# Cardiotonic Agents. 5. Fragments from the Heterocycle–Phenyl–Imidazole Pharmacophore

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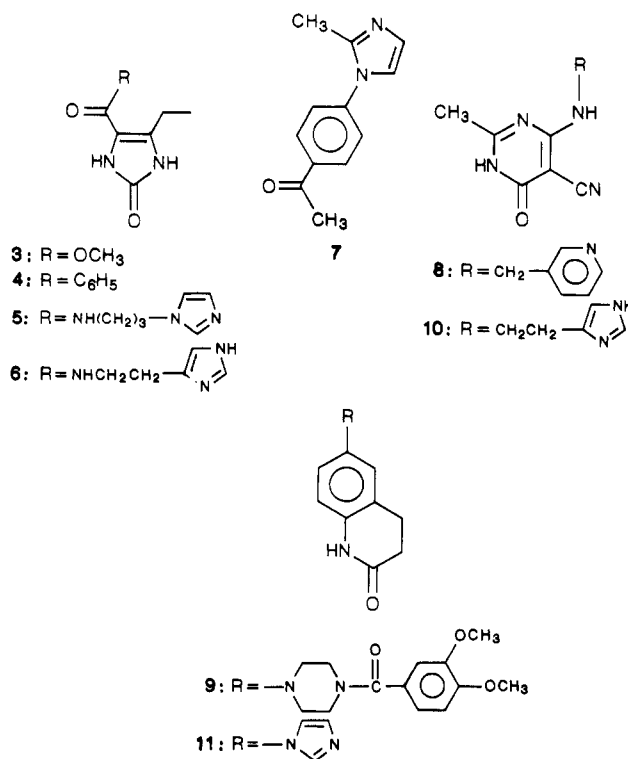
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To examine the role of each component in the heterocycle–phenyl–imidazole inotropic pharmacophore, several imidazolone derivatives, an arylimidazole, a substituted 3,4-dihydro-4-oxopyrimidine, and a quinolin-2(1*H*)-one derivative were prepared as structural fragments or representatives from this relationship. Tests for cardiac inotropic activity in ferret papillary muscle strips (FPM) and for inhibition of crude cAMP phosphodiesterase obtained from canine cardiac tissue suggest that, while all three components contribute significantly toward potent activity (active at less than 1 μM concentrations in FPM), any combination of two components, in approximately a preferred geometry, represents the minimal requirements for weak activity (active at less than 25 μM concentrations). No single component appears to be requisite in an absolute sense.

An interest in cardiotonic drugs[1] led us to the pharmacophoric relationship heterocycle–phenyl–imidazole (H–P–I),[2,3] which, in turn, formed the basis for our design of structures 1 and 2.[4] Compound 1 is a potent inotropic agent and vasodilator that inhibits cAMP phosphodiesterase in vitro.[5] Compound 2, while somewhat less potent, is extremely selective in its inotropic action.[5]

1: R = H
2: R = CH$_3$
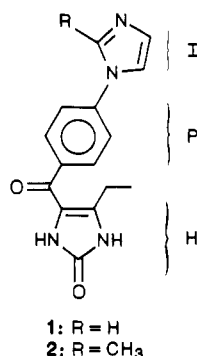
To further test the specific requirements for H, P, and I within 1 and 2, we have prepared compounds 3–7. Fragment structure 4 lacks component I, structures 5 and 6 lack component P, and structure 7 lacks component H. Fragment 3 lacks both the P and I components. In addition, to probe the generality of the overall relationship, we have applied it to the reported cardiotonic structures 8 (Pelrinone)[6] and 9 (OPC-8212),[7] providing analogues 10 and 11,[8] respectively.

