr:  $\delta$  9.21 (s, 1H), 7.81 (m, 2H), 7.53 (m, 2H), 7.40 (m, 1H), 2.39 (s, 3H); ms:  $m/z$  (relative intensity) 183 ( $M^+$ , 100), 167 (5), 155 (26).

#### 1-Phenyl-3-methyl-4-pyrazolethiocarboxamide (4).

A stirred mixture of **3** (1.00 g, 5.46 mmoles) in 1.22 g (6.55 mmoles) of *O,O*-diethyldithiophosphoric acid and 118 mg (6.55 mmoles) of water was stirred at 80° for three hours and then dissolved in ethyl acetate. The solution was washed with 5% sodium bicarbonate (2 x 20 ml), dried over magnesium sulfate and evaporated to a thick yellow oil. The oil was scratched until solidification was complete, triturated with 4:1 hexanes/ethyl acetate and recrystallized from ethyl acetate to give 905 mg (76% yield) of sand-colored solid, mp 154-156°;  $^1H$  nmr:  $\delta$  9.45 (br s, 1H), 9.01 (br s, 1H), 8.78 (s, 1H), 7.78 (m, 2H), 7.50 (m, 2H), 7.32 (m, 1H), 2.52 (s, 3H); ms:  $m/z$  (relative intensity) 217 ( $M^+$ , 91), 201 (11), 184 (100); ir: 3326, 3147, 1646, 1544, 1389, 1182, 861, 761  $cm^{-1}$ .

*Anal.* Calcd. for  $C_{11}H_{11}N_3S$ : C, 60.80; H, 5.10; N, 19.34. Found: C, 60.57; H, 4.99; N, 19.20.

#### 1,3-Diphenyl-4-cyanopyrazole (5).

The title cyanopyrazole was obtained in 75% yield by the interaction of 1,3-diphenyl-4-cyano-5-aminopyrazole [15] (4.42 g, 16.98 mmoles) and isopentylinitrite (3.98 g, 33.96 mmoles) in tetrahydrofuran as previously described, mp 136-138°; lit [16] mp 142-143.5°;  $^1H$  nmr:  $\delta$  9.45 (s, 1H), 7.96 (m, 4H), 7.56 (m, 5H), 7.46 (m, 1H); ms:  $m/z$  (relative intensity) 245 ( $M^+$ , 100), 217 (8), 142 (35).

#### 1,3-Diphenyl-4-pyrazolethiocarboxamide (6).

The title thiouamide was prepared in 62% yield by the reaction of **5** (1.50 g, 6.12 mmoles), *O,O*-diethyldithiophosphoric acid (2.28 g, 12.23 mmoles) and water (220 mg, 12.23 mmoles) in a manner analogous to that for compound **2**, mp 185-187°;  $^1H$  nmr:  $\delta$  9.77 (br s, 1H), 9.21 (br s, 1H), 8.77 (s, 1H), 7.91 (m, 2H), 7.71 (m, 2H), 7.53 (m, 2H), 7.41 (m, 4H); ms:  $m/z$  (relative intensity) 279 ( $M^+$ , 100), 246 (30); ir: 3417, 3266, 3145, 1628, 1576, 1242, 830  $cm^{-1}$ .

*Anal.* Calcd. for  $C_{16}H_{13}N_3S$ : C, 68.79; H, 4.69; N, 15.04. Found: C, 68.61; H, 4.59; N, 14.89.

