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BENZIMIDAZOLE DERIVATIVES AS MODULATORS OF IgE

Background of the Invention

This invention relates to small molecule inhibitors of the IgE response to allergens that are useful in the treatment of allergy and/or asthma or any diseases where IgE is pathogenic.

An estimated 10 million persons in the United States have asthma, about 5% of the population. The estimated cost of asthma in the United States exceeds $6 billion. About 25% of patients with asthma who seek emergency care require hospitalization, and the largest single direct medical expenditure for asthma has been inpatient hospital services (emergency care), at a cost of greater than $1.6 billion. The cost for prescription medications, which increased 54% between 1985 and 1990, was close behind at $1.1 billion (Kelly, *Pharmacotherapy* 12:13S-21S (1997)).

According to the National Ambulatory Medical Care Survey, asthma accounts for 1% of all ambulatory care visits, and the disease continues to be a significant cause of missed school days in children. Despite improved understanding of the disease process and better drugs, asthma morbidity and mortality continue to rise in this country and worldwide (U.S. Department of Health and Human Services; 1991, publication no. 91-3042). Thus, asthma constitutes a significant public health problem.

The pathophysiologic processes that attend the onset of an asthmatic episode can be broken down into essentially two phases, both marked by bronchoconstriction, that causes wheezing, chest tightness, and dyspnea. The first, early phase asthmatic response is triggered by allergens, irritants, or exercise. Allergens cross-link immunoglobulin E (IgE) molecules bound to receptors on mast cells, causing them to release a number of pre-formed inflammatory mediators, including histamine. Additional triggers include the osmotic changes in airway tissues following exercise or the inhalation of cold, dry air. The second, late phase response that follows is characterized by infiltration of activated eosinophils and other inflammatory cells into airway tissues, epithelial desquamonon, and by the presence of highly viscous mucus within the airways. The damage caused by this inflammatory response leaves the airways "primed" or sensitized, such that smaller triggers are required to elicit subsequent asthma symptoms.

A number of drugs are available for the palliative treatment of asthma; however, their efficacies vary markedly. Short-acting β_2-adrenergic agonists, terbutaline and albuterol, long the mainstay of asthma treatment, act primarily during the early phase as bronchodilators. The newer

long-acting β_2-agonists, salmeterol and formoterol, may reduce the bronchoconstrictive component of the late response. However, because the β_2-agonists do not possess significant antiinflammatory activity, they have no effect on bronchial hyperreactivity.

Numerous other drugs target specific aspects of the early or late asthmatic responses. For example, antihistamines, like loratadine, inhibit early histamine-mediated inflammatory responses. Some of the newer antihistamines, such as azelastine and ketotifen, may have both antiinflammatory and weak bronchodilatory effects, but they currently do not have any established efficacy in asthma treatment. Phosphodiesterase inhibitors, like theophylline/xanthines, may attenuate late inflammatory responses, but there is no evidence that these compounds decrease bronchial hyperreactivity. Anticholinergics, like ipratopium bromide, which are used in cases of acute asthma to inhibit severe bronchoconstriction, have no effect on early or late phase inflammation, no effect on bronchial hyperreactivity, and therefore, essentially no role in chronic therapy.

The corticosteroid drugs, like budesonide, are the most potent antiinflammatory agents. Inflammatory mediator release inhibitors, like cromolyn and nedocromil, act by stabilizing mast cells and thereby inhibiting the late phase inflammatory response to allergen. Thus, cromolyn and nedocromil, as well as the corticosteroids, all reduce bronchial hyperreactivity by minimizing the sensitizing effect of inflammatory damage to the airways. Unfortunately, these antiinflammatory agents do not produce bronchodilation.

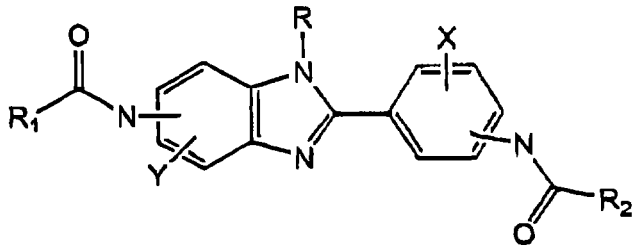
Several new agents are currently being developed that inhibit specific aspects of asthmatic inflammation. For instance, leukotriene receptor antagonists (ICI-204, 219, accolate), specifically inhibit leukotriene-mediated actions. The leukotrienes have been implicated in the production of both airway inflammation and bronchoconstriction.

Thus, while numerous drugs are currently available for the treatment of asthma, these compounds are primarily palliative and/or have significant side effects. Consequently, new therapeutic approaches which target the underlying cause rather than the cascade of symptoms would be highly desirable. Asthma and allergy share a common dependence on IgE-mediated events. Indeed, it is known that excess IgE production is the underlying cause of allergies in general and allergic asthma in particular (Duplantier and Cheng, *Ann. Rep. Med. Chem.* 29:73-81 (1994)). Thus, compounds that lower IgE levels may be effective in treating the underlying cause of asthma and allergy.

None of the current therapies eliminate the excess circulating IgE. The hypothesis that lowering plasma IgE may reduce the allergic response, was confirmed by recent clinical results with chimeric anti-IgE antibody, CGP-51901, and recombinant humanized monoclonal antibody, rhuMAB-E25. Indeed, three companies, Tanox Biosystems, Inc., Genentech Inc. and Novartis AG are collaborating in the development of a humanized anti-IgE antibody (BioWorld® Today, February 26, 1997, p. 2) which will treat allergy and asthma by neutralizing excess IgE. Tanox has already successfully tested the anti-IgE antibody, CGP-51901, which reduced the severity and duration of nasal symptoms of allergic rhinitis in a 155-patient Phase II trial (Scrip #2080, Nov 24, 1995, p.26). Genentech recently disclosed positive results from a 536 patient phase-II/III trials of its recombinant humanized monoclonal antibody, rhuMAB-E25 (BioWorld® Today, November 10, 1998, p. 1). The antibody, rhuMAB-E25, administered by injection (highest dose 300 mg every 2 to 4 weeks as needed) provided a 50% reduction in the number of days a patient required additional "rescue" medicines (antihistimines and decongestants), compared to placebo. An NDA filing for this product is projected to be in the year 2000. The positive results from anti-IgE antibody trials suggest that therapeutic strategies aimed at IgE down-regulation may be effective.

Summary of the Invention

The present invention discloses a family of related compounds for use in the treatment of a condition associated with an excess IgE level. The benzimidazole inhibitors of IgE in accordance with the present invention are represented by the generic formula:

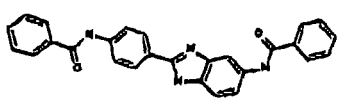


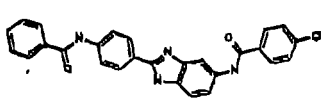
X and Y are independently selected from the group consisting of H, alkyl, alkoxy, aryl, substituted aryl, hydroxy, halogen, amino, alkylamino, nitro, cyano, CF_3, OCF_3, $CONH_2$, CONHR and $NHCOR_1$. R is selected from the group consisting of H, CH_3, C_2H_5, C_3H_7, C_4H_9,

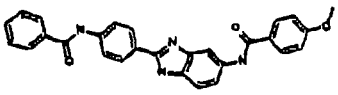
CH_2Ph, and $CH_2C_6H_4$-F(p-). R_1 and R_2 are independently selected from the group consisting of H, aryl, substituted aryl, cycloaryl substituted cycloaryl, multi-ring cycloaryl, benzyl, substituted benzyl and the like. Substitutions are alkyl, aryl, CF3, CH3, OCH_3, OH, CN, COOR, COOH and the like.

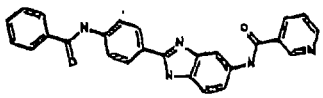
In accordance with another aspect of the invention, there is disclosed a composition for use in the treatment of an allergic condition comprising the diacyl benzimidazole inhibitor of IgE disclosed above and at least one additional active ingredient, combined in a pharmaceutically acceptable diluent. The additional active ingredients may be selected from the group consisting of short-acting β_2-adrenergic agonists, like terbutaline and albuterol, long-acting β_2-adrenergic agonists, like salmeterol and formoterol, antihistamines, like loratadine, azelastine and ketotifen, phosphodiesterase inhibitors, anticholinergic agents, corticosteroids, inflammatory mediator release inhibitors and leukotriene receptor antagonists.

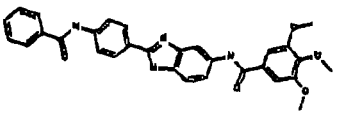
In accordance with another aspect of the invention, there is disclosed a family of symmetric and asymmetric diacyl and monoacyl benzimidazole compounds for use in the treatment of an allergic condition comprising the following species:

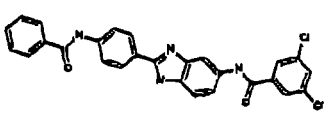
Structure	BIAA
	$C_{27}H_{20}N_4O_2$
	CLOGP 5.47

Structure	BIAB
	$C_{27}H_{19}ClN_4O_2$
	CLOGP 6.24

Structure	BIAC
	$C_{28}H_{22}N_4O_3$
	CLOGP 5.50

Structure	BIAD
	$C_{26}H_{18}N_5O_2$
	CLOGP 4.26

Structure	BIAE
	$C_{30}H_{26}N_4O_5$
	CLOGP 4.02

Structure	BIAF
	$C_{27}H_{18}Cl_2N_4O_2$
	CLOGP 6.97

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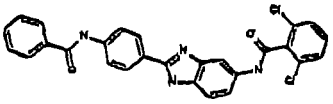
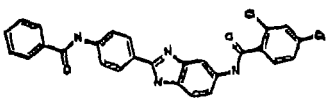
	$C_{27}H_{18}Cl_2N_4O_2$
	CLOGP 5.31

Structure	BIAH
	$C_{27}H_{18}Cl_2N_4O_2$
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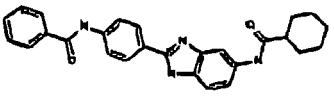	$C_{27}H_{26}N_4O_2$
	CLOGP 6.01

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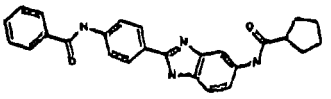	$C_{26}H_{24}N_4O_2$
	CLOGP 5.45

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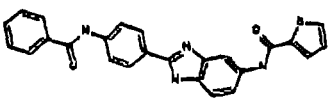	$C_{25}H_{18}N_4O_2S$
	CLOGP 5.20

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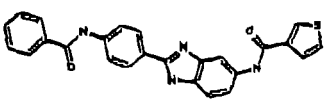	$C_{25}H_{18}N_4O_2S$
	CLOGP 5.20

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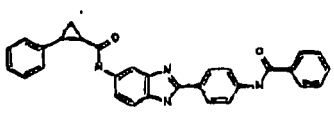	$C_{30}H_{24}N_4O_2$
	CLOGP 5.74

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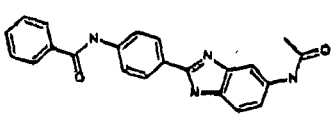	$C_{22}H_{18}N_4O_2$
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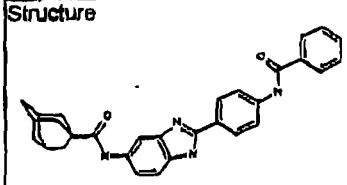	$C_{31}H_{30}N_4O_2$
	CLOGP 6.64

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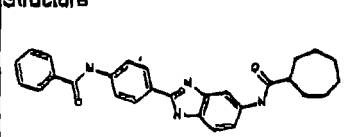	$C_{28}H_{28}N_4O_2$
	CLOGP 6.57

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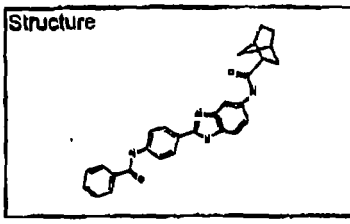	$C_{28}H_{26}N_4O_2$
	CLOGP 5.76

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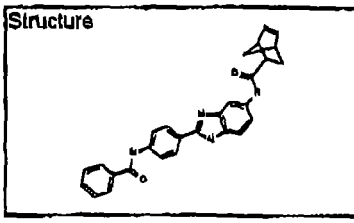
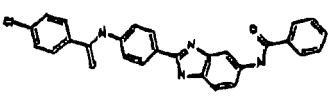
	$C_{28}H_{24}N_4O_2$
	CLOGP 5.26