3: R = OCH$_3$
4: R = C$_6$H$_5$
5: R = NH(CH$_2$)$_3$—
6: R = NHCH$_2$CH$_2$—

7

8: R = CH$_2$—
10: R = CH$_2$CH$_2$—

9: R =
11: R =

Chemistry

Compound 3, prepared by analogy to the reported[9] ethyl ester, was either reacted directly with 1-(3-aminopropyl)-1*H*-imidazole and with histamine to obtain 5 and 6, respectively, or was hydrolyzed to its acid prior to Friedel–Crafts acylation[4,5,10] with benzoic acid to provide 4. Compound 7 was prepared from 4-fluoroacetophenone by nucleophilic displacement with 2-methylimidazole.[11] Compound 10 was prepared from 1,4-dihydro-6-(methylthio)-4-oxopyrimidine-5-carbonitrile[12] by nucleophilic displacement of the methylthio group with histamine. Compound 11 was obtained after a Marckwald imidazole synthesis[13] on 6-aminoquinolin-2(1*H*)-one.[14,15]

(1) Erhardt, P. W. *J. Med. Chem.* **1987**, *30*, 231.
(2) Davey, D.; Erhardt, P. W.; Lumma, W. C., Jr.; Wiggins, J.; Sullivan, M.; Pang, D.; Cantor, E. *J. Med. Chem.* **1987**, *30*, 1337.
(3) A similar pharmacophoric relationship is present in Imazodan; e.g. see: Sircar, I.; Duell, B. L.; Bobowski, G.; Bristol, J. A.; Evans, D. B. *J. Med. Chem.* **1985**, *28*, 1405.
(4) Erhardt, P. W.; Hagedorn, A. A., III; Lumma, W. C., Jr.; Wohl, R. A. U.S. Patent 4,556,665, 1985.
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(6) Bagli, J.; Bogri, T.; Palameta, B.; Rakhit, S.; Peseckis, S.; McQuillan, J.; Lee, D. K. H. *J. Med. Chem.* **1988**, *31*, 814.
(7) Tiara, N.; Endoh, M.; Ijima, T.; Satoh, K.; Yanagisawa, T.; Yamashita, S.; Maruyama, M.; Kawada, M.; Morita, T.; Wada, Y. *Arzneim.-Forsch.* **1984**, *34*, 347.
(8) Alkylphenyl and alkylimidazole analogues closely related to 11 are claimed in: Roberts, D. A.; Campbell, S. F. European Patent 166,533, 1986.

(9) Duschinsky, R.; Dolan, L. A. *J. Am. Chem. Soc.* **1945**, *67*, 2079.
(10) Erhardt, P. W.; Hagedorn, A. A., III; Lumma, W. C., Jr.; Wohl, R. A. U.S. Patent 4,709,043, 1987.
(11) Bader, H.; Hansen, A. R.; McCarty, F. J. *J. Org. Chem.* **1966**, *31*, 2319.
(12) Kisaki, S.; Tominaga, Y.; Matsuda, Y.; Kobayashi, G. *Chem. Pharm. Bull.* **1974**, *22*, 2246.
(13) See, for example: Johnson, A. L.; Kauer, J. C.; Sharma, D. C.; Dorfman, R. I. *J. Med. Chem.* **1969**, *12*, 1024.

Table I. Biological Data

no.	inotropic act.:[a] CF C_{20}, μM	inhibn of cAMP phosphodiesterase:[b] IC_{50}, μM
1	0.05	2
2	0.7	37
3	NR	NR (10)
4	2	54
5	NR	NR (5)
6	10[c]	NR (25)
7	25	NR (15)
8[d]	0.2	4
9[e]	2.3	32
10	0.2[c]	4
11	1.6	71

[a] Drug concentration (μM) causing a 20% increase in contractile force (CF) of ferret papillary muscle. Data represent the mean from at least two determinations. Ranges for all data were within ±10%. For all active compounds the inotropic effect was not altered by coadministration of 1 μM propranolol, thus ruling out the possibility that the observed responses were mediated through β-adrenergic receptors.[5] NR indicates a CF C_{20} was not reached at 100 μM. [b] Drug concentration (μM) causing 50% inhibition (IC_{50}) of crude cAMP phosphodiesterase obtained from canine cardiac tissue homogenates.[2] Data represent the mean from at least three determinations. Ranges for all data were within ±10%. NR indicates that an IC_{50} was not reached at 100 μM. For these cases the percent of inhibition observed at 100 μM of drug is recorded in parentheses. [c] The inotropic activity was not altered by coadministration of 10 μM cimetidine, thus ruling out the possibility that the observed response was mediated through H_2 histaminergic receptors.[16] [d] Pelrinone. [e] OPC-8212.

