Section II - PHARMACODYNAMIC AGENTS

Editor: John Krapcho, Squibb Institute for Medical Research, Princeton, N.J. 08540

Chapter 6. Pulmonary and Anti-Allergy Drugs

Stanley C. Bell, Wyeth Laboratories, Inc. Radnor, PA 19087.
Robert J. Capetola, Ortho Pharmaceutical Corp. Raritan, NJ 08869.

Introduction - The main pathophysiological changes underlying asthma are narrowing of the airway due to constriction of the bronchial muscles, edema of the bronchial mucosa, leucocytic infiltration, and hypersecretion of a tenacious sputum, leading to mechanical obstruction of parts of the bronchial tree.[1] The allergic reaction is classified as a Type I inflammatory reaction. The union of sensitizing antigen or hapten with receptive IgE immunoglobulins bound to host mast cells and basophils triggers a series of intracellular events that culminate in the release of various pharmacological mediators. These mediators include histamine, slow reacting substance of anaphylaxis (SRS-A), eosinophil chemotactic factor of anaphylaxis (ECF-A), serotonin, platelet activating factor (PAF), kinins and prostaglandins. More recently, a neutrophil chemotactic factor of anaphylaxis (NCF-A) was described during IgE-mediated asthma in humans.[2]

Several papers have appeared that review the autoregulatory mechanisms and pharmacological control of mediator release.[3-5] It is becoming clearer that both positive and negative feedback mechanisms controlled by these chemical mediators through intermediary cyclic nucleotides provide important means for the intrinsic modulation of Type I inflammatory reactions. For example, the modulation process may be divided into two distinct phases, inhibition and enhancement.[3] Autonomic inhibition of mediator release is achieved principally by β-agonists and is specifically inhibited by β-antagonists such as propranolol. Inhibition of mediator release is also accomplished by histamine stimulation of H_2 receptors (on mast cells and basophils) and by E-series prostaglandins, through negative feedback mechanisms. These inhibitory substances act by increasing cyclic AMP levels which, through mechanisms not completely understood, in turn inhibit mediator release. Enhancement of mediator release is achieved by α-agonists and prostaglandins such as $F_2\alpha$ which probably act by antagonizing the action of cyclic AMP.

Cyclic AMP and cyclic GMP have opposing actions in regulating IgE dependent mediator release. The pathophysiology of asthma may depend therefore on the sum of the effects of the endogenous mediators which alter the ratio of cyclic nucleotides.[3]

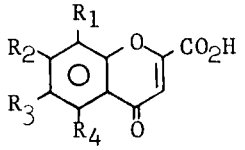
Histamine has long been regarded as one of the prime mediators of asthma in humans. However the inability to consistently block the action of histamine with classical antihistamines suggests that SRS-A may be the

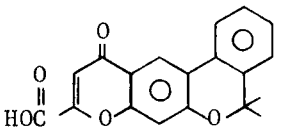
ISBN 0-12-040513-X

major bronchoconstrictor in human asthma. Recently a report appeared that provides clear evidence that both are involved.[6] Therefore pharmacological control of human airways in vivo may require a drug with polypharmacology, i.e. one that inhibits the release of many mediators or a combination of specific antagonists.

Inhibitors of Mediator Release - The pharmacologic actions of mediators of anaphylaxis and immune and biochemical mechanisms in asthma have been reviewed.[4,5] Disodium cromoglycate (DSCG) continues to be the subject of a number of papers. A study on histamine induced reflex bronchoconstriction in the dog suggests that DSCG may reduce the activity of lung irritant receptors.[7] Two new chromone derivatives FPL52757 (1) and (FPL57787 2) were reported to be active by inhalation or the oral route in experimental and clinical asthma.[8] The administration of 1, given either by inhalation as an aqueous aerosol up to 10 min. before antigen challenge, or in single or multiple oral doses of 50 to 100 mg from 2 to 12 hours before challenge, afforded protection from anaphylactic bronchoconstriction. In a limited study of the tricyclic chromone 2 in experimental asthma good activity was obtained with single or multiple oral doses of 4 to 10 mg.