Structure	BIBA
	$C_{27}H_{19}ClN_4O_2$
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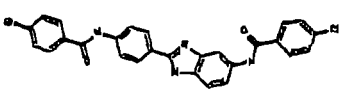	$C_{27}H_{18}Cl_2N_4O_2$
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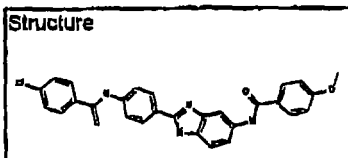	$C_{28}H_{21}ClN_4O_3$
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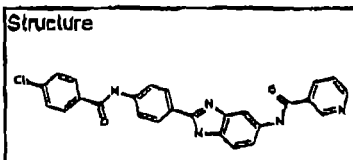	$C_{26}H_{18}ClN_5O_2$
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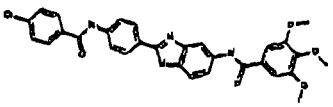	$C_{30}H_{25}ClN_4O_5$
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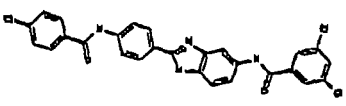	$C_{27}H_{17}Cl_3N_4O_2$
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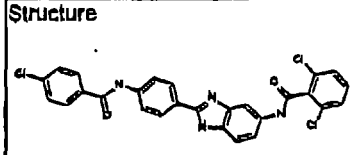	$C_{27}H_{17}Cl_3N_4O_2$
	CLOGP 6.11

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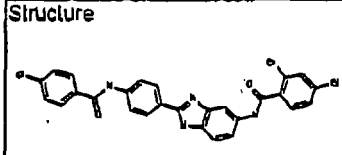	$C_{27}H_{17}Cl_3N_4O_2$
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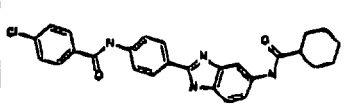	$C_{27}H_{25}ClN_4O_2$
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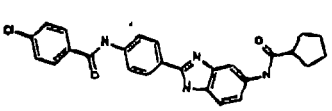	$C_{26}H_{23}ClN_4O_2$
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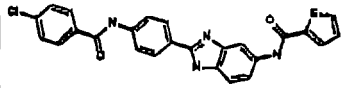	$C_{25}H_{17}ClN_4O_2S$
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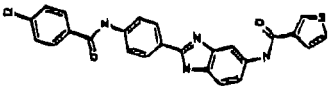	$C_{25}H_{17}ClN_4O_2S$
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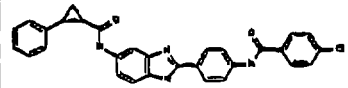	$C_{30}H_{23}ClN_4O_2$
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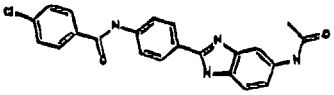	$C_{22}H_{17}ClN_4O_2$
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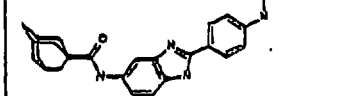
Structure	BIBO
	$C_{31}H_{29}ClN_4O_2$
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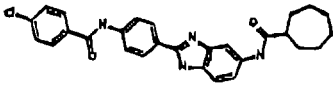	$C_{28}H_{27}ClN_4O_2$
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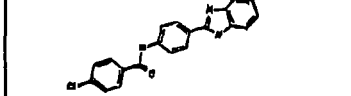	$C_{28}H_{25}ClN_4O_2$
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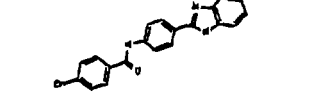
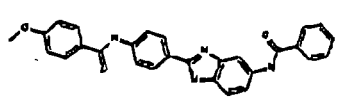
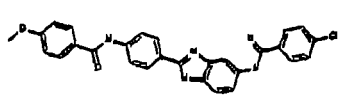
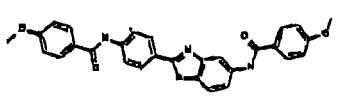
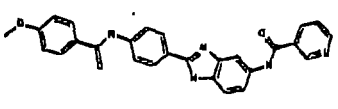
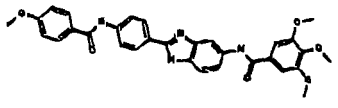
	$C_{28}H_{23}ClN_4O_2$
	CLOGP 6.08

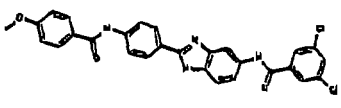
Structure	BICA
	$C_{28}H_{22}N_4O_3$
	CLOGP 5.58

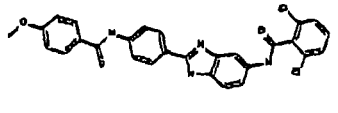
Structure	BICB
	$C_{28}H_{21}ClN_4O_3$
	CLOGP 6.35

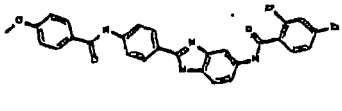
Structure	BICC
	$C_{29}H_{24}N_4O_4$
	CLOGP 5.70

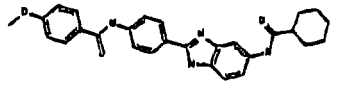
Structure	BICD
	$C_{27}H_{21}N_5O_3$
	CLOGP 4.39

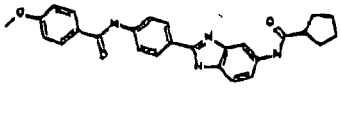
Structure	BICE
	$C_{31}H_{28}N_4O_6$
	CLOGP 4.93

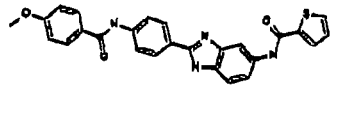
Structure	BICF
	$C_{28}H_{20}Cl_2N_4O_3$
	CLOGP 7.09

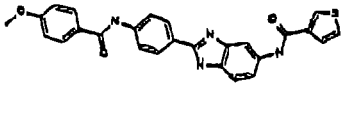
Structure	BICG
	$C_{28}H_{20}Cl_2N_4O_3$
	CLOGP 5.43

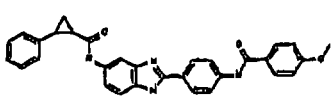
Structure	BICH
	$C_{28}H_{20}Cl_2N_4O_3$
	CLOGP 6.28

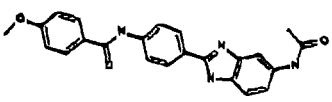
Structure	BICI
	$C_{28}H_{28}N_4O_3$
	CLOGP 6.12

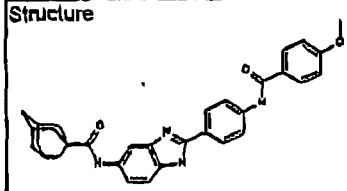
Structure	BICJ
	$C_{27}H_{26}N_4O_3$
	CLOGP 5.56

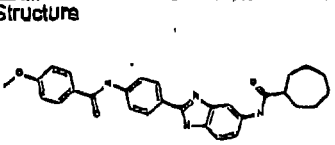
Structure	BICK
	$C_{26}H_{20}N_4O_3S$
	CLOGP 5.32

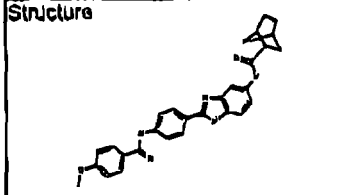
Structure	BICL
	$C_{26}H_{20}N_4O_3S$
	CLOGP 5.32

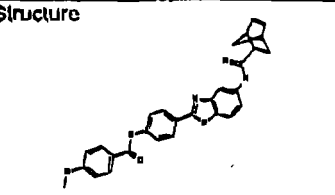
Structure	BICM
	$C_{31}H_{26}N_4O_3$
	CLOGP 5.85

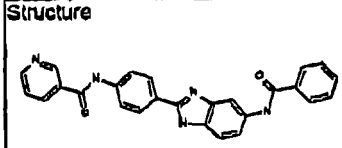
Structure	BICN
	$C_{23}H_{20}N_4O_3$
	CLOGP 4.09

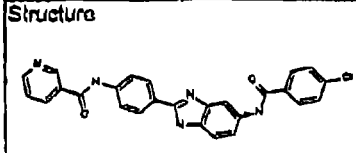
Structure	BICO
	$C_{32}H_{32}N_4O_3$
	CLOGP 6.75

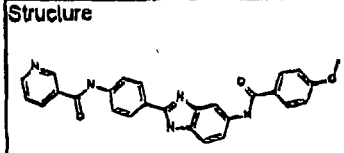
Structure	BICP
	$C_{28}H_{30}N_4O_3$
	CLOGP 5.86

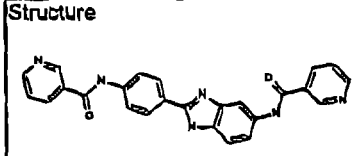
Structure	BICQ
	$C_{29}H_{28}N_4O_3$
	CLOGP 5.88

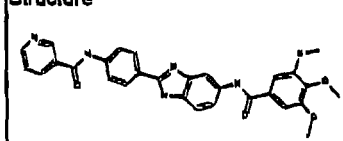
Structure	BICR
	$C_{29}H_{26}N_4O_3$
	CLOGP 5.39

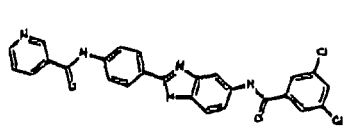
Structure	BIDA
	$C_{26}H_{19}N_5O_2$
	CLOGP 4.60

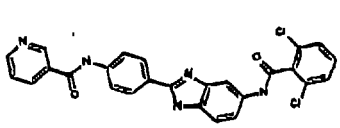
Structure	BIDB
	$C_{26}H_{18}ClN_5O_2$
	CLOGP 5.37

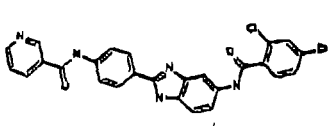
Structure	BIDC
	$C_{27}H_{21}N_5O_3$
	CLOGP 4.71

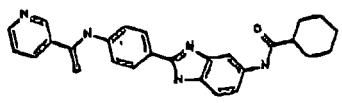
Structure	BIDD
	$C_{25}H_{18}N_6O_2$
	CLOGP 3.41

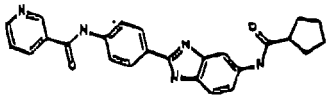
Structure	BIDE
	$C_{29}H_{25}N_5O_5$
	CLOGP 3.95

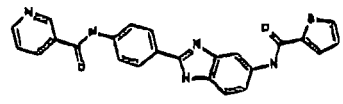
Structure	BIDF
	$C_{26}H_{17}Cl_2N_5O_2$
	CLOGP 6.10

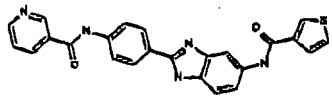
Structure	BIDG
	$C_{26}H_{17}Cl_2N_5O_2$
	CLOGP 4.44

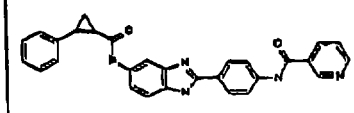
Structure	BIDH
	$C_{26}H_{17}Cl_2N_5O_2$
	CLOGP 5.27

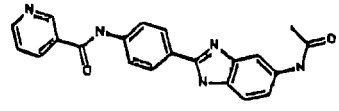
Structure	BIDI
	$C_{26}H_{25}N_5O_2$
	CLOGP 5.14

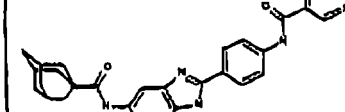
Structure	BIDJ
	$C_{25}H_{23}N_5O_2$
	CLOGP 4.58

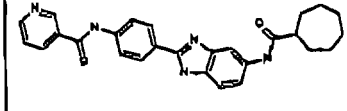
Structure	BIDK
	$C_{24}H_{17}N_5O_2S$
	CLOGP 4.33

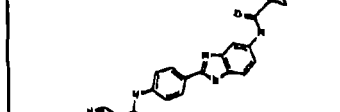
Structure	BIDL
	$C_{24}H_{17}N_5O_2S$
	CLOGP 4.33

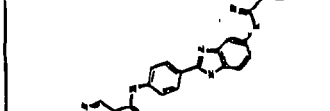
Structure	BIDM
	$C_{29}H_{23}N_5O_2$
	CLOGP 4.67

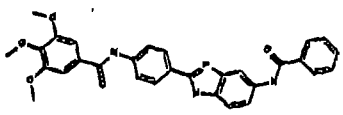
Structure	BIDN
	$C_{21}H_{17}N_5O_2$
	CLOGP 3.11

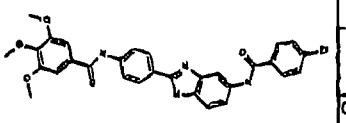
Structure	BIDO
	$C_{30}H_{29}N_5O_2$
	CLOGP 5.77

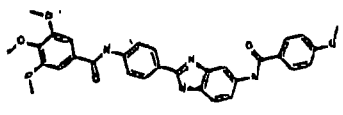
Structure	BIDP
	$C_{27}H_{27}N_5O_2$
	CLOGP 5.70