Results and Discussion

The inotropic potency for each of the compounds was determined in vitro in ferret papillary muscle.[5] Inhibition of crude cAMP phosphodiesterase was measured in preparations obtained from canine cardiac tissue homogenates.[2] Both results are presented in Table I.

Inotropic activity and inhibition of phosphodiesterase are largely attenuated when H is removed (**7**) from **2** and when P is removed (**5** or **6**) from **1**. Activity is also diminished, although to a lesser degree, in both screens, when I is removed (**4**) from **1** and **2**. Removal of both P and I leaves H as an essentially inactive fragment (**3**).[17] These results suggest that in structures **1** and **2**, all three components play an important role in producing potent inotropic activity and contribute significantly toward inhibition of cAMP phosphodiesterase.[18] The latter is reflected in a recently reported[19] receptor model for cardiac cAMP phosphodiesterase in which each of these components (or electronic surrogates) can be shown to be involved in a specific receptor interaction. For example, Figure 1 shows how compound **1** binds to the model. With use of **1** as an assembled version of all of the fragments, it follows that compound **3** should be able to interact with receptor sites 1 and 2, compound **4** with sites 1, 2, and 3, compounds **5** and **6** with sites 1, 2, and 6, and finally, compound **7** with

(14) Tominaga, M.; Yo, E.; Ogawa, H.; Yamashita, S.; Yabuuchi, Y.; Nakagawa, K. *Chem. Pharm. Bull.* **1984**, *32*, 2100.

(15) Ueda, H. *Proc. Imp. Acad. (Tokyo)* **1939**, *15*, 148.

(16) Owens, A. H.; Goehring, R. R.; Lampe, J. W.; Erhardt, P. W.; Lumma, W. C., Jr.; Wiggins, J. *Eur. J. Med. Chem.* **1988**, *23*, 295.

(17) At least weak inotropic activity has been observed in canines for the closely related ethyl ester[9] as disclosed in: Schnettler, R. A.; Dage, R. C.; Grisar, J. M. U.S. Patent 4,418,071, 1983.

(18) These results contrast the conclusion obtained for closely related pyridazinone structures where the phenyl ring "...acts mainly as a spacer...": Sircar, I.; Weishaar, R. E.; Kobylarz, D.; Moos, W. H.; Bristol, J. A. *J. Med. Chem.* **1987**, *30*, 1955.

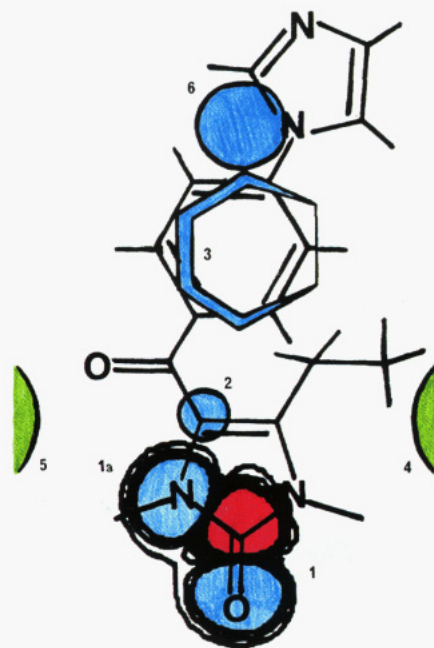(19) Erhardt, P. W.; Hagedorn, A. A., III; Sabio, M. *Mol. Pharmacol.* **1988**, *33*, 1.