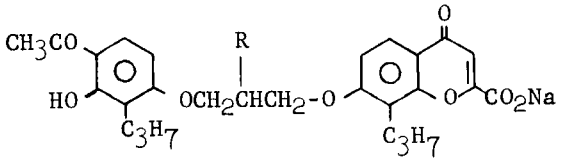
Benzosubstituted analogs 2-5 of DSCG have been assigned generic names.[9] Terbucromil 3 was also found to have dose related uricosuric properties in man.[10] A series of analogs of the tetracyclic chromone 6 (PR-D-92-EA) were tested for antiallergic activity in the rat PCA.[11] 6 had an ED_{50} of .11 mg/kg. A series of chromonone-2-carboxylic acids with anti-SRS-A activity was reported.[12] The deshydroxy analog (7) of FPL55712 (8) was more potent than 8 (IC_{50}=0.001 μg/ml) but offered no in vivo advantage. Neither 6 nor 8 was reported to be active against bovine SRS-A.[13] The chromone 3-tetrazole 9 and related compounds were reported to be slightly more potent than DSCG.[14]



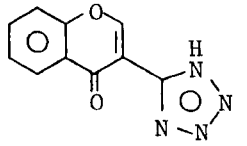


6

1 R_1, R_3 = Et, R_4 = OH, R_2 = H
2 R_1 = C_3H_7, R_4 = OH, R_2, R_3 = $(CH_2)_4$ Proxicromil
3 R_1, R_3 = $C(CH_3)_3$, R_2, R_4 = H Terbucromil
4 R_1 = C_3H_7, R_4 = H, R_2, R_3 = $(CH_2)_4$ Procromil
5 R_1 = Et, R_2 = H, R_3 = $CH{=}CH_2$, R_4 = OH Evicromil

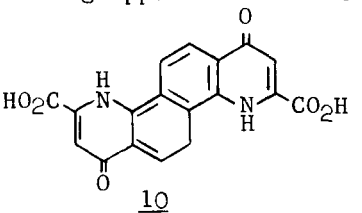


7 R = H
8 R = OH

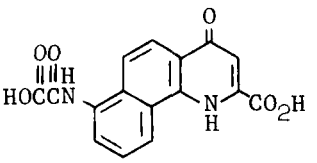


9

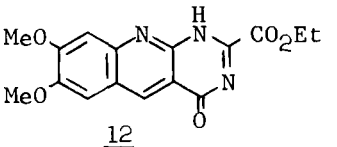
A fused bisquinoline carboxylic acid derivative 10 was reported to be 500 x more potent (ID_{50}=.005 mg/kg) than DSCG in the rat PCA[15] administered iv at the time of antigen challenge or ip 30 min. before antigen challenge. The quinoline 11 containing an oxamate group on the fused benzo ring was active *in vivo* (25 x DSCG) in the rat PCA.[16] Pyrimidoquinolin-2-carboxylates were described as being 10-100 x more potent than DSCG with the ester being orally active.[17a] Pirolate 12 the dimethoxy analog appears to be the compound of choice.[17b]



10

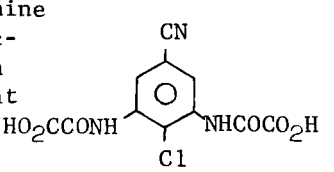


11



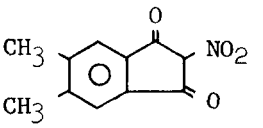
12

A clinical study of lodoxamide 13 tromethamine on asthmatic patients has shown it to be an effective and potent antiallergy compound. Inhalation doses of 0.01, 0.1 and 1.0 mg increased the amount of allergen necessary to cause a $\geq$ 20% fall in forced expiratory volume.[18]



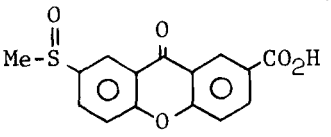
13 Lodoxamide

A variety of diones were found to be potent inhibitors of mediator release. Nivimedone (BRL10833) (14) was studied in seven asthmatic patients both by aerosol (40 mg) and by the oral route (2-10 mg/kg) and was without significant effect.[19]

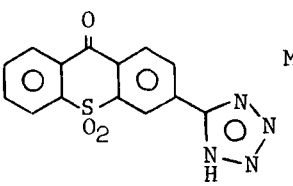


14 Nivimedone

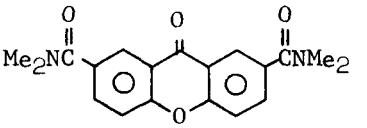
Xanthones and related tricyclics continue to be of considerable interest. Clinical studies of tixanox (R57337) (15), given as an aerosol, report it to be significantly better than placebo in exercise-induced-bronchospasm[20] while studies with doxantrazole 16 (up to 400 mg orally) show it to be ineffective in exercise-induced asthma.[21] Conversion of orally inactive xanthone acids to amides 17 produced compounds with some oral activity (rat PCA).[22]