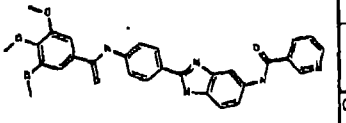
Structure	BIDQ
	$C_{27}H_{25}N_5O_2$
	CLOGP 4.89

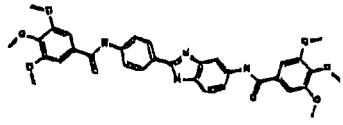
Structure	BIDR
	$C_{27}H_{23}N_5O_2$
	CLOGP 4.41

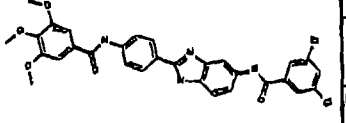
Structure	BIEA
	$C_{30}H_{26}N_4O_5$
	CLOGP 4.02

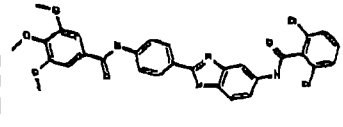
Structure	BIEB
	$C_{30}H_{25}ClN_4O_5$
	CLOGP 5.59

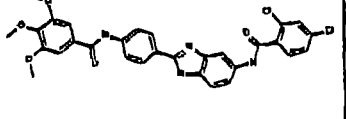
Structure	BIEC
	$C_{31}H_{28}N_4O_6$
	CLOGP 4.93

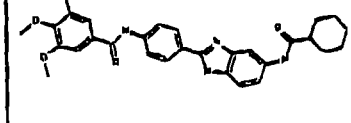
Structure	BIED
	$C_{29}H_{25}N_5O_5$
	CLOGP 3.69

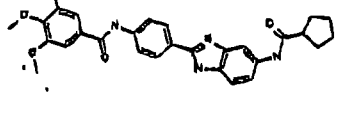
Structure	BIEE
	$C_{33}H_{32}N_4O_8$
	CLOGP 4.17

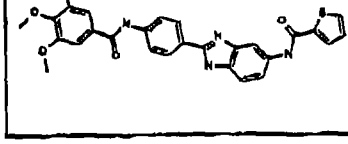
Structure	BIEF
	$C_{30}H_{24}Cl_2N_4O_5$
	CLOGP 6.32

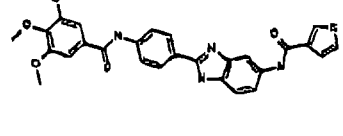
Structure	BIEG
	$C_{30}H_{24}Cl_2N_4O_5$
	CLOGP 4.66

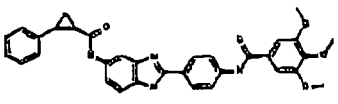
Structure	BIEH
	$C_{30}H_{24}Cl_2N_4O_5$
	CLOGP 5.49

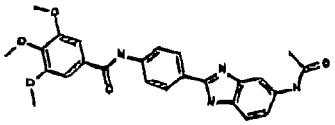
Structure	BIEI
	$C_{30}H_{32}N_4O_5$
	CLOGP 5.36

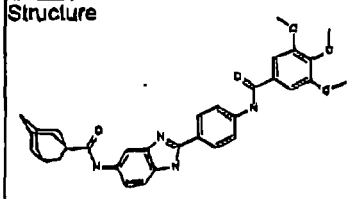
Structure	BIEJ
	$C_{29}H_{30}N_4O_5$
	CLOGP 4.80

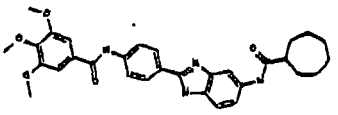
Structure	BIEK
	$C_{28}H_{24}N_4O_5S$
	CLOGP 4.56

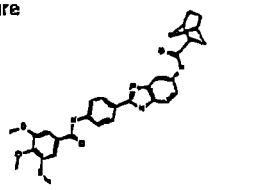
Structure	BIEL
	$C_{28}H_{24}N_4O_5S$
	CLOGP 4.95

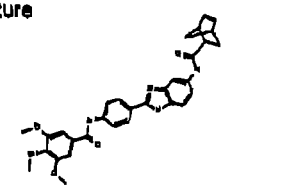
Structure	BIEM
	$C_{33}H_{30}N_4O_5$
	CLOGP 5.09

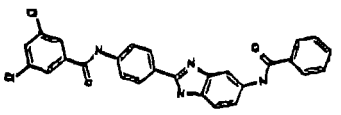
Structure	BIEN
	$C_{25}H_{24}N_4O_5$
	CLOGP 3.33

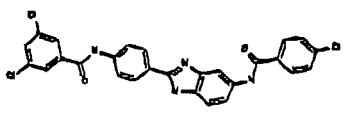
Structure	BIEO
	$C_{34}H_{36}N_4O_5$
	CLOGP 5.99

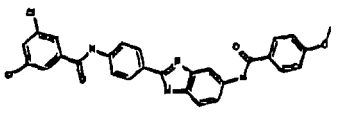
Structure	BIEP
	$C_{31}H_{34}N_4O_5$
	CLOGP 6.92

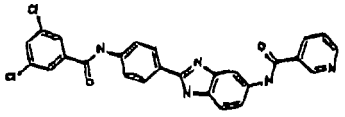
Structure	BIEQ
	$C_{31}H_{32}N_4O_5$
	CLOGP 5.11

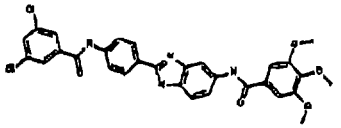
Structure	BIER
	$C_{31}H_{30}N_4O_5$
	CLOGP 4.63

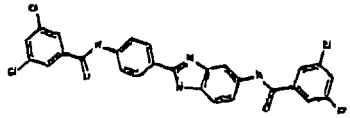
Structure	BIFA
	$C_{27}H_{18}Cl_2N_4O_2$
	CLOGP 7.00

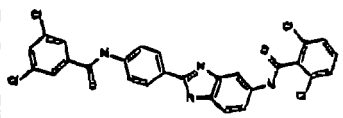
Structure	BIFB
	$C_{27}H_{17}Cl_3N_4O_2$
	CLOGP 7.78

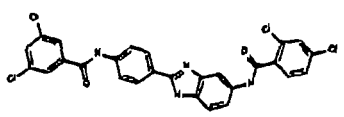
Structure	BIFC
	$C_{28}H_{20}Cl_2N_4O_3$
	CLOGP 7.12

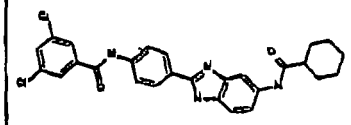
Structure	BIFD
	$C_{26}H_{17}Cl_2N_5O_2$
	CLOGP 5.82

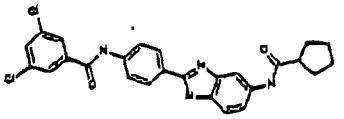
Structure	BIFE
	$C_{30}H_{24}Cl_2N_4O_5$
	CLOGP 6.35

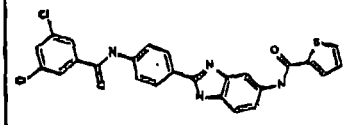
Structure	BIFF
	$C_{27}H_{16}Cl_4N_4O_2$
	CLOGP 8.51

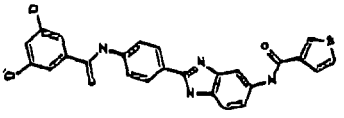
Structure	
	BIFG $C_{27}H_{16}Cl_4N_4O_2$ CLOGP 6.85

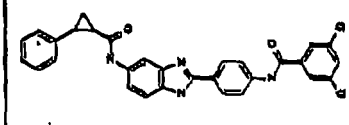
Structure	
	BIFH $C_{27}H_{16}Cl_4N_4O_2$ CLOGP 7.69

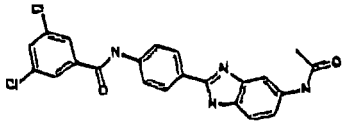
Structure	
	BIFI $C_{27}H_{24}Cl_2N_4O_2$ CLOGP 7.54

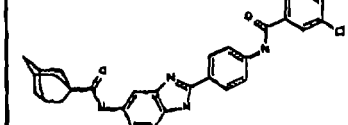
Structure	
	BIFJ $C_{26}H_{22}Cl_2N_4O_2$ CLOGP 6.99

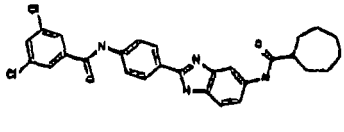
Structure	
	BIFK $C_{25}H_{16}Cl_2N_4O_2S$ CLOGP 6.74

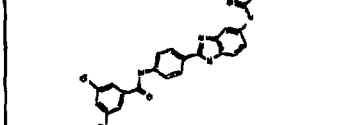
Structure	
	BIFL $C_{25}H_{16}Cl_2N_4O_2S$ CLOGP 6.74

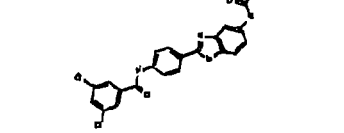
Structure	
	BIFM $C_{30}H_{22}Cl_2N_4O_2$ CLOGP 7.28

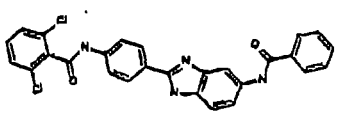
Structure	
	BIFN $C_{22}H_{16}Cl_2N_4O_2$ CLOGP 5.51

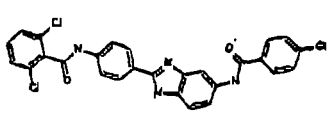
Structure	
	BIFO $C_{31}H_{28}Cl_2N_4O_2$ CLOGP 8.17

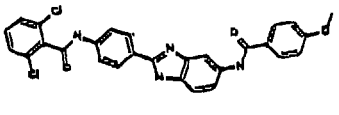
Structure	
	BIFP $C_{28}H_{26}Cl_2N_4O_2$ CLOGP 8.10

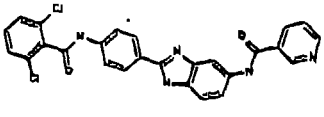
Structure	
	BIFQ $C_{28}H_{24}Cl_2N_4O_2$ CLOGP 7.30

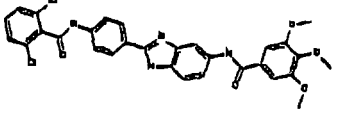
Structure	
	BIFR $C_{28}H_{22}Cl_2N_4O_2$ CLOGP 6.82

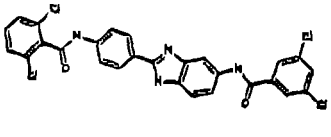
Structure	BIGA
	$C_{27}H_{18}Cl_2N_4O_2$
	CLOGP 5.34

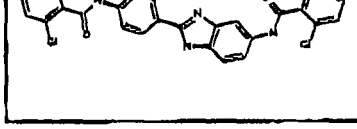
Structure	BIGB
	$C_{27}H_{17}Cl_3N_4O_2$
	CLOGP 6.12

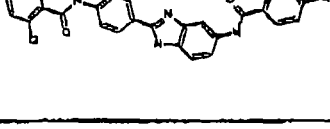
Structure	BIGC
	$C_{28}H_{20}Cl_2N_4O_3$
	CLOGP 5.46

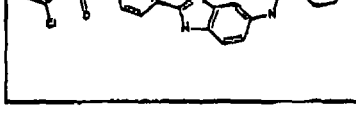
Structure	BIGD
	$C_{26}H_{17}Cl_2N_5O_2$
	CLOGP 4.16

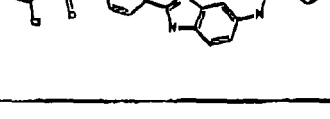
Structure	BIGE
	$C_{30}H_{24}Cl_2N_4O_5$
	CLOGP 4.69

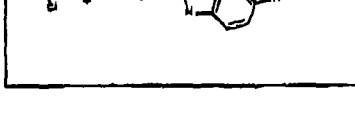
Structure	BIGF
	$C_{27}H_{16}Cl_4N_4O_2$
	CLOGP 6.85

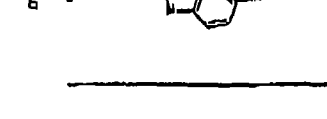
Structure	BIGG
	$C_{27}H_{16}Cl_4N_4O_2$
	CLOGP 5.19

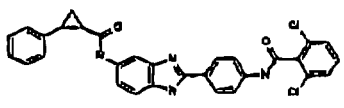
Structure	BIGH
	$C_{27}H_{16}Cl_4N_4O_2$
	CLOGP 6.02