Figure 1. Overhead view depicting the interaction of **1** with a topographical model of the cardiac cAMP phosphodiesterase receptor. In this binding scheme H interacts with a resonance-dipole site (1, 1a) and with a site for an electron-rich center (site 2); P interacts, from below with a π-electron system (site 3) that is above and at an approximate 15–20° angle to the perpendicular of the plane containing sites 1 and 2; and I interacts with a site for an electron-rich system (site 6). Regions 4 and 5 are steric protrusions or boundaries that must be avoided by structures attempting to bind with the receptor. Additional details and Cartesian coordinates for the various sites have been published previously.[19]

sites 3 and 6. In addition, it is important to note that compounds **4**, **7**, and **6** show at least weak activity in both screens while lacking I, H, and P, respectively, such that none of the individual components appear to be requisite for activity in an absolute sense. In general, it appears that any combination of a least two of these components in approximately the correct geometry represents a minimal requirement for weak activity.

With regard to the analogues of the reported cardiotonics **8** and **9**, it is interesting to note that application of the H–P–I relationship to the pyrimidone nucleus, with subsequent synthesis of a single compound (**10**), resulted in an inotropic agent comparable in potency to "the most potent cardiotonic agent among the pyrimidone derivatives" recently reported[6] for a series of ca. 30 analogues. A similar success (**11**[20]) was obtained from the tetrahydroquinolone parent **9** even though inhibition of cAMP phosphodiesterase does not appear to fully account for the positive inotropic activity observed for these compounds. Finally, when **10** is compared to **8**, the identical potencies in both screens suggest that imidazole is probably similar to pyridine[21] in terms of preference for interaction

(20) A detailed analysis of how compounds **9** and **11** may interact with additional pictorial versions of the cAMP phosphodiesterase receptor model can be found in ref 19. The descriptive synthesis of **11** and the actual biological data obtained for these compounds are reported herein.

(21) This result is in agreement with the conclusion obtained for closely related pyridazinone structures where "...the imidazole and pyridine rings are virtually indistinguishable...": Robertson, D. W.; Krushinski, J. H.; Pollock, G. D.; Hayes, J. S. *J. Med. Chem.* **1988**, *31*, 461.

with site 6 on the receptor model. Without knowing the contribution afforded by the 3,4-dimethoxybenzoyl group and because the inotropic and phosphodiesterase inhibition data diverge significantly in this case, it becomes speculative to suggest any receptor preference for imidazole versus piperazine on the basis of the **9, 11** structural pair.

Experimental Section

Melting points were taken on a Fisher-Johns melting point apparatus and are uncorrected. IR spectra were obtained on either a Sargent/Welch 3-300 spectrophotometer or a Beckman Aculab 2 spectrophotometer. ^{1}H NMR spectra were recorded on a Varian XL-300 spectrometer. Elemental analyses were performed by the Berlex Analytical Department of Galbraith Laboratories, Inc. Column chromatography was carried out on Merck silica gel 60, 230–400 mesh. Thin-layer chromatography (TLC) was performed with Merck silica gel 60 F254 plates.

5-Ethyl-2,3-dihydro-2-oxo-1H-imidazole-4-carboxylic Acid Methyl Ester (3). A solution of 293 g (4.03 mol) of sodium nitrite in 650 mL of water was added dropwise to a stirred solution of 500 g (3.84 mol) of methyl 3-oxopentanoate in 560 mL of glacial acetic acid while the reaction temperature was kept near 15 °C. Two liters of water was then added and the mixture, without cooling, was stirred for an additional 2 h. To consume unreacted nitrite, 25 g of urea in 50 mL of water was added and the total aqueous mixture was stirred for 30 min prior to its extraction with CH_2Cl_2 (5 × 150 mL). The combined organic phases were washed once with 150 mL of water, four times with 150 mL of saturated aqueous $NaHCO_3$ (foaming), and then dried over anhydrous Na_2SO_4. The CH_2Cl_2 was evaporated under reduced pressure while the pot temperature was kept below 50 °C[22] to provide 525 g (86%) of oily, orange oxime intermediate: NMR (CDCl$_3$) δ 1.12 (t, 3 H), 2.83 (q, 2 H), 3.90 (s, 3 H), 8.4 (br s, 1 H). A mixture of 159 g (1.0 mol) of the oxime intermediate in 440 mL of ethanol and 667 mL of 1.5 M HCl and 7 g of 10% palladium was hydrogenated under 50 psi H_2 for 4 h. The mixture was then filtered through Celite, the latter was washed once with 100 mL of ethanol, and the resulting combined yellow solution of the amino keto ester hydrochloride intermediate was concentrated to ca. 500 mL on a rotary evaporator while the pot temperature was kept below 40 °C. This solution was then used directly in the next reaction.