15 Tixanox

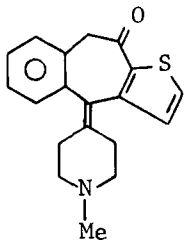


16 Doxantrazole



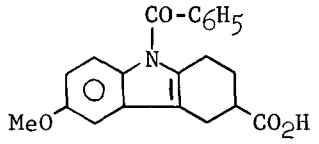
17

The cycloheptathiophene HC20-511 (18) was shown to be effective in the clinic against allergen bronchoprovocation for up to 6 hours with a dose of 1 mg po.[23] The drug was reportedly well tolerated. A review of the pharmacology of ketotifen 18 has appeared.[24]

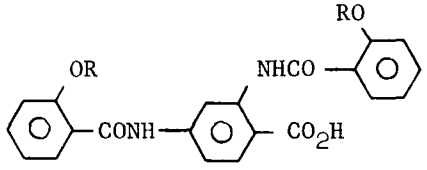


18 Ketotifen (Zatiden®)

A tetrahydrocarbazole derivative, oxarbazole (19) was studied in 24 asthmatic patients. Oral doses of 200 mg and 300 mg b.i.d. afforded significant protection against allergen-induced asthma.[25] Compound AB-50 (20), a bis (2-acetylsalicylamido) benzoic acid and AB-23 (21), the desacetoxy analog were compared to DSCG in the rat PCA and in vitro histamine release (antigen + 48/80).[26] 21 was reported to be more active than DSCG in vitro.

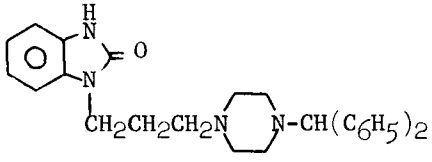


19 Oxarbazole

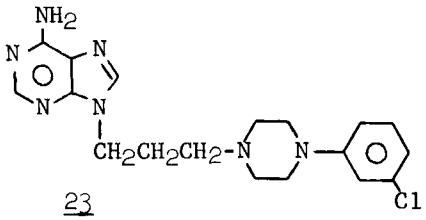


20 R = Ac
21 R = H

The piperazinopropylbenzimidazole (oxatomide R35443) 22 demonstrated clinical effectiveness in a large sample of patients with allergic rhinitis.[27] Oxatomide prevents mediator release and is also a potent H_1 antagonist as well as being orally active.[28] 23 is an orally active piperazinopropyladenine derivative capable of preventing ascaris-induced bronchospasm in dogs.[29]



22 Oxatomide



23

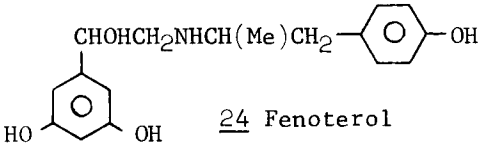
β-Adrenergic Stimulants - The most common side effect of long-term maintenance therapy with the newer β_2-stimulants is muscle tremor.[30,31] This effect is mediated by β_2 receptors in skeletal muscle.[32] The search for new agents with greater selectivity for bronchial versus skeletal muscle should continue.

Most new β-stimulants and those undergoing clinical investigation continue to be substituted β-hydroxy-α-phenethylamines. The effects of these substitutuions on β-adrenergic cyclases have been reviewed.[33] The interaction of the receptor and the aromatic moiety of several adrenergic

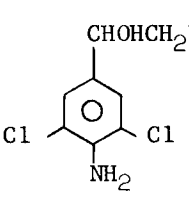
drugs was studied by the SCF-MO-LCAO method.[34] These authors conclude that the "affinity" of the drugs is due to the ethanolamine side chain and the regions of electrophilicity of the phenyl ring and the substituents, while the "intrinsic activity" can be explained by the regions of nucleophilicity of the aromatic ring and the substituents.