#### Ethyl 2-[4-(1-Phenylpyrazolyl)]-4-thiazolylcarboxylate (7).

A stirred mixture of **2** (500 mg, 2.46 mmoles) and ethyl bromopyruvate (640 mg, 2.95 mmoles at 90% purity) in 20 ml of ethanol was refluxed for thirty minutes and allowed to cool to room temperature overnight. The precipitate was collected and dried to furnish 630 mg (86% yield) of pure title compound, mp 163-164°;  $^1H$  nmr:  $\delta$  9.24 (s, 1H), 8.40 (s, 1H), 8.30 (s, 1H), 7.96 (m, 2H), 7.53 (m, 2H), 7.38 (m, 1H), 4.33 (q, 2H,  $J = 7.4$  Hz), 1.32 (t, 3H,  $J = 7.4$  Hz); ms:  $m/z$  (relative intensity) 299 ( $M^+$ , 91) 271 (5), 254 (23), 227 (100), 171 (50); ir: 3118, 2974, 1728, 1596, 1201  $cm^{-1}$ .

*Anal.* Calcd. for  $C_{15}H_{13}N_3O_2S$ : C, 60.18; H, 4.38; N, 14.04. Found: C, 60.17; N, 4.04; N, 13.89.

#### 2-[4-(1-Phenylpyrazolyl)]-4-thiazolylcarboxylic Acid (8).

A stirred suspension of **7** (595 mg, 1.99 mmoles) in 15 ml of 2*N* sodium hydroxide was diluted with 5 ml of ethanol and warmed to reflux for thirty minutes. The solution was cooled to room temperature, acidified to pH 2 with concentrated hydrochloric acid and filtered to furnish the pure title compound (489 mg, 91% yield) as a white solid, mp 203-205°;  $^1H$  nmr:  $\delta$  9.22 (s, 1H), 8.40 (s, 1H), 8.28 (s, 1H), 7.96 (m, 2H), 7.53 (m, 2H), 7.38 (m, 1H); ms:  $m/z$  (relative intensity) 271 ( $M^+$ , 99), 254 (8), 227 (31), 198 (11), 187 (55), 171 (100); ir: 3390 (br), 3112, 2630, 1719, 1580, 1508, 1253, 972, 757  $cm^{-1}$ .

*Anal.* Calcd. for  $C_{15}H_9N_3O_2S$ : C, 57.55; H, 3.34; N, 15.49. Found: C, 57.19; H, 3.27; N, 15.29.

#### Ethyl 2-[4-(1-Phenyl-3-methylpyrazolyl)]-4-thiazolylcarboxylate Hydrobromide (9).

A stirred mixture of **4** (750 mg, 3.45 mmoles) and ethyl bromopyruvate (898 mg, 4.14 mmoles at 90% purity) in 25 ml of ethanol was refluxed for forty-five minutes, cooled briefly and evaporated. The residue was triturated with 1:1 hexanes/ethyl acetate and filtered to give 1.01 (74% yield) of the pure salt, mp 185-188°;  $^1H$  nmr:  $\delta$  9.12 (5, 1H), 8.48 (s, 1H), 7.92 (m, 2H), 7.51 (m, 2H), 7.38 (m, 1H), 4.32 (q, 2H,  $J = 7.4$  Hz), 2.56 (s, 3H), 1.31 (t, 3H,  $J = 7.4$  Hz); ms:  $m/z$  (relative intensity) 313 ( $M^+$ , 100), 284 (4), 268 (12), 239 (96); ir: 3108, 3038, 2671 (br), 1731, 1553, 1303, 1230, 1012, 881  $cm^{-1}$ .

*Anal.* Calcd. for  $C_{16}H_{15}N_3O_2S \cdot HBr$ : C, 48.74; H, 4.09; N, 10.66. Found: C, 48.62; H, 4.03; N, 10.67.

#### 2-[4-(1-Phenyl-3-methylpyrazolyl)]-4-thiazolylcarboxylic Acid (10).

A suspension of **9** (800 mg, 2.03 mmoles) in 20 ml of 2*N* sodium hydroxide was saponified and worked up as described for acid **8**. Pure **10** (544 mg, 94% yield) was obtained as an off-white solid, mp 191-193°;  $^1H$  nmr:  $\delta$  9.10 (s, 1H), 8.41 (s, 1H), 7.91 (m, 2H), 7.50 (m, 2H), 7.34 (m, 1H), 2.56 (s, 3H); ms:  $m/z$  (relative intensity) 285 ( $M^+$ , 100), 271 (75), 239 (48), 185 (33), 171 (100); ir: 3380, 3149, 1771, 1564, 1515, 1334, 1234, 999, 760  $cm^{-1}$ .