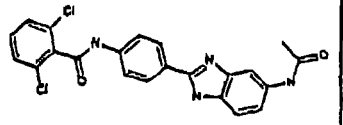
Structure	BIGI
	$C_{27}H_{24}Cl_2N_4O_2$
	CLOGP 6.88

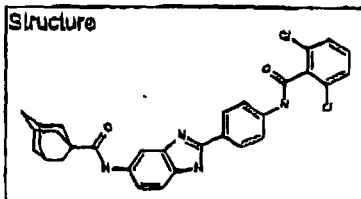
Structure	BIGJ
	$C_{26}H_{22}Cl_2N_4O_2$
	CLOGP 5.33

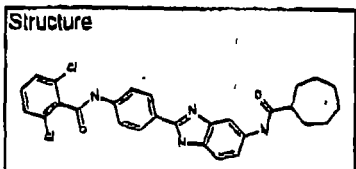
Structure	BIGK
	$C_{25}H_{18}Cl_2N_4O_2S$
	CLOGP 5.08

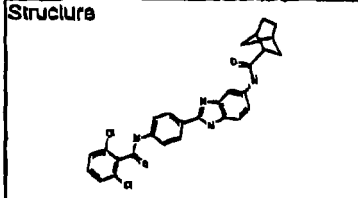
Structure	BIGL
	$C_{25}H_{16}Cl_2N_4O_2S$
	CLOGP 5.08

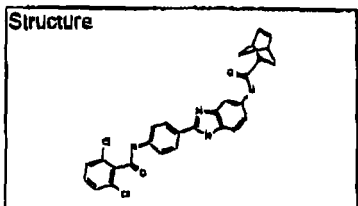
Structure	BIGM
	$C_{30}H_{22}Cl_2N_4O_2$
	CLOGP 5.62

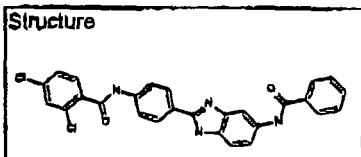
Structure	BIGN
	$C_{22}H_{16}Cl_2N_4O_2$
	CLOGP 3.88

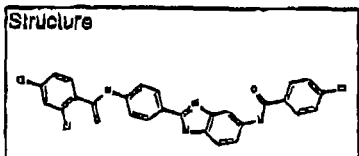
Structure	BIGO
	$C_{31}H_{28}Cl_2N_4O_2$
	CLOGP 6.51

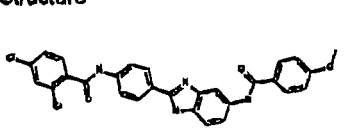
Structure	BIGP
	$C_{28}H_{26}Cl_2N_4O_2$
	CLOGP 6.44

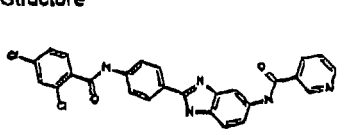
Structure	BIGQ
	$C_{28}H_{24}Cl_2N_4O_2$
	CLOGP 5.84

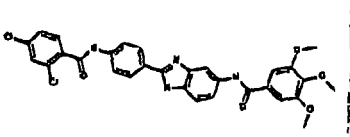
Structure	BIGR
	$C_{28}H_{22}Cl_2N_4O_2$
	CLOGP 5.16

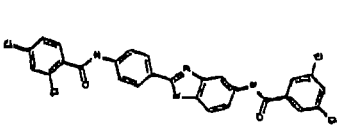
Structure	BIHA
	$C_{27}H_{18}Cl_2N_4O_2$
	CLOGP 6.17

Structure	BIHB
	$C_{27}H_{17}Cl_3N_4O_2$
	CLOGP 6.95

Structure	BIHC
	$C_{28}H_{20}Cl_2N_4O_3$
	CLOGP 6.29

Structure	BIHD
	$C_{26}H_{17}Cl_2N_5O_2$
	CLOGP 4.99

Structure	BIHE
	$C_{30}H_{24}Cl_2N_4O_5$
	CLOGP 5.52

Structure	BIHF
	$C_{27}H_{16}Cl_4N_4O_2$
	CLOGP 7.68

Structure	BIHG
	$C_{27}H_{16}Cl_4N_4O_2$
	CLOGP 6.02

Structure	BIHH
	$C_{27}H_{16}Cl_4N_4O_2$
	CLOGP 6.65

Structure	BIHI
	$C_{27}H_{24}Cl_2N_4O_2$
	CLOGP 6.71

Structure	BIHJ
	$C_{25}H_{22}Cl_2N_4O_2$
	CLOGP 6.16

Structure	BIHK
	$C_{25}H_{16}Cl_2N_4O_2S$
	CLOGP 5.91

Structure	BIHL
	$C_{25}H_{16}Cl_2N_4O_2S$
	CLOGP 5.91

Structure	BIHM
	$C_{30}H_{22}Cl_2N_4O_2$
	CLOGP 6.45

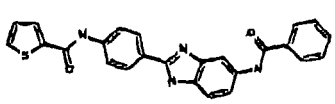
Structure	BIHN
	$C_{22}H_{16}Cl_2N_4O_2$
	CLOGP 4.68

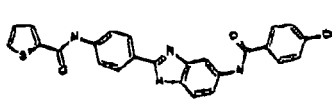
Structure	BIHO
	$C_{31}H_{28}Cl_2N_4O_2$
	CLOGP 7.34

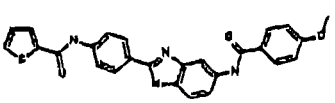
Structure	BIHP
	$C_{28}H_{26}Cl_2N_4O_2$
	CLOGP 7.27

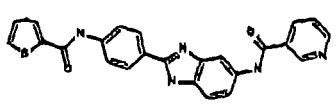
Structure	BIHQ
	$C_{28}H_{24}Cl_2N_4O_2$
	CLOGP 6.47

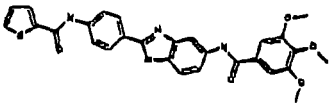
Structure	BIHR
	$C_{28}H_{22}Cl_2N_4O_2$
	CLOGP 5.89

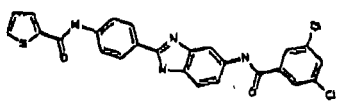
Structure	BIKA
	$C_{25}H_{18}N_4O_2S$
	CLOGP 5.20

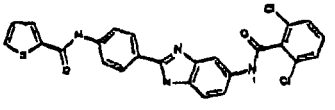
Structure	BIKB
	$C_{25}H_{17}ClN_4O_2S$
	CLOGP 5.98

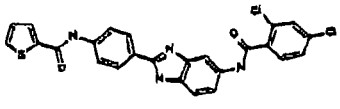
Structure	BIKC
	$C_{26}H_{20}N_4O_3S$
	CLOGP 5.32

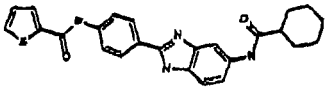
Structure	BIKD
	$C_{24}H_{17}N_5O_2S$
	CLOGP 4.02

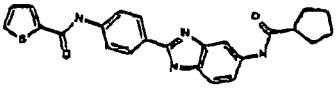
Structure	BIKE
	$C_{28}H_{24}N_4O_5S$
	CLOGP 4.55

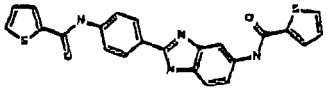
Structure	BIKF
	$C_{25}H_{16}Cl_2N_4O_2S$
	CLOGP 6.71

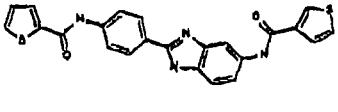
Structure	BIKG
	$C_{25}H_{16}Cl_2N_4O_2S$
	CLOGP 5.05

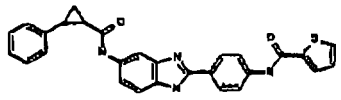
Structure	BIKH
	$C_{25}H_{16}Cl_2N_4O_2S$
	CLOGP 5.88

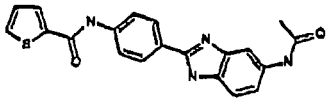
Structure	BIKI
	$C_{25}H_{24}N_4O_2S$
	CLOGP 5.74

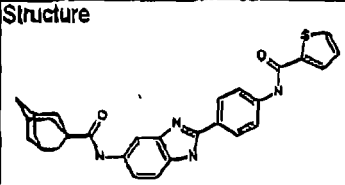
Structure	BIKJ
	$C_{24}H_{22}N_4O_2S$
	CLOGP 5.19

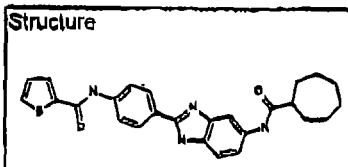
Structure	BIKK
	$C_{23}H_{16}N_4O_2S_2$
	CLOGP 4.94

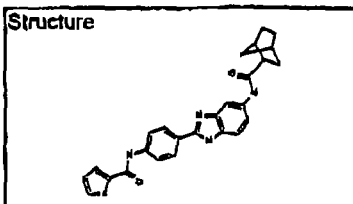
Structure	BIKL
	$C_{23}H_{16}N_4O_2S_2$
	CLOGP 4.94

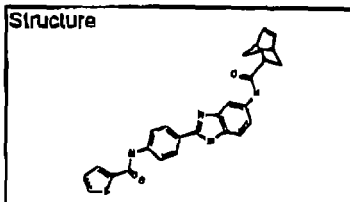
Structure	BIKM
	$C_{28}H_{22}N_4O_2S$
	CLOGP 5.48

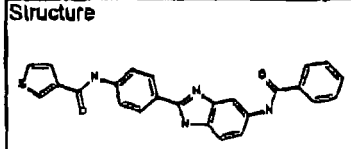
Structure	BIKN
	$C_{20}H_{16}N_4O_2S$
	CLOGP 3.71

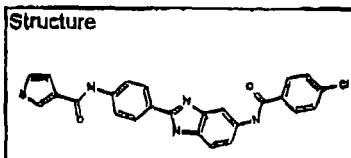
Structure	BIKO
	$C_{29}H_{28}N_4O_2S$
	CLOGP 6.37

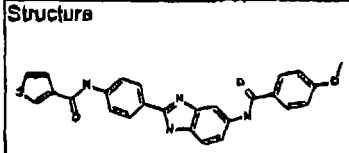
Structure	BIKP
	$C_{28}H_{26}N_4O_2S$
	CLOGP 6.30

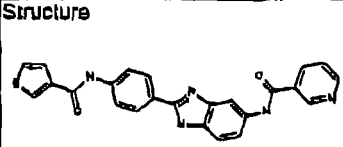
Structure	BIKQ
	$C_{26}H_{24}N_4O_2S$
	CLOGP 5.50

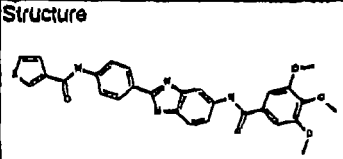
Structure	BIKR
	$C_{26}H_{22}N_4O_2S$
	CLOGP 5.02

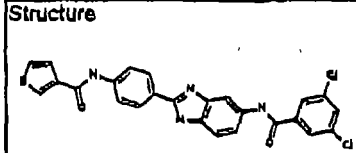
Structure	BILA
	$C_{25}H_{18}N_4O_2S$
	CLOGP 5.20

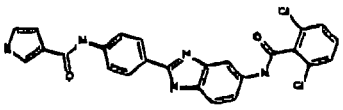
Structure	BILB
	$C_{25}H_{17}ClN_4O_2S$
	CLOGP 5.96

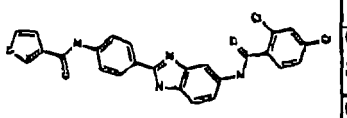
Structure	BILC
	$C_{26}H_{20}N_4O_3S$
	CLOGP 5.32

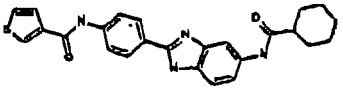
Structure	BILD
	$C_{24}H_{17}N_5O_2S$
	CLOGP 4.02

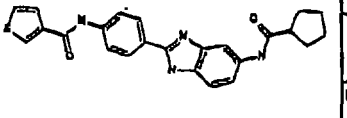
Structure	BILE
	$C_{28}H_{24}N_4O_5S$
	CLOGP 4.55

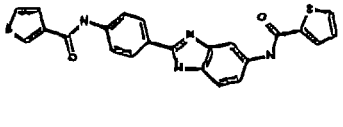
Structure	BILF
	$C_{25}H_{16}Cl_2N_4O_2S$
	CLOGP 6.71

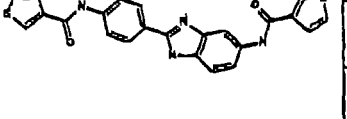
Structure	BILG
	$C_{25}H_{16}Cl_2N_4O_2S$
	CLOGP 5.05