Clinical studies in the U.S. continue with fenoterol 24, a potent bronchodilator used for years in Europe.[35,36] It has a rapid onset of action with a duration superior to isoproterenol.[36] In patients with reversible airway obstruction, clenbuterol (NAB365) 25 was found to be about 100 x more potent that salbutamol 26 po.[37] Side effects were similar and included moderate to moderately severe tremors. Orally 25 reaches maximum plasma concentration in 2 hours and has a half-life of 35 hours.[37] In another study 25 was shown to be equiactive with 24 but more potent (24 μg vs. 5 mg given by inhalation).[38a] The bronchodilating effect of salbutamol 26 was significantly superior and of longer duration than that of isoproterenol in another clinical study.[38b] No significant changes in heart rate or blood pressure were noted with 26.

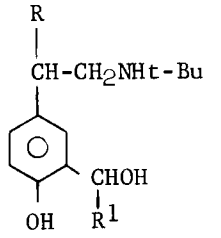
Modification of the aromatic hydroxymethyl group of salbutamol 26 produced compounds 27 of slightly less activity[39] while substitutions of the β-hydroxy group with hydroxymethyl[40] 28 greatly decreases potency. The formamido derivative BD-40-A (29) was 43 x more potent as a bronchodilator than 26 given orally in guinea pigs.[41]



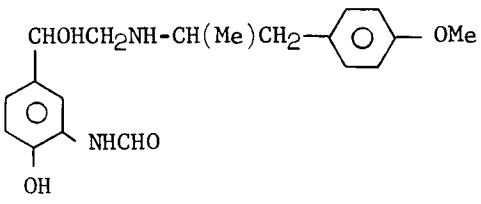
24 Fenoterol



25 Clenbuterol

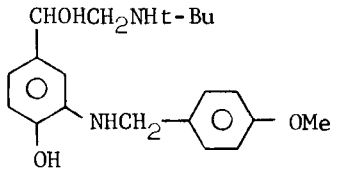


26 R = OH, R^1 = H, Salbutamol
27 R^1 = Me, R = OH
28 R^1 = H, R = CH_2OH

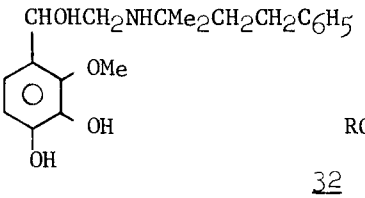


29

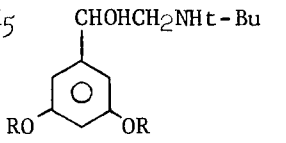
Animal data suggest that QH25 (30) is a more selective bronchodilator than both isoproterenol and salbutamol.[42] A study of Sm 220 Cl (31) demonstrates species differences and suggests there would be no tracheobronchial vs. cardiac selectivity in man.[43] Ibuterol 32 (KWD2058), the di-isobutyric ester of terbutaline 33 caused significantly less increase in heart rate, tremor ratio, and pulse amplitude in man when doses causing equal bronchodilation were infused.[44]



30

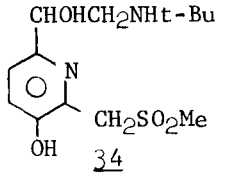


31

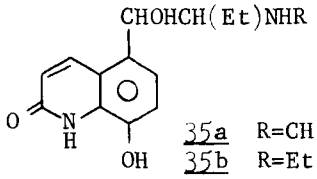


32 R=$COCHMe_2$ Ibuterol
33 R=H Terbutaline

Replacement of the phenyl ring of sulfonterol with pyridyl yielded a compound 34 of equal potency but, more β_2-selective.[45] Carbostyryl derivatives 35a (OPC-2009), and 35b (OPC-2030) [(-) erythro] show high β_2-selectivity in dogs[46] and data suggest their action is mediated through increasing cAMP concentration.[47]

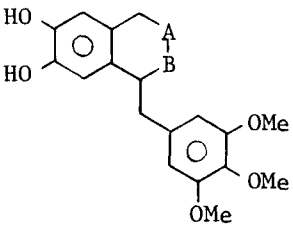


34

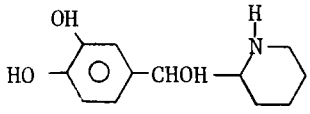


35a R=$CH(CH_3)_2$
35b R=Et

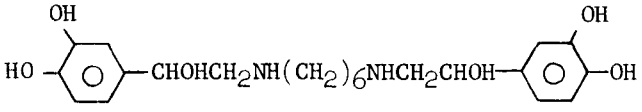
The bronchodilating effect of β-agonists such as isoproterenol, salbutamol and chlorprenaline was shown to be markedly enhanced when combined with the α-blocker, dihydroergotoxin.[48] The isoquinoline, trimetoquinol(AQ-110), 36 was compared with a series of analogs[49,50] and the isomer 37 was found to be more β_2 selective although not as potent.[97] Detailed pharmacological and therapeutic reviews have appeared for rimiterol 38[51] and hexoprenaline 39.[52]