*Anal.* Calcd. for  $C_{14}H_{11}N_3O_2S$ : C, 58.93; H, 3.89; N, 14.73. Found: C, 58.82; H, 3.74; N, 14.72.

#### Ethyl 2-[4-(1,3-Diphenylpyrazolyl)]-4-thiazolylcarboxylate Hydrobromide (11).

The title ester was prepared by the reaction of **6** (400 mg, 1.43 mmoles) and ethyl bromopyruvate (372 mg, 1.72 mmoles at 90% purity) in 25 ml of ethanol as described for **9**. The pure salt (420 mg, 64% yield) was obtained as an off-white solid, mp 178-180°;  $^1H$  nmr:  $\delta$  9.17 (s, 1H), 8.44 (s, 1H), 8.01 (m, 2H), 7.73 (m, 2H), 7.55 (m, 2H), 7.47 (m, 2H), 7.40 (m, 2H), 4.31 (q, 2H,  $J = 7.1$  Hz), 1.31 (t, 3H,  $J = 7.1$  Hz); ms:  $m/z$  (relative intensity) 375 ( $M^+$ , 100), 346 (17), 330 (6), 303 (32), 270 (20), 263 (21); ir: 3004, 2754 (br), 1732, 1596, 1257, 763  $cm^{-1}$ .

*Anal.* Calcd. for  $C_{22}H_{17}N_3O_2S \cdot HBr$ : C, 55.27; H, 3.97; N, 9.21. Found: C, 55.29; H, 4.02; N, 9.34.

#### 2-[4-(1,3-Diphenylpyrazolyl)]-4-thiazolylcarboxylic Acid (12).

A stirred suspension of **11** (395 mg, 0.87 mmole) in 15 ml of 2*N* sodium hydroxide was diluted with ~1 ml of ethanol and the mixture was warmed to reflux for 2 hours. The insoluble sodium salt was collected, resuspended in water and acidified with 2 ml of concentrated hydrochloric acid. After stirring at room temperature for one hour the mixture was filtered and the collected solid dried under vacuum to give pure **12** (254 mg, 84% yield) as a white solid, mp 212-214°;  $^1H$  nmr:  $\delta$  9.14 (s, 1H), 8.32 (s, 1H), 8.01 (m, 2H), 7.71 (m, 2H), 7.54 (m, 2H), 7.47 (m, 3H), 7.39 (m, 1H); ms:  $m/z$  (relative intensity) 347 ( $M^+$ , 21), 332 (18), 302 (20), 263 (12), 221 (18), 180 (30), 151 (100); ir: 3117 (br), 1710, 1505, 1221, 757  $cm^{-1}$ .

*Anal.* Calcd. for  $C_{19}H_{13}N_3O_2S$ : C, 65.69; H, 3.77; N, 12.10. Found: C, 65.88; H, 3.63; N, 11.85.

#### Ethyl 2-[4-(1-Phenylpyrazolyl)]-4-thiazolylacetate Hydrochloride (13).

A stirred mixture of **2** (500 mg, 2.46 mmoles) and ethyl 4-chloroacetate (810 mg, 4.92 mmoles) in 20 ml of ethanol was refluxed for three hours. The pure salt was obtained by evaporation of the solvent and trituration of the residue with a 1:1 mixture of hexanes/ethyl acetate. The total yield of title compound was 714 mg (83% yield), mp 171-173°; <sup>1</sup>H nmr: δ 9.13 (s, 1H), 8.22 (s, 1H), 7.95 (m, 2H), 7.52 (m, 2H), 7.45 (s, 1H), 7.37 (m, 1H), 4.11 (q, 2H, J = 7.4 Hz), 3.85 (s, 2H), 1.20 (t, 3H, J = 7.4 Hz); ms: m/z (relative intensity) 313 (M<sup>+</sup>, 95), 240 (100), 170 (68); ir: 3146, 3066, 2368, 1837, 1725, 1599, 1511, 1262 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>16</sub>H<sub>15</sub>N<sub>3</sub>O<sub>2</sub>S·HCl: C, 54.93; H, 4.61; N, 12.01. Found: C, 54.92; H, 4.24; N, 11.87.