A four-necked flask equipped with a thermometer, addition funnel, and mechanical stirrer and fitted with a small rubber balloon (to accommodate changes in pressure while maintaining a closed system) was charged with a solution of 121.6 g (1.5 mol) of KOCN in 500 mL of water. The ca. 500 mL solution of amino keto ester hydrochloride intermediate was mixed with 100 mL of 5 M HCl and this solution was added dropwise over the course of ca. 2 h to the charged four-necked flask while the temperature was kept below 40 °C. After the addition, the mixture was stirred at room temperature for 18 h. The suspension was cooled to 5 °C and stirred for an additional 2 h, and then the product was collected by filtration. This solid was washed with 2 × 500 mL of cold methanol/water (1:1) and 2 × 500 mL of cold water. It was finally dried in a vacuum oven at ca. 100 °C to provide 125 g (74% from oxime) of **3**: mp 213–215 °C; NMR (DMSO-d_6) δ 1.10 (t, 3 H), 2.65 (q, 2 H), 3.70 (s, 3 H), 10.2 (br s, 1 H), 10.7 (br s, 1 H). Anal. ($C_7H_{10}N_2O_3$) C, H, N.

4-Benzoyl-5-ethyl-1,3-dihydro-2H-imidazol-2-one (4). A solution of 68.1 g (0.4 mol) of methyl ester **3** in 400 mL of 3 M NaOH was stirred at 60–65 °C for 2 h. The mixture was quickly cooled to room temperature (prolonged heating leads to decarboxylation), after which it was filtered and then it was added dropwise to a stirred solution of concentrated H_2SO_4 (75 g) in water (500 mL). This suspension was stirred for 2 h and then it was filtered. This solid was washed with 2 × 500 mL of water and then it was dried at ca. 100 °C to provide 51.5 g (92%) of acid intermediate, which was suitable for use in the next reaction step. An analytical sample was similarly obtained by treating a small portion of the material, which was first redissolved in

aqueous NaOH, with aqueous HCl followed by several aqueous washes and a final drying of the reprecipitated intermediate: mp 210–212 °C; NMR (DMSO-d_6) δ 1.07 (t, 3 H), 2.62 (q, 2 H), 11.0 (s, 1 H), 11.56 (s, 1 H), 13.4 (s, 1 H). Anal. ($C_6H_8N_2O_3$) C, H, N.

A mixture of 5.02 g (35.8 mmol) of the acid intermediate and 4.15 g (34 mmol) of benzoic acid was stirred in a mixture of 150 g of polyphosphoric acid and 22 g of methanesulfonic acid while the temperature was gradually (ca. 3 h) raised to 100 °C, where it was maintained for 30 min. The reaction mixture was then poured into 500 g of ice and the mixture was stirred for 2 h. The resulting pink suspension was filtered and the collected solid was washed with 50 mL of H_2O. This solid was then stirred in 300 mL of H_2O while 50% aqueous NaOH was added until the pH was 9–10. This basic suspension was stirred for 30 min and filtered, and then the collected solid was washed with 2 × 50 mL of water and 1 × 50 mL of ether. After air-drying, the pasty solid was recrystallized from methanol/water (1:1) to provide 4.1 g (56%) of **4** as white crystals: mp 234–236 °C; NMR (DMSO-d_6) δ 0.98 (t, 3 H), 2.13 (q, 2 H), 7.58 (m, 2 H), 7.61 (m, 3 H), 10.34 (br s, 1 H), 10.96 (br s, 1 H). Anal. ($C_{12}H_{12}N_2O_2$) C, H, N.

