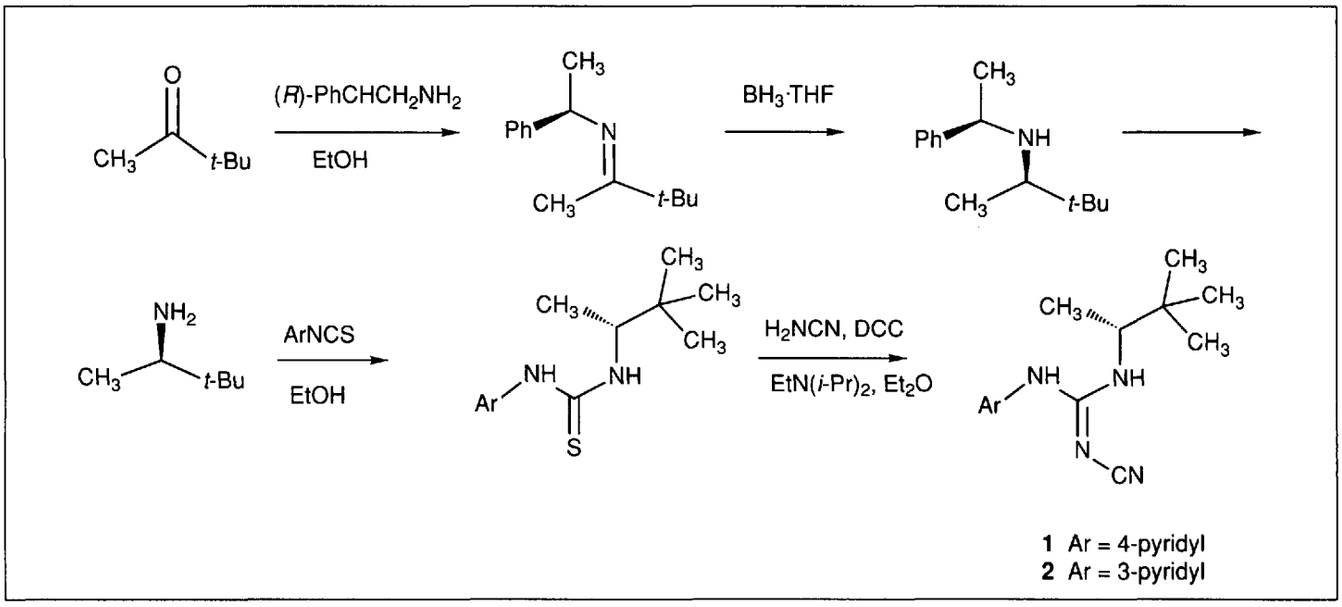
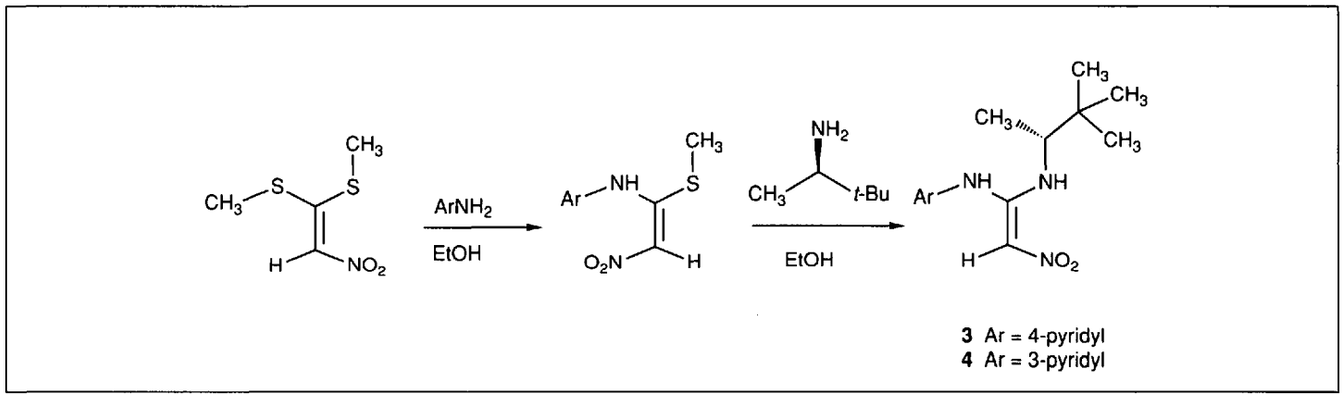
Scheme 1



Scheme 2



bition of spontaneous mechanical activity (pIC_{50}) and stimulation of ^{86}Rb-efflux (pEC_{15}) in rat portal veins [6], and revealed that K-channel opening activity was stereoselective with (*R*)-pinacidil (pIC_{50} = 7.6) being 12 times more potent than (*S*)-pinacidil (pIC_{50} = 6.1). Similar stereoselectivity was found for the 3-pyridyl analogues of pinacidil (**2**). Paradoxically, however, with the nitroethenediamines, as illustrated for the 3-pyridyl analogue **4**, the stereoselectivity for K-channel opening was reversed, with the (*S*)-enantiomer (pIC_{50} = 8.0) being 100-fold more active than its corresponding (*R*)-enantiomer (pIC_{50} = 6.0).