A portion of the above product was dried at 70° under vacuum (0.05 mm) for ~12 hours to furnish the free base, mp 163-166°.

Anal. Calcd. for C<sub>16</sub>H<sub>15</sub>N<sub>3</sub>O<sub>2</sub>S: C, 61.32; H, 4.82; N, 13.41. Found: C, 61.24; H, 4.69; N, 13.26.

#### 2-[4-(1-Phenylpyrazolyl)]-4-thiazolylacetic Acid (**14**).

A stirred suspension of **13** (690 mg, 1.97 mmoles) in 40 ml of 2N sodium hydroxide was diluted with 5 ml of ethanol and warmed to reflux for one hour. The solution was cooled to room temperature, carefully acidified to pH 4.5 with 1N hydrochloric acid and the precipitated solid extracted with ethyl acetate. The organic layer was dried over magnesium sulfate and evaporated to an oil which gradually solidified. Trituration with 1:1 hexanes/ethyl acetate gave 450 mg (80% yield) of white solid, mp 180-182°; <sup>1</sup>H nmr: δ 9.11 (s, 1H), 8.20 (s, 1H), 7.94 (m, 2H), 7.52 (m, 2H), 7.41 (s, 1H), 7.36 (m, 1H), 3.76 (s, 2H); ms: m/z (relative intensity) 285 (M<sup>+</sup>, 49), 255 (43), 241 (100), 184 (16), 170 (39); ir: 3419 (br), 1733, 1575, 1508, 1343, 1248, 1083, 953, 761 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>14</sub>H<sub>11</sub>N<sub>3</sub>O<sub>2</sub>S: C, 58.93; H, 3.89; N, 14.73. Found: C, 58.82; H, 3.69; N, 14.75.

#### Ethyl 2-[4-(1-Phenyl-3-methylpyrazolyl)]-4-thiazolylacetate Hydrochloride (**15**).

A stirred solution of **4** (500 mg, 2.30 mmoles) and ethyl 4-chloroacetate (757 mg, 4.60 mmoles) in 20 ml of ethanol was refluxed for four hours and allowed to stand overnight at room temperature. The crystalline precipitate was collected to give 552 mg (66% yield) of pure salt, mp 193-195°; <sup>1</sup>H nmr: δ 9.02 (s, 1H), 7.91 (m, 2H), 7.48 (m, 2H), 7.45 (s, 1H), 7.27 (m, 1H), 4.11 (q, 2H, J = 7.4 Hz), 3.85 (s, 2H), 2.52 (s, 3H), 1.20 (t, 3H, J = 7.4 Hz); ms: m/z (relative intensity) 327 (M<sup>+</sup>, 100), 255 (58), 184 (40); ir: 3118, 2981, 2373, 1731, 1561, 1195 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>17</sub>H<sub>17</sub>N<sub>3</sub>O<sub>2</sub>S·HCl: C, 56.11; H, 4.99; N, 11.55. Found: C, 56.16; H, 4.91; N, 11.52.