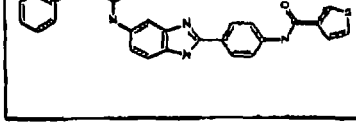
Structure	BILH
	$C_{25}H_{16}Cl_2N_4O_2S$
	CLOGP 5.86

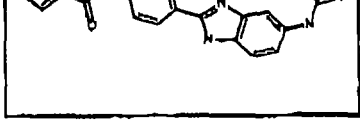
Structure	BILI
	$C_{25}H_{24}N_4O_2S$
	CLOGP 5.74

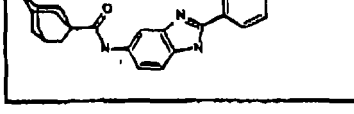
Structure	BILJ
	$C_{24}H_{22}N_4O_2S$
	CLOGP 5.19

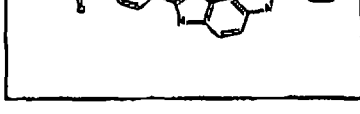
Structure	BILK
	$C_{23}H_{16}N_4O_2S_2$
	CLOGP 4.94

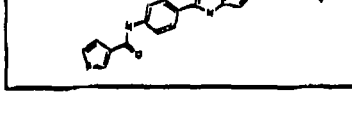
Structure	BILL
	$C_{23}H_{16}N_4O_2S_2$
	CLOGP 4.94

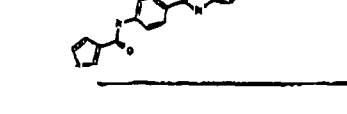
Structure	BILM
	$C_{28}H_{22}N_4O_2S$
	CLOGP 5.48

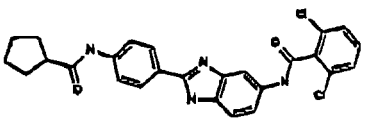
Structure	BILN
	$C_{20}H_{16}N_4O_2S$
	CLOGP 3.71

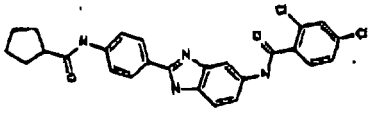
Structure	BILO
	$C_{29}H_{28}N_4O_2S$
	CLOGP 6.37

Structure	BILP
	$C_{26}H_{26}N_4O_2S$
	CLOGP 6.30

Structure	BILQ
	$C_{26}H_{24}N_4O_2S$
	CLOGP 5.50

Structure	BILR
	$C_{26}H_{22}N_4O_2S$
	CLOGP 5.02

Structure	BIJG
	$C_{26}H_{22}Cl_2N_4O_2$
	CLOGP 5.29

Structure	BIJH
	$C_{26}H_{22}Cl_2N_4O_2$
	CLOGP 6.12

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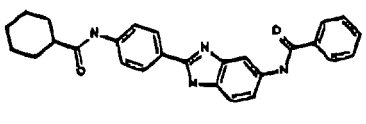
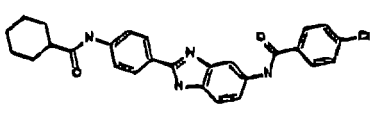
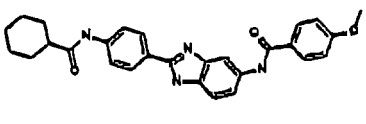
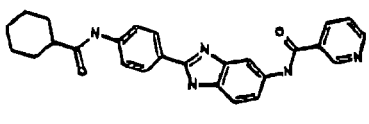
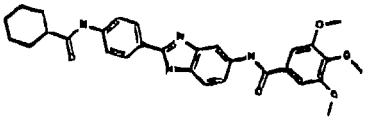
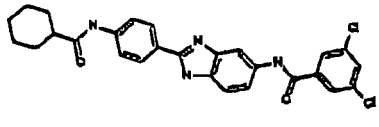
Structure	BIIA
	$C_{27}H_{26}N_4O_2$
	CLOGP 6.01

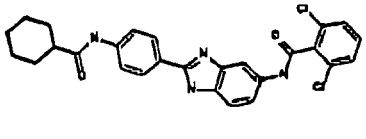
Structure	BIIB
	$C_{27}H_{25}ClN_4O_2$
	CLOGP 6.78

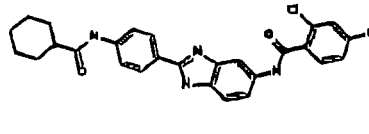
Structure	BIIC
	$C_{28}H_{28}N_4O_3$
	CLOGP 6.12

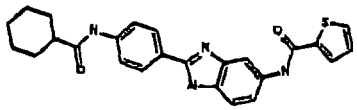
Structure	BIID
	$C_{26}H_{25}N_5O_2$
	CLOGP 4.82

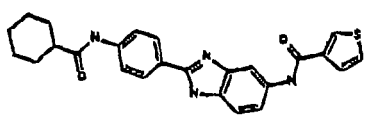
Structure	BIIE
	$C_{30}H_{32}N_4O_5$
	CLOGP 5.36

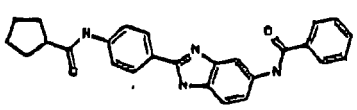
Structure	BIIF
	$C_{27}H_{24}Cl_2N_4O_2$
	CLOGP 7.51

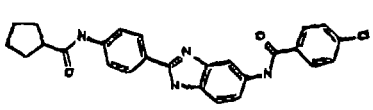
Structure	BIIG
	$C_{27}H_{24}Cl_2N_4O_2$
	CLOGP 5.85

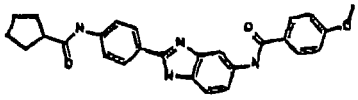
Structure	BIIH
	$C_{27}H_{24}Cl_2N_4O_2$
	CLOGP 6.66

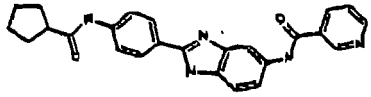
Structure	BIIK
	$C_{25}H_{24}N_4O_2S$
	CLOGP 5.74

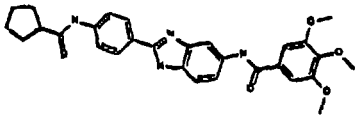
Structure	BIIL
	$C_{25}H_{24}N_4O_2S$
	CLOGP 5.74

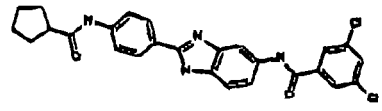
Structure	BIJA
	$C_{26}H_{24}N_4O_2$
	CLOGP 5.45

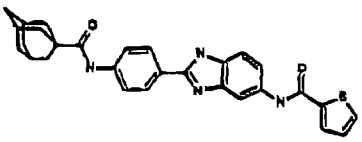
Structure	BIJB
	$C_{26}H_{23}ClN_4O_2$
	CLOGP 6.22

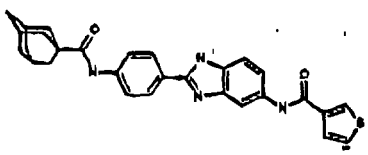
Structure	BIJC
	$C_{27}H_{26}N_4O_3$
	CLOGP 5.56

Structure	BIJD
	$C_{25}H_{23}N_5O_2$
	CLOGP 4.26

Structure	BIJE
	$C_{29}H_{30}N_4O_5$
	CLOGP 4.80

Structure	BIJF
	$C_{28}H_{22}Cl_2N_4O_2$
	CLOGP 6.95

Structure	BIOK
	$C_{29}H_{28}N_4O_2S$
	CLOGP 6.37

Structure	BIOL
	$C_{29}H_{28}N_4O_2S$
	CLOGP 6.37

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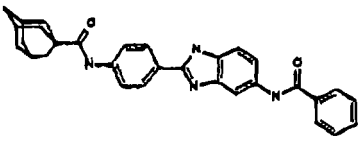
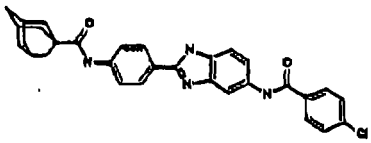
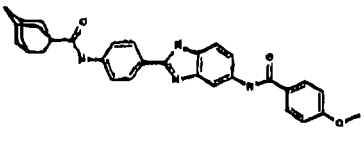
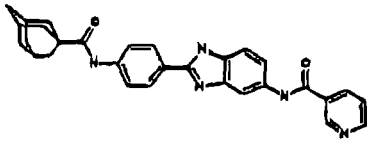
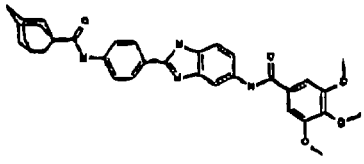
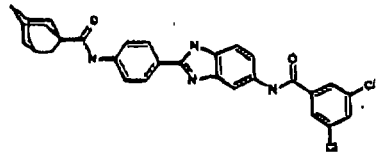
Structure	BIOA
	$C_{31}H_{30}N_4O_2$
	CLOGP 6.64

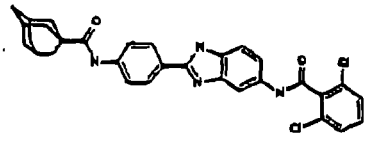
Structure	BIOB
	$C_{31}H_{29}ClN_4O_2$
	CLOGP 7.41

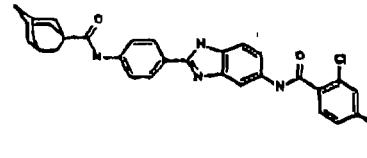
Structure	BIOC
	$C_{32}H_{32}N_4O_3$
	CLOGP 6.75

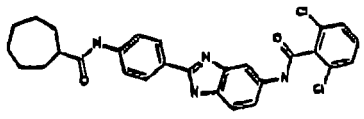
Structure	BIOD
	$C_{30}H_{29}N_5O_2$
	CLOGP 5.45

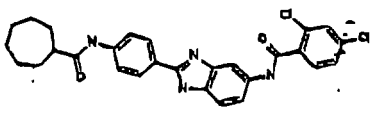
Structure	BIOE
	$C_{34}H_{36}N_4O_5$
	CLOGP 5.99

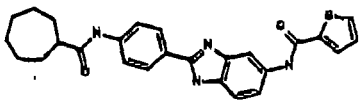
Structure	BIOF
	$C_{31}H_{28}Cl_2N_4O_2$
	CLOGP 8.14

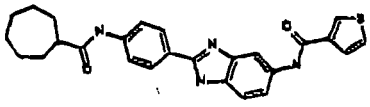
Structure	BIOG
	$C_{31}H_{28}Cl_2N_4O_2$
	CLOGP 6.48

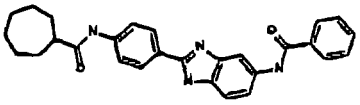
Structure	BIOH
	$C_{31}H_{28}Cl_2N_4O_2$
	CLOGP 7.31

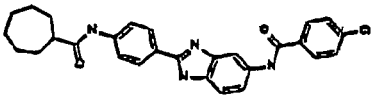
Structure	BIPG
	$C_{28}H_{26}Cl_2N_4O_2$
	CLOGP 6.41

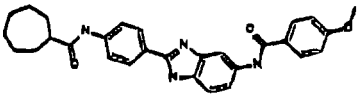
Structure	BIPH
	$C_{28}H_{26}Cl_2N_4O_2$
	CLOGP 7.24

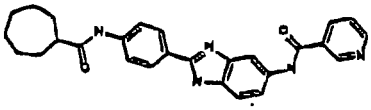
Structure	BIPK
	$C_{26}H_{26}N_4O_2S$
	CLOGP 6.30

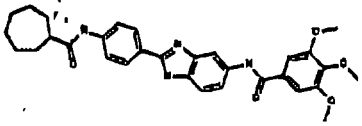
Structure	BIPL
	$C_{26}H_{26}N_4O_2S$
	CLOGP 6.30

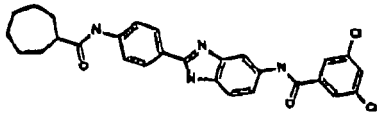
Structure	BIPA
	$C_{28}H_{28}N_4O_2$
	CLOGP 6.57

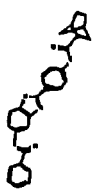
Structure	BIPB
	$C_{28}H_{27}ClN_4O_2$
	CLOGP 7.34

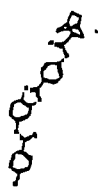
Structure	BIPC
	$C_{29}H_{30}N_4O_3$
	CLOGP 6.68

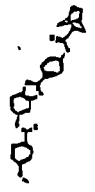
Structure	BIPD
	$C_{27}H_{27}N_5O_2$
	CLOGP 5.38

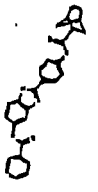
Structure	BIPE
	$C_{31}H_{34}N_4O_5$
	CLOGP 5.92