N-[3-(1H-Imidazol-1-yl)propyl]-5-ethyl-2,3-dihydro-2-oxo-1H-imidazole-4-carboxamide (5). A mixture of 2.2 g (12 mmol) of **3** and 5.4 g (40 mmol) of 1-(3-aminopropyl)-1H-imidazole was heated neat at 110 °C for 16 h. The reaction mixture was treated with 75 mL of methanol and then it was filtered. The collected solid was washed once with 75 mL of methanol and then it was dried at 100 °C to provide 2.1 g (66%) of a white solid: mp 250–252 °C; NMR (DMSO-d_6) δ 1.06 (t, 3 H), 1.88 (q, 2 H), 2.69 (q, 2 H), 3.11 (q, 2 H), 3.99 (t, 2 H), 6.89 (s, 1 H), 7.19 (s, 1 H), 7.35 (t, 1 H), 7.63 (s, 1 H), 9.80 (br s, 1 H), 10.44 (br s, 1 H). Anal. ($C_{12}H_{17}N_5O_2$) C, H, N.

N-[2-(1H-Imidazol-4-yl)ethyl]-5-ethyl-2,3-dihydro-2-oxo-1H-imidazole-4-carboxamide Hydrochloride (6). This compound was prepared from **3** in a manner identical with that for **5** except that the product was initially washed with water and then it was treated with methanolic HCl to form the hydrochloride salt during workup. Crystallization of the salt was accomplished from methanol/ether (2:1) to provide **6** in 30% overall yield: mp 250–252 °C dec; NMR (DMSO-d_6) δ 1.1 (t, 3 H), 2.66 (q, 2 H), 2.86 (t, 2 H), 3.12 (s, 1 H), 3.50 (m, 2 H), 7.50 (s, 1 H), 8.04 (t, 1 H), 9.03 (s, 1 H), 10.10 (s, 1 H), 10.25 (s, 1 H). Anal. ($C_{11}H_{15}N_5O_2$·HCl·0.1H_2O) C, H, N.

1-[4-(2-Methyl-1H-imidazol-1-yl)phenyl]ethanone (7). A stirred mixture of 100 g (0.72 mol) of 4-fluoroacetophenone, 89.2 g (1.09 mol) of 2-methylimidazole, and 200 g (1.45 mol) of anhydrous K_2CO_3 in 100 mL of DMSO was heated at 135 °C under N_2 for 54 h. The reaction mixture was cooled to ca. 70 °C, after which 500 mL of water was added, and then it was cooled to room temperature. The resulting oil layer was extracted into 2 × 300 mL of CH_2Cl_2. The organic extracts were combined with 100 mL of water and treated with 6 N HCl until the aqueous phase was acidic (pH ca. 1). The phases were separated and the organic phase was extracted with another 300 mL of acidified water (pH ca. 1). The combined aqueous phases were basified with 4 N NaOH and then they were decanted from the resulting precipitate. The solid was dissolved in 2 × 300 mL of CH_2Cl_2 and the solution was dried over Na_2SO_4, followed by treatment with 5 g of decolorizing carbon. It was then filtered through Celite and was evaporated under reduced pressure. This solid was recrystallized from 200 mL of acetone to provide 60 g (66%) of white crystals: mp 128–130 °C; NMR (CDCl$_3$) δ 2.42 (s, 3 H), 2.66 (s, 3 H), 7.05 (m, 2 H), 7.41 (d, 2 H), 8.09 (d, 2 H). Anal. ($C_{12}H_{12}N_2O$) C, H, N.