#### 2-[4-(1-Phenyl-3-methylpyrazolyl)]-4-thiazolylacetic Acid (**16**).

A stirred mixture of **15** (823 mg, 2.26 mmoles) in 50 ml of 2N sodium hydroxide was diluted with 5 ml of ethanol and refluxed for forty-five minutes. The solution was cooled briefly, acidified to pH 3-4 with 1N hydrochloric acid and filtered to furnish pure **16** (621 mg, 92% yield) as a white solid, mp 144-145°; <sup>1</sup>H nmr: δ 9.00 (s, 1H), 7.91 (m, 2H), 7.49 (m, 2H), 7.42 (s, 1H), 7.32 (m, 1H), 3.77 (s, 2H), 2.52 (s, 3H); ms: m/z (relative intensity) 299 (M<sup>+</sup>, 100), 255 (60), 184 (48); ir: 3406 (br), 3143, 1716, 1564, 1510, 1241, 1168, 764 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>15</sub>H<sub>13</sub>N<sub>3</sub>O<sub>2</sub>S: C, 60.18; H, 4.38; N, 14.04. Found: C, 60.16; H, 4.23; N, 13.96.

#### Ethyl 2-[4-(1,3-Diphenylpyrazolyl)]-4-thiazolylacetate Hydrochloride (**17**).

Preparation of the title compound was accomplished in 68% yield from 652 mg (2.33 mmoles) of **6** and 768 mg (4.67 mmoles) of ethyl 4-chloroacetate as described for compound **13**, mp 144-147°; <sup>1</sup>H nmr: δ 9.05 (s, 1H), 7.99 (m, 2H), 7.73 (m, 2H), 7.53 (m, 2H), 7.43 (m, 4H), 7.38 (m, 1H), 4.27 (q, 2H, J = 7.1 Hz), 3.82 (s, 2H), 1.18 (t, 3H, J = 7.1 Hz); ms: m/z (relative intensity) 389 (M<sup>+</sup>, 100), 316 (72), 246 (56); ir: 3058, 2202 (br), 1857, 1727, 1599, 1546, 1254, 732 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>22</sub>H<sub>19</sub>N<sub>3</sub>O<sub>2</sub>S·0.7HCl: C, 63.67; H, 4.79; N, 10.13. Found: C, 63.78; H, 4.79; N, 10.21.

#### 2-[4-(1,3-Diphenylpyrazolyl)]-4-thiazolylacetic Acid (**18**).

A stirred slurry of **17** (610 mg, 1.47 mmoles) in 40 ml of 2N sodium hydroxide was warmed to reflux and ethanol was added until all of the oily ester had dissolved (~15 ml). After refluxing for three hours the solution was evaporated to one-half volume and the residual sodium salt worked up as described for **12**. The pure title compound (456 mg, 86% yield) was obtained as a white solid, mp 169-171°; <sup>1</sup>H nmr: δ 9.06 (s, 1H), 8.00 (m, 2H), 7.75 (m, 2H), 7.52 (m, 2H), 7.43 (m, 4H), 7.38 (m, 1H); ms: m/z (relative intensity) 361 (M<sup>+</sup>, 80), 317 (100); ir: 3440 (br), 3160, 3100, 3050, 1728, 1599, 1552, 1505, 1393, 1226, 1063 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>20</sub>H<sub>15</sub>N<sub>3</sub>O<sub>2</sub>S: C, 66.46; H, 4.18; N, 11.63. Found: C, 66.16; H, 3.99; N, 11.63.

#### 1-Phenyl-4-pyrazolecarboxylic Acid (**19**).

A suspension of 3.79 g (17.53 mmoles) of ethyl 1-phenyl-4-pyrazolecarboxylate [**6**] in 60 ml of 2N sodium hydroxide was diluted with 5 ml of ethanol and warmed to 90° for thirty minutes. The solution was cooled to room temperature and acidified to pH 2 with concentrated hydrochloric acid. The precipitated solid was collected and dried to give the title compound (3.28 g, 99% yield) as a white solid, mp 220-221°; lit [9] mp 218-220°; <sup>1</sup>H nmr: δ 9.01 (s, 1H), 8.08 (s, 1H), 7.91 (m, 2H), 7.52 (m, 2H), 7.38 (m, 1H); ms: m/z (relative intensity) 188 (M<sup>+</sup>, 100), 171 (40).