36 Trimetoquinol A = CH_2, B = NH
37 A = NH, B = CH_2

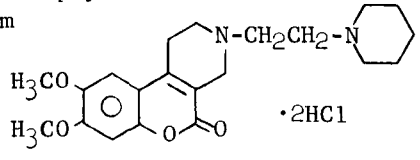


38 Rimiterol



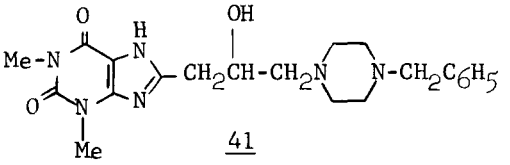
39 Hexoprenaline

The pharmacology of W10,294A (40) has been outlined. The bronchodilator activity was compared to that of aminophylline and shown to be more potent. The mechanism of action is apparently unrelated to beta stimulation or phosphodiesterase inhibition. 40 reached peak plasma levels in 1.7 hr. with a half-life of 1-2 hours.[53,54]

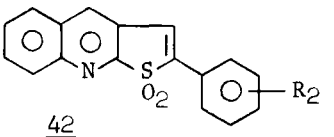


40

Phosphodiesterase Inhibitors - A basically substituted derivative of theophylline 41 was shown to inhibit edema formation or delayed contact allergy (DNCB) in guinea pigs.[55] Interestingly this derivative is a potent competitive antagonist of histamine (H_1).[55] A series of thieno-quinoline-1,1-dioxides 42, prepared as potential antiinflammatory agents, was found to possess phosphodiesterase inhibiting activity in the range of theophylline.[56]



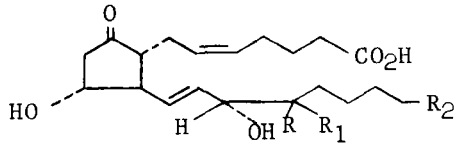
41



42

A study characterizing the phosphodiesterases in human lung tissue has appeared.[57]

Prostaglandins - The use of prostaglandins as bronchodilators continues to be of considerable interest. Historically, their use has been limited due to pharyngeal irritation and cough when administered by inhalation. 16 (S)-Methyl-20-methoxy PGE_2 (YPG-209) 43, given intraduodenally, was a potent inhibitor (ED_{50} of 19 μg/kg) of increased airway resistance induced by histamine in anesthetized guinea pigs.[58] Intravenously it was 230 x more potent than PGE_2. The substitution of alkoxy groups in the 16 position of PGE_2 generally produces bronchodilators of less potency 44[59] while substitution of 16,16-trimethylene derivatives of PGE_1 and PGE_2 (45)[60] yields compounds with comparable potency but produces a short-lived pulmonary hypertension.

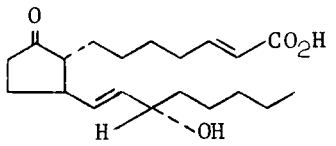


43 R = Me, R_1 = H, R_2 = OMe

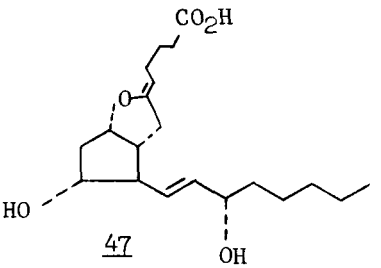
44 R = OMe, R_1, R_2 = H

45 R, R_1 = $(CH_2)_3$, R_2 = H

11-Deoxy-15-hydroxy-2,13-diene prostaglandin (46) showed bronchodilating activity comparable to PGA_2 while the isomeric 16-hydroxy-2,14-diene analogs were bronchoconstricting.[61] Prostacyclin, 47 an interesting substance that may be a naturally occurring inhibitor of platelet aggregation was also reported to have significant bronchodilating activity.[62]