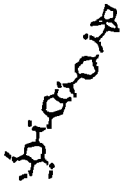
Structure	BIPF
	$C_{28}H_{26}Cl_2N_4O_2$
	CLOGP 6.07

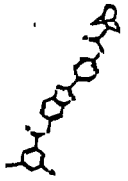
Structure	BIQA
	$C_{28}H_{26}N_4O_2$
	CLOGP 5.76

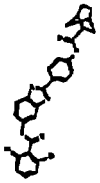
Structure	BIQB
	$C_{28}H_{25}ClN_4O_2$
	CLOGP 6.54

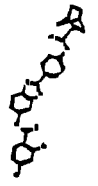
Structure	BIQC
	$C_{29}H_{28}N_4O_3$
	CLOGP 5.66

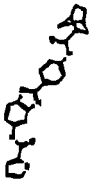
Structure	BIQD
	$C_{27}H_{25}N_5O_2$
	CLOGP 4.57

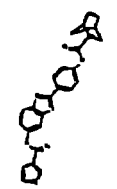
Structure	BIQE
	$C_{31}H_{32}N_4O_5$
	CLOGP 5.11

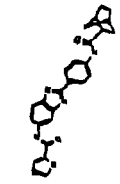
Structure	BIQF
	$C_{28}H_{24}Cl_2N_4O_2$
	CLOGP 7.27

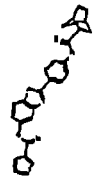
Structure	BIQG
	$C_{28}H_{24}Cl_2N_4O_2$
	CLOGP 5.61

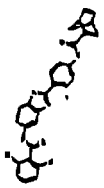
Structure	BIQH
	$C_{28}H_{24}Cl_2N_4O_2$
	CLOGP 6.44

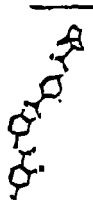
Structure	BIQK
	$C_{28}H_{24}N_4O_2S$
	CLOGP 5.60

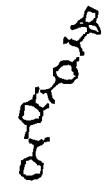
Structure	BIQL
	$C_{28}H_{24}N_4O_2S$
	CLOGP 6.60

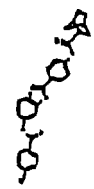
Structure	BIRK
	$C_{26}H_{22}N_4O_2S$
	CLOGP 5.02

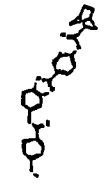
Structure	BIRL
	$C_{26}H_{22}N_4O_2S$
	CLOGP 5.02

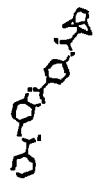
Structure	BIRG
	$C_{28}H_{22}Cl_2N_4O_2$
	CLOGP 5.12

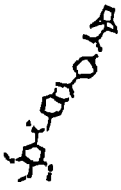
Structure	BIRH
	$C_{26}H_{22}Cl_2N_4O_2$
	CLOGP 5.85

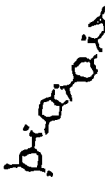
Structure	BIRA
	$C_{26}H_{24}N_4O_2$
	CLOGP 5.28

Structure	BIRB
	$C_{28}H_{23}ClN_4O_2$
	CLOGP 6.05

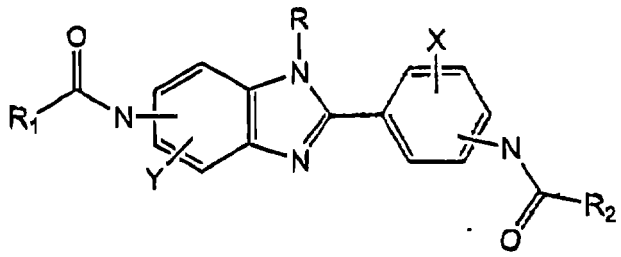
Structure	BIRC
	$C_{29}H_{26}N_4O_3$
	CLOGP 5.39

Structure	BIRD
	$C_{27}H_{23}N_5O_2$
	CLOGP 4.09

Structure	BIRE
	$C_{31}H_{30}N_4O_5$
	CLOGP 4.63

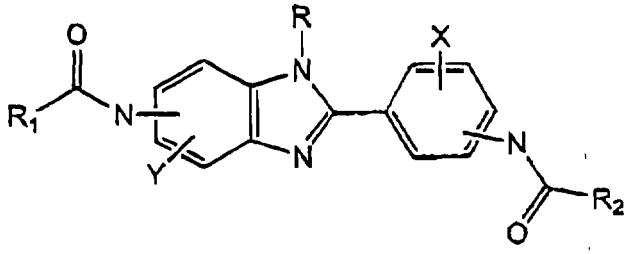
Structure	BIRF
	$C_{28}H_{22}Cl_2N_4O_2$
	CLOGP 6.76

In accordance with another aspect of the present invention, there is disclosed a method for the preparation of a medicament for treatment of a condition associated with an excess IgE level. The compound has the formula:



X and Y are independently selected from the group consisting of H, alkyl, alkoxy, aryl, substituted aryl, hydroxy, halogen, amino, alkylamino, nitro, cyano, CF_3, OCF_3, $CONH_2$, CONHR and $NHCOR_1$. R is selected from the group consisting of H, CH_3, C_2H_5, C_3H_7, C_4H_9, CH_2Ph, and $CH_2C_6H_4$-F(p-). R_1 and R_2 are independently selected from the group consisting of H, aryl, substituted aryl, cycloaryl substituted cycloaryl, multi-ring cycloaryl, benzyl, substituted benzyl and the like. Substitutions are alkyl, aryl, CF3, CH3, OCH_3, OH, CN, COOR, COOH and the like.

In accordance with another aspect of the present invention, there is disclosed a method of treating a mammal having a condition associated with an excess IgE level. The method comprises administering to the mammal an amount of a compound sufficient to reduced IgE levels in the mammal. The compound has the formula:



X and Y are independently selected from the group consisting of H, alkyl, alkoxy, aryl, substituted aryl, hydroxy, halogen, amino, alkylamino, nitro, cyano, CF_3, OCF_3, $CONH_2$, CONHR and $NHCOR_1$. R is selected from the group consisting of H, CH_3, C_2H_5, C_3H_7, C_4H_9,

CH_2Ph, and $CH_2C_6H_4$-F(p-). R_1 and R_2 are independently selected from the group consisting of H, aryl, substituted aryl, cycloaryl substituted cycloaryl, multi-ring cycloaryl, benzyl, substituted benzyl, alkyl, cycloalkyl substituted cycloalkyl, multi-ring cycloalkyl, fused-ring aliphatic, cyclopropyl, substituted cyclopropyl, cyclobutyl, substituted cyclobutyl, cyclopentyl, substituted cyclopentyl, cyclohexyl, substituted cyclohexyl, cycloheptyl, substituted cycloheptyl, bicycloheptyl, bicyclooctyl, bicyclononyl, substituted bicycloalknyl, adamantyl, substituted adamantyl and the like, wherein at least one of R1 and R2 are aromatic groups. Substitutions are alkyl, aryl, CF3, CH3, OCH_3, OH, CN, COOR, COOH and the like.

In a variation of the above-disclosed method, at least one additional active ingredient may be administered in conjunction with the administration of the compound. The additional active ingredient may be combined with said compound in a pharmaceutically acceptable diluent and co-administered to the mammal. The additional active ingredient may be a short-acting β_2-adrenergic agonist selected from the group consisting of terbutaline and albuterol. In a variation, the additional active ingredient may be a long-acting β_2-adrenergic agonist selected from the group consisting of salmeterol and formoterol or an antihistamine selected from the group consisting of loratadine, azelastine and ketotifen. In another variation, the additional active ingredient may be a phosphodiesterase inhibitor, an anticholinergic agent, a corticosteroid, an inflammatory mediator release inhibitor or a leukotriene receptor antagonist.

The compound is preferably administered at a dose of about 0.01 mg to about 100 mg per kg body weight per day in divided doses of said compound for at least two consecutive days at regular periodic intervals.

Other variations within the scope of the present invention may be more fully understood with reference to the following detailed description.

Detailed Description of the Preferred Embodiment

The present invention is directed to small molecule inhibitors of IgE (synthesis and/or release) which are useful in the treatment of allergy and/or asthma or any diseases where IgE is pathogenic. The particular compounds disclosed herein were identified by their ability to suppress IgE levels in both *ex vivo* and *in vivo* assays. Development and optimization of clinical treatment regimens can be monitored by those of skill in the art by reference to the *ex vivo* and *in vivo* assays described below.

Ex Vivo Assay

This assay begins with *in vivo* antigen priming and measures secondary antibody responses *in vitro*. The basic protocol was documented and optimized for a range of parameters including: antigen dose for priming and time span following priming, number of cells cultured *in vitro*, antigen concentrations for eliciting secondary IgE (and other Ig's) response *in vitro*, fetal bovine serum (FBS) batch that will permit optimal IgE response *in vitro*, the importance of primed CD4+ T cells and hapten-specific B cells, and specificity of the ELISA assay for IgE (Marcelletti and Katz, *Cellular Immunology* 135:471-489 (1991); incorporated herein by reference).

The actual protocol utilized for this project was adapted for a more high throughput analyses. BALB/cByj mice were immunized i.p. with 10 μg DNP-KLH adsorbed onto 4 mg alum and sacrificed after 15 days. Spleens were excised and homogenized in a tissue grinder, washed twice, and maintained in DMEM supplemented with 10% FBS, 100 U/ml penicillin, 100 μg/ml streptomycin and 0.0005% 2-mercaptoethanol. Spleen cell cultures were established (2-3 million cells/ml, 0.2 ml/well in quadruplicate, 96-well plates) in the presence or absence of DNP-KLH (10 ng/ml). Test compounds (2 μg/ml and 50 ng/ml) were added to the spleen cell cultures containing antigen and incubated at 37° C for 8 days in an atmosphere of 10% CO_2.

Culture supernatants were collected after 8 days and Ig's were measured by a modification of the specific isotype-selective ELISA assay described by Marcelletti and Katz (*Supra*). The assay was modified to facilitate high throughput. ELISA plates were prepared by coating with DNP-KLH overnight. After blocking with bovine serum albumin (BSA), an aliquot of each culture supernatant was diluted (1:4 in phosphate buffered saline (PBS) with BSA, sodium azide and Tween 20), added to the ELISA plates, and incubated overnight in a humidified box at 4° C. IgE levels were quantitated following successive incubations with biotinylated-goat antimouse IgE (b-GAME), AP-streptavidin and substrate.

Antigen-specific IgG1 was measured similarly, except that culture supernatants were diluted 200-fold and biotinylated-goat antimouse IgG1 (b-GAMG1) was substituted for b-GAME. IgG2a was measured in ELISA plates that were coated with DNP-KLH following a 1:20 dilution of culture supernatants and incubation with biotinylated-goat antimouse IgG2a (b-GAMG2a). Quantitation of each isotype was determined by comparison to a standard curve. The level of detectability of all

antibody was about 200-400 pg/ml and there was less than 0.001% cross-reactivity with any other Ig isotype in the ELISA for IgE.

In Vivo Assay

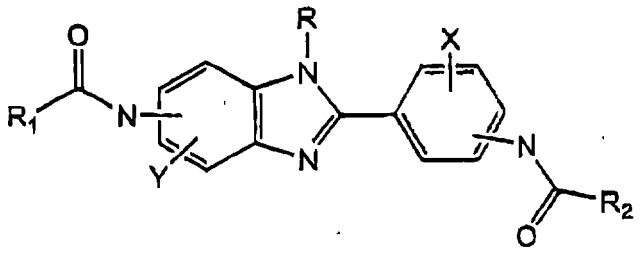
Compounds found to be active in the *ex vivo* assay (above) were further tested for their activity in suppressing IgE responses *in vivo*. Mice receiving low-dose radiation prior to immunization with a carrier exhibited an enhanced IgE response to sensitization with antigen 7 days later. Administration of the test compounds immediately prior to and after antigen sensitization, measured the ability of that drug to suppress the IgE response. The levels of IgE, IgG1 and IgG2a in serum were compared.

Female BALB/cByj mice were irradiated with 250 rads 7 hours after initiation of the daily light cycle. Two hours later, the mice were immunized i.p. with 2 μg of KLH in 4 mg alum. Two to seven consecutive days of drug injections were initiated 6 days later on either a once or twice daily basis. Typically, i.p. injections and oral gavages were administered as suspensions (150 μl/injection) in saline with 10% ethanol and 0.25% methylcellulose. Each treatment group was composed of 5-6 mice. On the second day of drug administration, 2 μg of DNP-KLH was administered i.p. in 4 mg alum, immediately following the morning injection of drug. Mice were bled 7-21 days following DNP-KLH challenge.