#### 1-Phenyl-4-(2-bromoacetyl)pyrazole (**20**).

A 500 mg (2.66 mmoles) portion of **19** was suspended in 10 ml of thionyl chloride and refluxed for thirty minutes. The solution was evaporated and the crude acid chloride was dissolved in 10 ml of warm diethyl ether. The solution was added dropwise with ice bath cooling to a dry ethereal solution of diazomethane which had been prepared from 1.95 g (13.29 mmoles) of 1-methyl-3-nitro-1-nitrosoguanidine. The solution was stirred cold for one hour and then stored at 0° overnight. The resulting suspension was treated with gaseous hydrogen bromide for thirty minutes and evaporated to a solid residue. Trituration with 5% sodium bicarbonate, filtration and drying gave 523 mg (74% yield) of title compound as an off-white solid, mp 130-132°, lit [11] 135-136.5°; <sup>1</sup>H nmr: δ 9.31 (s, 1H), 8.29 (s, 1H), 7.91 (m, 2H), 7.57 (m, 2H), 7.49 (m, 1H), 4.70 (s, 2H); ms: m/z (relative intensity) 264/266 (M<sup>+</sup>, 43), 171 (100).

#### 1-Phenyl-4-(2-bromoacetyl)-5-methylpyrazole (**21**).

To a stirred solution of 1-phenyl-4-acetyl-5-methylpyrazole (1.50 g, 7.49 mmoles) in 40 ml of chloroform was added five drops of 50% (v/v) 48% hydrobromic acid/glacial acetic acid followed by the dropwise addition of a solution of bromine (1.44 g, 8.99 mmoles) in 5 ml of chloroform. After stirring at room tempera-

ture for fifteen minutes the solvent was evaporated and the crude hydrobromide salt collected by trituration with ethyl acetate. This solid was stirred in 35 ml of 5% sodium bicarbonate solution for two hours, collected and recrystallized from 2-propanol to give 1.67 g (80% yield) of tan crystalline solid, mp 94-96°; <sup>1</sup>H nmr (deuteriochloroform): δ 8.05 (s, 1H), 7.48 (m, 3H), 7.40 (m, 2H), 4.25 (s, 2H), 2.57 (s, 3H); ms: m/z (relative intensity) 278/280 (M<sup>+</sup>, 8), 185 (100); ir: 3098, 2942, 1660, 1563, 1506, 1213, 933, 769 cm<sup>-1</sup>.

*Anal.* Calcd. for C<sub>12</sub>H<sub>11</sub>BrN<sub>2</sub>O: C, 51.63; H, 3.97; N, 10.04. Found: C, 51.72; H, 3.78; N, 9.90.

#### Methyl 4-[4-(1-Phenylpyrazolyl)]-2-thiazolylacetate Hydrobromide (22).

A stirred solution of **20** (505 mg, 1.90 mmoles) and methyl 2-thiocarbamoylacetate [7] (279 mg, 2.10 mmoles) in 20 ml of acetone was refluxed for three hours. The precipitate was collected and dried to give pure **22** (477 mg, 66% yield) as an off-white solid, mp 209-211°; <sup>1</sup>H nmr: δ 8.90 (s, 1H), 8.15 (s, 1H), 7.89 (m, 2H), 7.80 (s, 1H), 7.50 (m, 2H), 7.32 (m, 1H), 4.23 (s, 2H), 3.68 (s, 3H); ms: m/z (relative intensity) 299 (M<sup>+</sup>, 100), 240 (40), 200 (66); ir: 3129, 2585 (br), 1727, 1598, 1512, 1342, 935, 756 cm<sup>-1</sup>.

*Anal.* Calcd. for C<sub>15</sub>H<sub>13</sub>N<sub>3</sub>O<sub>2</sub>S·HBr: C, 47.38; H, 3.71; N, 11.05. Found: C, 47.53; H, 3.59; N, 11.20.