3,4-Dihydro-6-[[2-(1H-imidazol-4-yl)ethyl]amino]-2-methyl-4-oxopyrimidine-5-carbonitrile (10). A mixture of 6.7 g (37 mmol) of 1,4-dihydro-6-(methylthio)-4-oxopyrimidine-5-carbonitrile[12] and 4.0 g (35 mmol) of histamine in 40 mL of DMSO was heated at 125 °C for 24 h. After cooling, the reaction mixture was poured into 250 mL of CH_2Cl_2. The resulting precipitate was collected, washed with 50 mL of acetonitrile, and recrystallized from 90% ethanol to afford 2.1 g (23%) of yellow crystals: mp 235–237 °C; NMR (DMSO-d_6) δ 2.24 (s, 3 H), 2.74 (t, 2 H), 3.60 (m, 2 H), 6.84 (s, 1 H), 7.60 (s, 1 H), 7.92 (s, 1 H). Anal. ($C_{11}H_{12}N_6O$·0.4H_2O·0.1C_2H_6O) C, H, N.

3,4-Dihydro-6-(1H-imidazol-1-yl)quinolin-2(1H)-one (11).

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(22) Since there is the potential for vigorous decomposition upon strong heating, this temperature was used to provide a large safety factor: Touster, O. *Org. React.* **1953**, *VII*, 353.

A 4.2-g (36-mmol) quantity of thiophosgene was added dropwise to a stirred solution of 5.3 g (33 mmol) 6-aminoquinolin-2-(1H)-one[14,15] in 100 mL of 2 N HCl while under N_2. After the addition, the mixture was stirred for 1 h. The resulting solid was collected, washed with 25 mL of water, and dried to provide 4.7 g of the intermediate isothiocyanate.

A mixture of 4.5 g (22 mmol) of the isothiocyanate and 4.6 g (35 mmol) of aminoacetaldehyde diethyl acetal in 50 mL of absolute ethanol and 5.1 mL of triethylamine under N_2 was heated to reflux for 1 h. The solvent was then removed under reduced pressure and the resulting solid was taken up in 40 mL of 3 N HCl. The aqueous solution was heated to reflux for 1 h and then was cooled over ice to produce a brown solid. This solid was recrystallized from methanol/CH_2Cl_2 (1:2) to give 3.2 g (59%) of the intermediate 2-thioxoimidazolyl-substituted quinolinone: mp >310 °C; NMR (DMSO-d_6) δ 2.46–2.50 (m, 2 H), 2.90–2.95 (m, 2 H), 3.34 (s, 1 H), 6.93 (d, 1 H), 7.04 (t, 1 H), 7.20 (t, 1 H), 7.35 (dd, 1 H), 7.39 (s, 1 H), 10.36 (s, 1 H).

A 3.0-g (12-mmol) quantity of the thioxoimidazolyl intermediate was suspended in 30 mL of 20% nitric acid and the mixture was gently warmed with a hot air gun. After a vigorous evolution of gas, the mixture was heated to 100 °C and then it was allowed to cool to room temperature. The reaction mixture was treated with 10 mL of water followed by treatment with ammonium hydroxide until it was basic (pH 10) and then it was cooled over ice. The resulting solid was collected and was recrystallized three times from aqueous methanol (1:3) to provide 1.6 g (61%) of 10: mp 207–208 °C; NMR (CDCl₃) δ 2.68–2.73 (m, 2 H), 3.02–3.08

(m, 2 H), 6.93–6.96 (m, 1 H), 7.19–7.23 (m, 4 H), 7.80 (s, 1 H), 9.16 (s, 1 H). Anal. ($C_{12}H_{11}N_3O$) C, H, N.