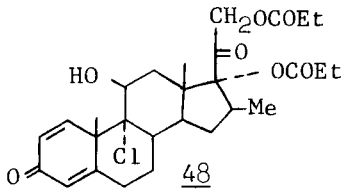
46



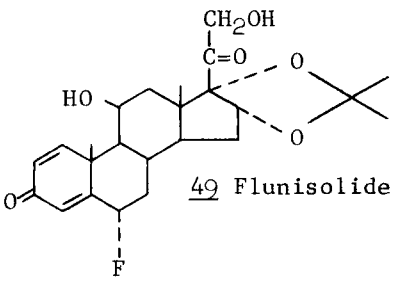
47

Steroids - Clinical testing of beclomethasone dipropionate 48 has been extensive. Its use is intended for the prophylactic treatment of steroid-

dependent asthmatics. Therapy with topical steroids yields maximal local and minimal systemic effects with oropharyngeal fungal infections being an important complication. Beclomethasone dipropionate 48 was tested in an 18 month study of steroid-dependent asthmatics and demonstrated a significant improvement with no Candida infections.[63] Flunisolide 49 was tested as a nasal spray in adult hay fever patients and shown to be safe and efficacious in the treatment of seasonal allergic rhinitis.[64]

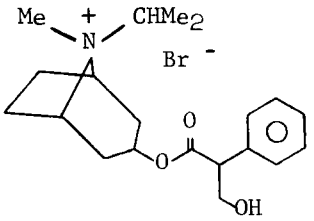


48



49 Flunisolide

Anticholinergics - The quaternary anticholinergic Schl000 (ipratropium bromide) (50) has been studied extensively in the clinic and demonstrated to be an effective bronchodilator in asthma. In a recent study 50



50 Ipratropium Bromide (Atrovent®)

was tested in patients with chronic bronchitis.[65] Doses of inhaled 50 ranged from 10 μg to 80 μg and these doses were superior in duration of action to isoproterenol (75 μg and 150 μg). Bronchodilatory response to 50 lasted up to 4 hours. No significant alterations of pulse or blood pressure were noted. Dryness of the mouth and scratching in the trachea were reported absent. 50 was also assessed alongside DSCG and shown to be effective in exercise-induced asthma.[66] Salbutamol (200 μg), administered as an aerosol, was found to produce a greater degree of bronchodilation during the initial 3 hours following drug administration than the quaternary anticholinergic Schl000 (40 μg) in asthmatic patients.[67] Comparable bronchodilation was achieved after 4 hours and a combination of the two drugs produced a longer duration of bronchodilation than either drug alone.

Peptides - Previously uncharacterized eosinophil chemotactic activity of apparent M.W. 1500 to 2500 was found preformed in rat peritoneal mast cells, was associated with mast cell granules and was released from sensitized mast cells.[68] Further purification revealed two peaks of eosinophil chemotactic activity. In other experiments, data suggest that histamine and the ECF-A peptides (Val-Gly-Ser-Glu and Ala-Gly-Ser-Glu) not only attract eosinophils selectively in chemotaxis but also increase the number of complement receptors on the eosinophil membrane.[69] The significance of this finding is not known at present.