Antigen-specific IgE, IgG1 and IgG2a antibodies were measured by ELISA. Periorbital bleeds were centrifuged at 14,000 rpm for 10 min, the supernatants were diluted 5-fold in saline, and centrifuged again. Antibody concentrations of each bleed were determined by ELISA of four dilutions (in triplicate) and compared to a standard curve: anti-DNP IgE (1:100 to 1:800), anti-DNP IgG2a (1:100 to 1:800), and anti-DNP IgG1 (1:1600 to 1:12800).

Diacyl Benzimidazole Inhibitors of IgE

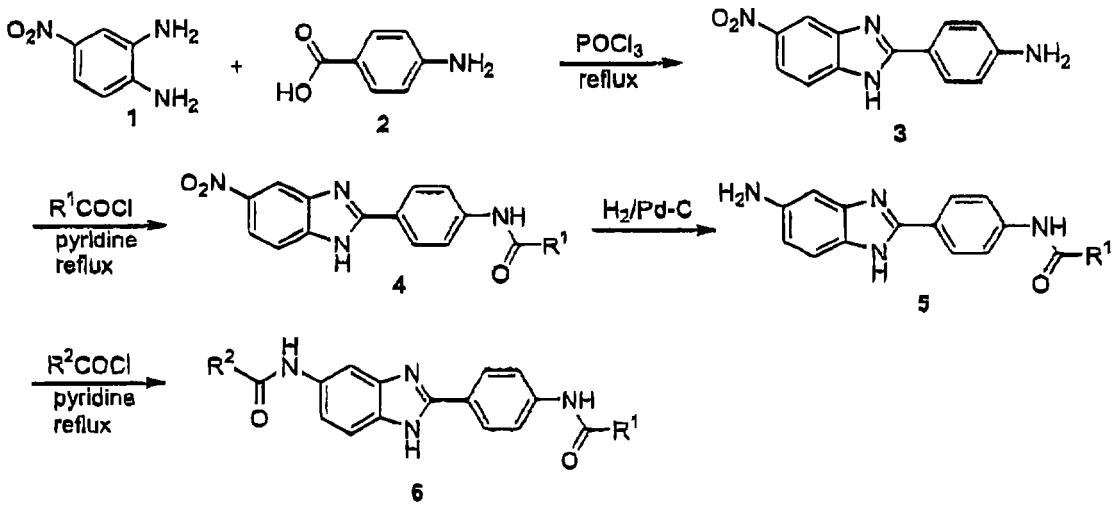
Several species embraced by the following generic formula were synthesized and evaluated for their effectiveness in down-regulating IgE in the *ex vivo* and *in vivo* assays.



X and Y are independently selected from the group consisting of H, alkyl, alkoxy, aryl, substituted aryl, hydroxy, halogen, amino, alkylamino, nitro, cyano, CF_3, OCF_3, $CONH_2$, CONHR and $NHCOR_1$. R is selected from the group consisting of H, CH_3, C_2H_5, C_3H_7, C_4H_9, CH_2Ph, and $CH_2C_6H_4$-F(p-). R_1 and R_2 are independently selected from the group consisting of H, aryl, substituted aryl, cycloaryl substituted cycloaryl, multi-ring cycloaryl, benzyl, substituted benzyl, alkyl, cycloalkyl substituted cycloalkyl, multi-ring cycloalkyl, fused-ring aliphatic, cyclopropyl, substituted cyclopropyl, cyclobutyl, substituted cyclobutyl, cyclopentyl, substituted cyclopentyl, cyclohexyl, substituted cyclohexyl, cycloheptyl, substituted cycloheptyl, bicycloheptyl, bicyclooctyl, bicyclononyl, substituted bicycloalknyl, adamantyl, substituted adamantyl and the like, wherein at least one of R1 and R2 are aromatic groups. Substitutions are alkyl, aryl, CF3, CH3, OCH_3, OH, CN, COOR, COOH and the like.

Synthesis of the Combinatorial Library

The diacyl benzimidazole compounds of the present invention were prepared using the following synthesis reactions, wherein the desired acid chlorides are selected from the R1 and R2 groups provided in the Table.



Synthesis of 3: 4-Nitro-1,2-phenylenediamine (10 g, 65.3 mmol) and 4-aminobenzoic acid (8.95 g, 65.3 mmol) were taken in a round bottomed flask and phosphorus oxychloride (95 ml) was added slowly. The reaction mixture was allowed to stir under reflux conditions. After 18 h, the reaction was allowed to cool and then poured slowly into an ice water mixture in an Erlenmeyer flask with vigorous stirring. Greenish yellow precipitate fell out which was then

filtered and washed with copious amounts of water. The residue was then dried to obtain 16.9 g of crude desired product. Mass spectrum analysis (positive ion) indicated presence of 3.

Synthesis of 4: Benzimidazole 3 (800 mg, 3.14 mmol) was dissolved in dry pyridine (5 ml) in a scintillation vial and the desired acid chlorides (1.1 eq) were added slowly. The reactions were carried out in an oven at 60C. After 16h, the reaction was cooled to RT and DI water was added. Precipitation took place, which was filtered off, washed with water and air dried. The aqueous layer was extracted with EtOAc (6 x 50 ml), dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo* to result in a colored solid. By positive ion MS the desired monoacylated product was found to be present in the initial precipitate as well as in the organic layer. Hence the solid residues obtained were combined and used as such for the reduction step.

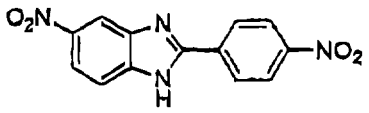
Reduction of 4: Crude monoacylated nitro benzimidazole 4 (1.22 g, 3.40 mmol) was dissolved in MeOH (20 ml) and minimum amount of THF was added for complete dissolution to occur. Catalytic amount of 10% Pd on C was added and the solution was degassed and allowed to stir at 3.4 atm pressure under H_2 atmosphere for 4 h. Upon completion of reaction as observed via TLC, the reaction mixture was filtered through celite and the solvent was removed under reduced pressure to afford 979 mg of crude residue.

General Organic Analyses

HPLC/MS data was obtained using a Gilson semi-prep HPLC with a Gilson 170 Diode Array UV detector and PE Sciex API 100LC MS based detector. A Waters 600E with a Waters 490E UV detector was also used for recording HPLC data. The compounds were eluted with a gradient of CH_3CN (with 0.0035% TFA) and H_2O(with 0.01% TFA). Both HPLC instruments used Advantage C18 60A 5µ 50mm x 4.6mm columns from Thomson Instrument Company. Mass spectra were obtained by direct injection and electrospray ionization on a PE Sciex API 100LC MS based detector. Thin layer chromatography was performed using Merck 60F-254 aluminum backed precoated plates. Flash chromatography was carried out on Merck silica gel 60 (230-400 mesh) purchased from EM Scientific.

Syntheses of Symmetrical Diamides

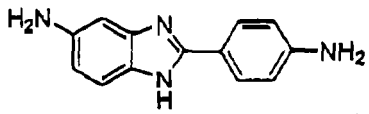
The symmetrical diacyl benzimidazole compounds of the present invention were generally prepared from 2-(4-aminophenyl)-5-aminobenzimidazole, which was obtained by reduction of 2-(4-nitrophenyl)-6-nitrobenzimidazole.



2-(4-nitrophenyl)-6-nitrobenzimidazole

The dinitro benzimidazole was prepared as follows: a mixture of 4-nitrophenylenediamine (6.4g, 41.83 mmol) and 4-nitrobenzoic acid (7.86 g, 47 mmol) was dissolved in $POCl_3$ (250 ml) and heated to reflux for 2 h. The reaction mixture was cooled, poured on to ice, and stirred for 30 min. The resulting solid was filtered and washed with methanol and sodium bicarbonate to remove unreacted acid and allowed to dry overnight to give the desired product as a brown solid (5.8 g). The product was characterized by electrospray mass spectroscopy (mp >300° C).

2-(4-Aminophenyl)-5-aminobenzimidazole was prepared by suspending the above solid (75 g) in THF (75 ml), to which was added Pd-C (10% Pd by weight). The flask was purged with hydrogen and stirred under a balloon of hydrogen over night. TLC and MS showed starting material was still present so the reaction was allowed to continue over the weekend. TLC indicated complete reaction, the reaction was filtered through celite and washed with methanol. The solvent was removed under reduced pressure to give a dark brown solid (0.37 g) that was used without further purification.

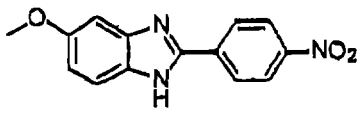


2-(4-aminophenyl)-5-aminobenzimidazole

Alternatively, the 2-(4-aminophenyl)-5-aminobenzimidazole was prepared by the following reduction: 2-(4-nitrophenyl)-6-nitrobenzimidazole (8.9 g, 31 mmole) was suspended in concentrated HCl (100 ml) to which was added stannous chloride (42.3 g 180 mmole). The reaction mixture was heated to reflux for 5 hrs. The mixture was cooled to RT and the HCl salt

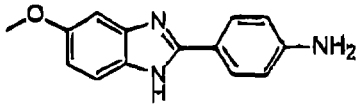
of the desired product was precipitated by the addition of ethanol. The resulting solid was filtered, re-dissolved in water and the solution made basic by the addition of concentrated ammonium hydroxide. The resulting precipitate was filtered and dried overnight under vacuum to yield the desired product as a gray solid (6.023 g, 26.9 mmole, 87%). The product characterized by electrospray mass spectroscopy and HPLC (mp. 222-227° C).

2-(4-Aminophenyl)-5-methoxy benzimidazole was synthesized from 2-(4-nitrophenyl)-5-methoxy benzimidazole, which was prepared as follows: 1,2-diamino-4-methoxybenzene (1.26 g, 10.0 mmole was mixed with 4-nitrobenzoic acid (1.67 g, 9.8 mmole) and dissolved in $POCl_3$ (10 ml) and heated to reflux for 2.5 hours. The reaction mixture was cooled and cautiously poured onto ice. The resulting solid was filtered, washed with $NaHCO_3$ and used without further purification.



2-(4-nitrophenyl)-5-methoxy benzimidazole

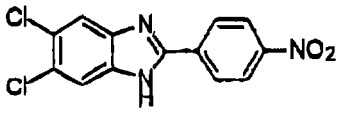
2-(4-Aminophenyl)-5-methoxy benzimidazole was prepared by dissolving 1 g of the above nitrobenzimidazole in 30% $Na_2S{\cdot}9H_2O$ (20 ml) with stirring at RT for 21 h. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic extracts were dried over sodium sulfate and concentrated under vacuum. The product was characterized by mass spectroscopy.



2-(4-aminophenyl)-5-methoxy benzimidazole

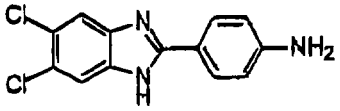
2-(4-Aminophenyl)-5,6-dichloro benzimidazole was synthesized from 2-(4-nitrophenyl)-5,6-dichloro benzimidazole, which was prepared as follows: 1,2-diamino-4,5-dichlorobenzene (1.68 g, 10.0 mmole) was mixed with 4-nitrobenzoic acid (1.58 g, 9.3 mmole), dissolved in $POCl_3$ (10 ml), and heated to reflux for 2.5 hours. The reaction mixture was cooled and

cautiously poured onto ice. The resulting solid was filtered, washed with $NaHCO_3$ and used without further purification.



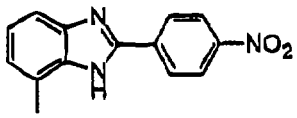
2-(4-nitrophenyl)-5,6-dichloro benzimidazole

2-(4-Aminophenyl)-5,6-dichloro benzimidazole was prepared by dissolving 1 g of the above nitrobenzimidazole in 30% $Na_2S \cdot 9H_2O$ (20 ml) with stirring at RT for 21 h. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic extracts were dried over sodium sulfate and concentrated under vacuum. The product was characterized by mass spectroscopy.



2-(4-Aminophenyl)-5,6-dichloro benzimidazole

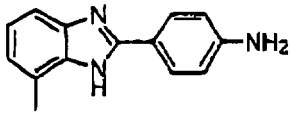
2-(4-aminophenyl)-7-methyl benzimidazole was synthesized from 2-(4-nitrophenyl)-7-methyl benzimidazole, which was prepared by mixing 1,2-diamino-3-methylbenzene (1.24 g, 10.0 mmole) with 4-nitrobenzoic acid (1.69 g, 9.8 mmole), dissolved in $POCl_3$ (10 ml), and heated to reflux for 2.5 hours. The reaction mixture was cooled and cautiously poured onto ice. The resulting solid was filtered, washed with $NaHCO_3$ and used without further purification.