Biological Studies. The in vitro determination of positive inotropic activity in ferret papillary muscle strips was conducted according to published procedures.[5] The biochemical determination of inhibition of crude cAMP phosphodiesterase obtained from canine cardiac tissue was also conducted according to published procedures.[2]

N-[(Arylmethoxy)phenyl] and N-[(Arylmethoxy)naphthyl] Sulfonamides: Potent Orally Active Leukotriene D₄ Antagonists of Novel Structure[1]

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Wyeth-Ayerst Research, CN 8000, Princeton, New Jersey 08543-8000. Received March 28, 1988

Two series of compounds, N-[(arylmethoxy)phenyl] sulfonamides and N-[(arylmethoxy)naphthyl] sulfonamides, were prepared as leukotriene D₄ (LTD₄) antagonists. In the phenyl series, N-[3-(2-quinolinylmethoxy)phenyl]-trifluoromethanesulfonamide (Wy-48,252, 16) was the most potent inhibitor of LTD₄-induced bronchoconstriction in the guinea pig. With an intragastric ID₅₀ of 0.1 mg/kg (2-h pretreatment), 16 was 300 times more potent than LY-171,883. Compound 16 also intragastrically inhibited ovalbumin-induced bronchoconstriction in the guinea pig with an ID₅₀ of 0.6 mg/kg. In vitro against LTD₄-induced contraction of isolated guinea pig trachea pretreated with indomethacin and L-cysteine, 16 produced a pK_B value of 7.7. In the rat PMN assay 16 inhibited both 5-lipoxygenase and cyclooxygenase (IC₅₀'s = 4.6 and 3.3 μM). In the naphthyl series, N-[7-(2-quinolinylmethoxy)-2-naphthyl]trifluoromethanesulfonamide (Wy-48,090, 47) in addition to potent LTD₄ antagonist activity (on isolated guinea pig trachea 47 had a pK_B value of 7.04) also had antiinflammatory activity (63% inhibition at 50 mg/kg in the rat carrageenan paw edema assay and 34% inhibition of TPA-induced inflammation at 1 mg/ear in the mouse ear edema model). Perhaps the antiinflammatory activity of 47 was due to its additional activity of inhibiting both 5-lipoxygenase and cyclooxygenase enzymes (IC₅₀'s = 0.23 and 11.9 μM, respectively, in rat PMN).

The need for new approaches to asthma therapy is underscored by the rising rate of deaths with current therapy.[2] The elucidation of the structure of slow-reacting substance of anaphylaxis (SRS-A) as a mixture of peptidoleukotrienes LTC₄, LTD₄, and LTE₄ has led to a new model of asthma.[3] In this model peptidoleukotrienes are proposed as the major mediators of an asthma attack,[4] and current evidence points to the LTD₄ receptor as the pharmacologically relevant peptidoleukotriene receptor with respect to asthma.[5] This suggests that a LTD₄ receptor antagonist may be effective in asthma. Indeed, early reports indicate that the LTD₄ receptor antagonist LY-171,883 may have clinical efficacy in antigen-induced asthma.[6]

Numerous research groups have synthesized LTD₄ antagonists by substantial modification of the right-hand

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(1) Presented in part at the 194th National Meeting of the American Chemical Society, New Orleans, LA, Sept 1987; MEDI 62.

(2) (a) Sly, R. M. *Ann. Allergy* **1986**, *56*, 207. (b) Benatar, S. R. *N. Engl. J. Med.* **1986**, *314*, 423. (c) Burney, P. G. *Lancet* **1986**, 323. (d) Sears, M. R.; Rea, H. H.; Rothwell, R. P.; O'Donnell, T. V.; Holst, P. E.; Gillies, A. J.; Bealehole, R. *Br. Med. J.* **1986**, *293*, 1342.

(3) For recent reviews of this model, see: Drazen, J. M. *Chest* **1986**, *89*, 414.

(4) A competing model proposed platelet-activating factor (PAF) rather than peptidoleukotrienes is responsible for the pathogenesis of asthma. Only clinical trials of both PAF and LTD₄ antagonists in asthma will resolve this controversy. For a recent review, see: Page, C. P.; Morley, J. *Pharmacol. Res. Commun.* **1986**, *18*, Suppl., 217.

(5) Samuelsson, B. *Science (Washington, D.C.)* **1983**, *220*, 568.