References

1. H. Formgren, Scand. J. Resp. Dis.(Suppl), 97, 1 (1977).
2. P.C. Atkins, M. Norman, H. Weiner, and B. Zweiman, Ann. Intern. Med., 86, 415 (1977).
3. M.C. Holroyde, J.F. Burka, P. Eyre, Agents and Actions, 7, 421 (1977).
4. P.J. Piper, Pharmac. Ther. B, 3, 75 (1977).
5. T.T. Hubscher, Ann. Allergy, 38, 83 (1977).
6. G.K. Adams III, L.M. Lichtenstein, Nature, 270, 255 (1977).
7. D. M. Jackson, I.M. Richards, Br. J. Pharmac., 61, 257 (1977).
8. J. Augstein, H. Cairns, D. Hunter, T.B. Lee, J. Suschitzky, R.E.C. Altounyan, D.M. Jackson, J. Mann, T.S.C. Orr, and P. Sheard, Agents and Actions, 7, 443 (1977).
9. Brit. Pharmacop. Comm. Approved Names (Suppl. 1), 6, Oct. 1, 1977.
10. J. Augstein, H. Cairns, A. Chambers, J.W. Burns, and H. Radziwonik, J. Pharm. Pharmac., 28, 919 (1976).
11. J.P. Devlin, K. Freter and P.B. Stewart, J. Med. Chem., 20, 205, (1977).
12. R.A. Appleton, J.R. Bantick, T.R. Chamberlain, D.N. Hardern, T.B. Lee, and A.D. Pratt, ibid., 20, 371 (1977).
13. J.F. Burka and P. Eyre, Eur. J. Pharmacol., 44, 169 (1977).
14. A. Nohara, H. Kuriki, T. Saijo, H. Sugihara, M. Kanno and Y. Sanno, J. Med. Chem., 20, 141 (1977).
15. C.M. Hall, J.B. Wright, H.G. Johnson, and A.J. Taylor, J. Med. Chem., 20, 1337 (1977).
16. J.B. Wright and H.G. Johnson, ibid., 20, 166 (1977).
17. a) J.H. Althuis, P.F. Moore, and H.J. Hess, A.C.S. 174 Nat'l Mtg., Chicago, Aug., 1977 Abstr. MEDI - 44. b) J.A.M.A., 238, 1407 (1977).
18. T. Bui, K, Burke, G. Watt, A. Bewtra, R. Townley, 34th Ann. Meeting Am. Acad. of Allergy, Abstr. No. 201 (1978).
19. S. Zwi, S. Hurwitz, H. Kallenbach and H. Goldman, Am. Rev. Resp. Dis., 115, 184 (1977).
20. a) R. R. Rosenthal, J. Oren, J.D. Johnson, and P.S. Norman, Congress Abstracts, Ann. Allergy, 38 #63 (1977). b) J.A.M.A., 236, 1992 (1977).
21. H. Poppius, and B. Stenius, Europ. J. Clin. Pharmacol., 11, 107 (1977).
22. W.J. Jones, Jr., W.L. Albrecht, N.L. Munro and K.T. Stewart, J. Med. Chem., 20, 594 (1977).
23. a) J. P. Girard and M. Cuevas, Acta. Allergol., 32, 27 (1977). b) E. Waldvogel, G. Schwarb, J. M. Bastian, and J.-P. Bourquiss, Helv. Chim. Acta., 59, 866 (1977).
24. U. Martin and D. Roemer, Monogr. Allergy, 12 145 (1977).
25. C.J. Falliers, T.S. Mingo, 34th Ann. Meeting Am. Acad. Allergy, Abst. No. 199 (1978).
26. Y. Ohsugi, T. Matsuno, and Y. Takagaki, Chem. Pharm. Bull., 25, 2437 (1977).
27. R. De Beule, E. Vannieuwenhuyse, J. Callier, W. Verstraete, F. Degreef, M. Gregoire, Y. Robience, W. Stevens and P. Libert, Acta. Allergol., 32, 278 (1977).
28. F. Awouter, C.J.E. Niemegeers, J. Vanden Bark, J.M. Van Nueten, F.M. Leneerts, M. Borgers, K.H.L. Schellekins, A. Broekaert, J. De Cree, and P.A.J. Janssen, Experientia, 33, 1657 (1977).
29. O.I. Zimmermann, W.T. Ulmer and A. Roesch., Arzneim-Forsch., 27 (II) 1999 (1977).
30. D.P. Tashkin, Chest., 71, 125 (1977).
31. M. Weinberger and L. Hendeles, Ration. Drug. Ther., 11, (6) (1977).
32. S. Larsson, Acta. Med. Scand. Suppl., 608 5 (1977).
33. H. Sheppard in "Annual Reports in Medicinal Chemistry", Vol. 12, F.H. Clark, Ed. Academic Press, New York, NY, 1977, P. 173.
34. C. Petrongolo, B. Macchia, F. Macchia, and A. Martinelli, J. Med. Chem., 20, 1645 (1977).
35. W.W. Simi and W.C. Miller, J. Allergy. Clin. Immunol., 59, 178 (1977).
36. C. Emirgil, K. Palmer, L. VanVoorhies, C. Wesson, B.J. Sobol, Ann. Allergy, 39, 415 (1977).
37. P. L. Kamburoff, F.J. Prime, and O.-P. Schmidt, Br. J. Clin. Pharmacol., 4, 67 (1977).
38. a) V.A. Dorow, Arzneim-Forsch., 27 (II) 2020 (1977). b) V.K. Mahajan, J.F. Tomashefski, G.L. Huber, Ann. Allergy, 39, 319 (1977).
39. J. Ven, J.S. Frazee, C. Kaiser, D.F. Colella and J.R. Wardell Jr., J. Med. Chem., 20 1029 (1977)
40. T. Jen, J.S. Frazee, M.S. Schwartz, K.F. Erhard, C. Kaiser, D.F. Colella, and J.R. Wardell Jr., J. Med. Chem., 20, 1263 (1977).
41. K. Murase, T. Mase, H. Ida, K. Takahashi and M. Murakami, Chem. Pharm. Bull., 25, 1368 (1977).
42. J.-J. Larsen and K. Hermansen, Acta. Pharmacol. et. Toxicol., 40, 42 (1977).
43. K. Bohmer and C. Raper, Clin. Exp. Pharmacol. Physiol., 4, 349 (1977).
44. S. Larsson, N. Svedymr, Europ. J. Clin. Pharmacol., 11, 429 (1977).
45. T. Jen, J.S. Frazee, M.S. Schwartz, C. Kaiser, D.F. Colella, and J.R. Wardell, Jr., J. Med. Chem., 20, 1258 (1977).
46. S. Yoshizaki, Y. Manabe, S. Tamada, K. Nakagawa, and S. Tei, J. Med. Chem., 20, 1103 (1977).
47. I. Takayanagi, N. Kondo, H. Yamashita, T. Hongo and K. Takagi, J. Pharm. Pharmac., 29, 187 (1977).