2-(4-nitrophenyl)-7-methyl benzimidazole

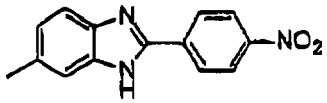
2-(4-Aminophenyl)-7-methyl benzimidazole was synthesized by dissolving 1 g of the above nitrobenzimidazole in 30% $Na_2S \cdot 9H_2O$ (20 ml) with stirring at RT for 4.5 h. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic extracts were

dried over sodium sulfate and concentrated under vacuum. The product was characterized by mass spectroscopy.



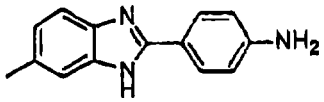
2-(4-aminophenyl)-7-methyl benzimidazole

2-(4-Aminophenyl)-6-methyl benzimidazole was synthesized from 2-(4-nitrophenyl)-6-methyl benzimidazole, which was prepared by mixing 1,2-diamino-4-methylbenzene (1.24 g, 9.8 mmole) with 4-nitrobenzoic acid (1.6 g, 9.9 mmole) and dissolved in $POCl_3$ (10 ml) and heated to reflux for 2.5 hours. The reaction mixture was cooled and cautiously poured onto ice. The resulting solid was filtered, washed with $NaHCO_3$ and used without further purification.



2-(4-nitrophenyl)-6-methyl benzimidazole

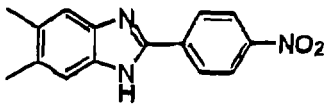
2-(4-Aminophenyl)-6-methyl benzimidazole was synthesized by dissolving 1 g of the above nitrobenzimidazole in 30% $Na_2S{\cdot}9H_2O$ (20 ml) with stirring at RT for 4.5 h. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic extracts were dried over sodium sulfate and concentrated under vacuum. The product was characterized by mass spectroscopy.



2-(4-aminophenyl)-6-methyl benzimidazole

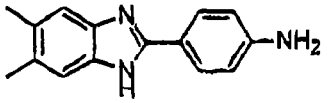
2-(4-Aminophenyl)-5,6-dimethyl benzimidazole was synthesized from 2-(4-nitrophenyl)-5,6-dimethyl benzimidazole, which was prepared by mixing 1,2-diamino-4,5-dimethylbenzene (1.38 g, 10.1 mmole) with 4-nitrobenzoic acid (1.69 g, 9.9 mmole) and dissolved in $POCl_3$ (10 ml) and heated to reflux for 2.5 hours. The reaction mixture was cooled and cautiously poured

onto ice. The resulting solid was filtered, washed with $NaHCO_3$ and used without further purification.



2-(4-nitrophenyl)-5,6-dimethyl benzimidazole

2-(4-Aminophenyl)-5,6-dimethyl benzimidazole was synthesized by dissolving 1 g of the above nitrobenzimidazole (31.1) in 30% $Na_2S \cdot 9H_2O$ (20 ml) with stirring at RT for 4.5 h. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic extracts were dried over sodium sulfate and concentrated under vacuum. The product was characterized by mass spectroscopy.



2-(4-aminophenyl)-5,6-dimethyl benzimidazole

The subsequent preparation of symmetrical diamides was accomplished by one of the following methods:

Method A: 2-(4-Aminophenyl)-6-aminobenzimidazole (1 mmole) was suspended in THF (5 ml) to which was added DIEA (2.5 mmole) and mixture cooled to –78° C. To the above cooled mixture was added the acid chloride (2.5 mmole) and let warm to RT overnight. Water (2 ml) is added to the reaction and extracted with EtOAc. The combined organic extracts were combined washed with $NaHCO_3$ (aq.) and concentrated under reduced pressure. The resulting residue was purified on silica gel (hexanes/EtOAc or $MeOH/CH_2Cl_2$) or reverse phase HPLC (CH_3CN/H_2O).

Method B: 2-(4-Aminophenyl)-6-aminobenzimidazole (1 mmole) and DMAP (cat.) was dissolved in pyridine (5 ml). To the above solution was added the acid chloride (2.5 mmole) and the reaction stirred overnight at 60° C. The reaction was cooled to room temperature and water added to precipitate the product. The resulting solid was collected by filtration with the solid

being washed by hexanes and water and $NaHCO_3$ (aq.). The resulting residue was purified on silica gel (hexanes/EtOAc or $MeOH/CH_2Cl_2$) or reverse phase HPLC (CH_3CN/H_2O).

Method C: 2-(4-Aminophenyl)-6-aminobenzimidazole (1 mmole) was suspended in THF (10 ml) to which was added K_2CO_3 (2.5 mmole) in water (0.5 ml), and mixture cooled to –78° C. To the above cooled mixture was added the acid chloride (2.5 mmole) and let warm to RT overnight. Water (10 ml) was added to the reaction and extracted with EtOAc. The combined organic extracts were combined washed with $NaHCO_3$ (aq.) and concentrated under reduced pressure. The resulting residue was purified on silica gel (hexanes/EtOAc or $MeOH/CH_2Cl_2$) or reverse phase HPLC (CH_3CN/H_2O).

Method D: The carboxylic acid (2.2 mmole), EDC (2.2 mmole) and DMAP (cat.) was dissolved in hot pyridine. To the above solution was added 2-(4-aminophenyl)-6-aminobenzimidazole (1 mmole) and heated to 60° C overnight. The cooled reaction mixture was partitioned between water and EtOAc. The organic layer was washed with $NaHCO_3$, dried over Na_2SO_4 and concentrated under vacuum. The resulting residue was purified on silica gel (hexanes/EtOAc or $MeOH/CH_2Cl_2$) or reverse phase HPLC (CH_3CN/H_2O).

Diacyl Benzimidazole Species

The following species encompassed within the disclosed generic formula were synthesized and tested for their ability to suppress IgE. The species are presented above in the Summary of the Invention

9 SEP 2002

IgE Down-Regulatory Activity

All of the disclosed species were tested for their ability to suppress IgE in both the *ex vivo* and *in vivo* assays. They were all active in both assays. Activities (IC_{50}) of the species in the *ex vivo* assay ranged from about 100 pM to 1 nM. In the *in vivo* assay, the IC_{50} dose ranged from approximately 100 μg/kg body weight/day to about 10 mg/kg body weight/day. The diacyl benzimidazole compounds were generally more potent than the monoacyl compounds.

Suppression of IgE Response

The inhibitory activity of the small molecules of the present invention were assayed using both the *ex vivo* and *in vivo* assays as described above. All of the compounds presented above were active in suppressing the IgE response. In the *ex vivo* assay, compounds in genuses I-XI produced 50% inhibition at concentrations ranging from 1 pM to 10 μM. In the *in vivo* assay, the compounds were effective at concentrations ranging from less than about 0.01 mg/kg/day to about 25 mg/kg/day, when administered in divided doses (e.g., two to four times daily) for at least two to seven consecutive days. Thus, the small molecule inhibitors of the present invention are disclosed as being useful in lowering the antigen-induced increase in IgE concentration, and consequently, in the treatment of IgE-dependent processes such as allergies in general and allergic asthma in particular.

Treatment Regimens

The amount of the IgE inhibitor compound which may be effective in treating a particular allergy or condition will depend on the nature of the disorder, and can be determined by standard clinical techniques. The precise dose to be employed in a given situation will also depend on the choice of compound and the seriousness of the condition, and should be decided according to the judgment of the practitioner and each patient's circumstances. Appropriate dosages can be determined and adjusted by the practitioner based on dose response relationships between the patient's IgE levels as well as standard indices of pulmonary and hemodynamic changes. Moreover, those skilled in the art will appreciate that dose ranges can be determined without undue experimentation by following the protocol(s) disclosed herein for *ex vivo* and *in vivo* screening (See

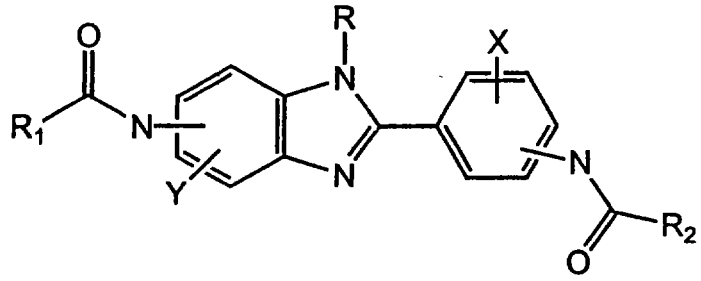
for example Hasegawa et al., *J. Med. Chem.* 40: 395-407 (1997) and Ohmori et al., *Int. J. Immunopharmacol.* 15:573-579 (1993); employing similar *ex vivo* and *in vivo* assays for determining dose-response relationships for IgE suppression by naphthalene derivatives; incorporated herein by reference).

Initially, suitable dosages of the compounds will generally range from about 0.001 mg to about 300 mg per kg body weight per day in divided doses, more preferably, between about 0.01 mg and 100 mg per kg body weight per day in divided doses. The compounds are preferably administered systemically as pharmaceutical formulations appropriate to such routes as oral, aerosol, intravenous, subcutaneously, or by any other route which may be effective in providing systemic dosing of the active compound. The compositions of pharmaceutical formulations are well known in the art. The treatment regimen preferably involves periodic administration. Moreover, long-term therapy may be indicated where allergic reactions appear to be triggered by continuous exposure to the allergen(s). Daily or twice daily administration has been effective in suppressing the IgE response to a single antigen challenge in animals when carried out continuously from a period of two to seven consecutive days. Thus, in a preferred embodiment, the compound is administered for at least two consecutive days at regular periodic intervals. However, the treatment regimen, including frequency of dosing and duration of treatment may be determined by the skilled practitioner, and modified as needed to provide optimal IgE down-regulation, depending on nature of the allergen, the dose, frequency, and duration of the allergen exposure, and the standard clinical indices.

In one embodiment of the present invention, an IgE-suppressing compound may be administered in conjunction with one or more of the other small molecule inhibitors disclosed, in order to produce optimal down-regulation of the patient's IgE response. Further, it is envisioned that one or more of the compounds of the present invention may be administered in combination with other drugs already known or later discovered for treatment of the underlying cause as well as the acute symptoms of allergy or asthma. Such combination therapies envisioned within the scope of the present invention include mixing of one or more of the small molecule IgE-inhibitors together with one or more additional ingredients, known to be effective in reducing at least one symptom of the disease condition. In a variation, the small molecule IgE-inhibitors herein disclosed may be administered separately from the additional drugs, but during the same course of the disease

condition, wherein both the IgE-inhibitor(s) and the palliative compounds are administered in accordance with their independent effective treatment regimens.

1. A pharmaceutical composition for treating or preventing an allergic reaction associated with increased IgE levels in a mammal comprising the following compounds:



wherein X and Y are independently selected from the group consisting of H, alkyl, alkoxy, aryl, substituted aryl, hydroxy, halogen, amino, alkylamino, nitro, cyano, CF_3, OCF_3. $CONH_2$, CONHR and $NHCOR_1$;

wherein R is selected from the group consisting of H, CH_3, C_2H_5, C_3H_7, C_4H_9, CH_2Ph, and $CH_2C_6H_4$-F(p-); and

wherein R_1 and R_2 are independently selected from the group consisting of H, aryl, substituted aryl, cycloaryl substituted cycloaryl, multi-ring clycloaryl, benzyl, substituted benzyl, alkyl, cycloalkyl substituted cycloalkyl, multi-ring cycloalkyl, fused-ring aliphatic, cyclopropyl, substituted cyclopropyl, cyclobutyl, substituted cyclobutyl, cyclopentyl, substituted cyclopentyl, cyclohexyl, substituted cyclohexyl, cycloheptyl, substituted cycloheptyl, bicycloheptyl, bicyclooctyl, bicyclononyl, substituted bicycloalknyl, adamantyl and substituted adamantyl, wherein at least one of R_1 and R_2 are aromatic groups.

2. The pharmaceutical composition of claim 1, wherein the substitutions for R_1 and R_2 are selected from the group consisting of alkyl, aryl, CF_3, CH_3, OCH_3, OH, CN, COOR and COOH.

3. The pharmaceutical composition of Claim 1, further comprising at least one additional ingredient which is active in reducing at least one symptom associated with said allergic reaction.

4. The pharmaceutical composition of Claim 3, wherein said additional ingredient is selected from the group consisting of a short-acting β_2-adrenergic agonist, a long-acting β_2-adrenergic agonist, an antihistamine, a phosphodiesterase inhibitor, an anticholinergic agent, a corticosteroid, and inflammatory mediator release inhibitor and a leukotriene receptor antagonist.

5. Use of the pharmaceutical composition of any one of Claims 1-4 in the preparation of a medicament for treating or preventing an allergic reaction associated with increased IgE levels in a mammal.

6. Use of the pharmaceutical composition of any one of Claims 1-4 in the preparation of a medicament for treating or preventing asthma in a mammal.