#### 4-[4-(1-Phenylpyrazolyl)]-2-thiazolylacetic Acid (23).

A stirred suspension of **22** (561 mg, 1.48 mmoles) in 25 ml of 2*N* sodium hydroxide was diluted with 1 ml of ethanol and warmed to 90° for ten minutes. The solution was filtered to remove some trace insolubles, cooled to room temperature and the precipitated sodium salt acidified to pH 4-5 with 1*N* hydrochloric acid. The product was collected and dried to furnish **23** (352 mg, 84% yield) as an off-white solid, mp 145-147°; <sup>1</sup>H nmr: δ 8.89 (s, 1H), 8.16 (s, 1H), 7.91 (m, 2H), 7.77 (s, 1H), 7.51 (m, 2H), 7.33 (m, 1H); ms: m/z (relative intensity) 285 (M<sup>+</sup>, 5), 241 (100), 200 (55), ir: 3116, 3101, 1702, 1598, 1503, 1299, 1204, 770 cm<sup>-1</sup>.

*Anal.* Calcd. for C<sub>14</sub>H<sub>11</sub>N<sub>3</sub>O<sub>2</sub>S: C, 58.93; H, 3.89; N, 14.73. Found: C, 58.76; H, 3.57; N, 14.65.

#### Methyl 4-[4-(1-Phenyl-5-methylpyrazolyl)]-2-thiazolylacetate Hydrobromide (24).

A stirred solution of **21** (476 mg, 1.71 mmoles) and methyl 2-thiocarbamoylacetate (250 mg, 1.88 mmoles) in 10 ml of acetone were reacted and worked up as described for **22** to give 462 mg (69% yield) of pure title compound as a cream-colored solid, mp 179-181°; <sup>1</sup>H nmr: δ 8.01 (s, 1H), 7.68 (s, 1H), 7.55 (m, 4H), 7.46 (m, 1H), 4.23 (s, 2H), 3.68 (s, 3H), 2.53 (s, 3H); ms: m/z (rela-

tive intensity) 313 (M<sup>+</sup>, 100), 254 (21), 213 (52); ir: 3119, 2637, 1745, 1608, 1329, 1189, 778 cm<sup>-1</sup>.

*Anal.* Calcd. for C<sub>16</sub>H<sub>15</sub>N<sub>3</sub>O<sub>2</sub>S·HBr: C, 48.74; H, 4.09; N, 10.66. Found: C, 48.78; H, 4.02; N, 10.62.

#### 4-[4-(1-Phenyl-5-methylpyrazolyl)]-2-thiazolylacetic Acid (25).

A stirred suspension of **24** (438 mg, 1.11 mmoles) in 20 ml of 2*N* sodium hydroxide was warmed to 70° for ten minutes, cooled and acidified to pH 4-5 with 1*N* hydrochloric acid. The precipitated oily product was extracted with ethyl acetate and the extracts dried over magnesium sulfate. Evaporation gave a tan gum which was induced to solidify by trituration with 4:1 hexanes/ethyl acetate and scratching. Filtration gave 257 mg (77% yield) of pure **25** as an off-white solid, mp 108-110°; <sup>1</sup>H nmr: δ 8.00 (s, 1H), 7.64 (s, 1H), 7.54 (m, 4H), 7.46 (m, 1H), 4.11 (s, 2H), 2.53 (s, 3H); ms: m/z (relative intensity) 299 (M<sup>+</sup>, 5), 255 (100), 213 (57); ir: 3340 (br), 1719, 1502, 1389, 1190, 762 cm<sup>-1</sup>.

*Anal.* Calcd. for C<sub>15</sub>H<sub>13</sub>N<sub>3</sub>O<sub>2</sub>S: C, 60.18; H, 4.38; N, 14.04. Found: C, 59.84; H, 4.39; N, 13.89.

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