48. S. Kitamura, Y. Ishihara, K. Sasaki, T. Shimizu, and M. Harasawa, Arzneim-Forsch., 27 (II) 1959 (1977).
49. K. Ikezawa, H. Takenaga, M. Sato, H. Nakajima, and A. Kiyomoto, Japan J. Pharmacol., 27 537 (1977).
50. P.F. Kador, R. Venkatraman, D.F. Feller, and D.D. Miller, J. Med. Chem., 20 891 (1977).
51. R.M. Pinder, R.N. Brogden, T.M. Speight, G.S. Avery, Drugs 14, 81 (1977).
52. R.M. Pinder, R.N. Brogden, T.M. Speight, G.S. Avery, Drugs, 14, 1 (1977).
53. F.-J. Leinweber and F.J. DeCarlo, Fed. Proc., 36, 3514 Abs., 1 Mar. 77.
54. R.E. Giles, J.C. Williams, M.P. Finkel, J.P.E.T., 203, 701 (1977).
55. R. Czarnecki, Pol. J. Pharmacol. Pharm., 29, 123 (1977).
56. E.A. Harrison, Jr., K.C. Rice and M.E. Rogers, J. Heterocyclic Chem., 14, 909 (1977).
57. D. Green, G. Guy, J.B. Moore, Jr. and H. Lopezb, Life Sciences 20, 1157 (1977).
58. K. Tomioka, M. Terai, and H. Maeno, Arch. Int. Pharmacodyn., 226, 224 (1977).
59. W.A. Hallett, A. Wissner, C.V. Grudzinskas, R. Partridge, J.E. Birnbaum, M.J. Wriss, and F. Dessy, Prostaglandins, 13, 409 (1977).
60. J.S. Skotnicki, R.E. Schaub, M.J. Weiss, and F. Dessy, J. Med. Chem., 20, 1042 (1977).
61. W. Bartmann, G. Beck, R. Kunstmann, U. Lerch, and H. Teufel, Tetrahedron Lett. 2563 (1977).
62. M.A. Wasserman, D.W. DuCharme, R.L. Griffen, M.G. Wendling and G.L. DeGraaf, The Pharmacologist, 19 ASPET Abstract No. 098 (1977).
63. I. Kass, S.V. Nair, K.D. Patil, Chest, 71, 703 (1977).
64. J.K. Kammermeyer, D.W. Rajtora, J. Anuras, and H.B. Richarson, J. Allergy. Clin. Immunol., 59 287 (1977).
65. W. Baigelman, S. Chodosh, Chest, 71, 324 (1977).
66. M. Chan-Yeung, Chest, 71, 320 (1977).
67. R.E. Ruffin, J.D. Fitzgerald and A.S. Rebuck, J. Allergy Clin. Immunol., 59, 136 (1977).
68. R.N. Boswell, K.F. Austen, E.J. Goetzl, J. Immunol., 120, 15, (1978).
69. A.R.E. Anwar and A.B. Kay, Nature, 269, 522 (1977).