(Abstract by the authors)

Received: November 30, 1990

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[5] R. Gompper, H. Schaefer, *Chem. Ber.* **1967**, *100*, 591.
[6] U. Quast, *Br. J. Pharmacol.* **1987**, *91*, 569.

Chimia 45 (1991) 89–90

The Search for Peptidoleukotriene Antagonists

Andreas von Sprecher*, Alfred Sallmann, Andreas Beck, Werner Breitenstein, Hansruedi Wiestner, Sabine Kimmel, Wayne H. Anderson, Gary P. Anderson, Natarajan Subramanian, and **Michael A. Bray**

The peptidoleukotrienes LTC_4, LTD_4, and LTE_4 are thought to play a major role in allergic asthma, due to their potent bronchoconstrictor and inflammatory properties. The first leukotriene (LT) antagonist, *FPL55712*, was discovered in 1973 six years before the structures of the LT's were defined by *Samuelsson* and *Corey*. Initial chemical approaches to the discovery of new LT antagonists were based mainly on the structure of *FPL55712* and, after 1980, on the structure of LTD_4. *LY171883, L-648051, Ro23-3544, CGP35949D*, and *YM-16638* are examples of *FPL55712* analogs that are or were in clinical development. However, the clinical data reported so far are not encouraging. These compounds, as well as the first LT analogs, can be considered to be 'first generation' antagonists showing antagonist potency in the range of *FPL55712*. Recently 'second generation' antagonists with greatly enhanced potency have been

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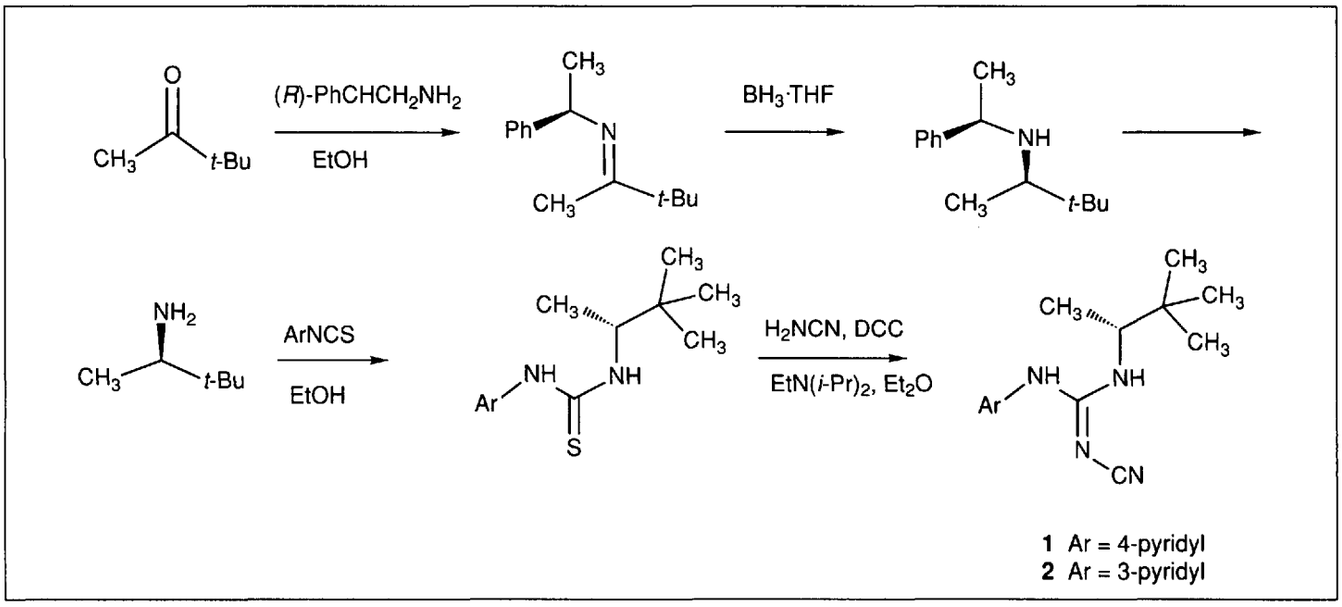
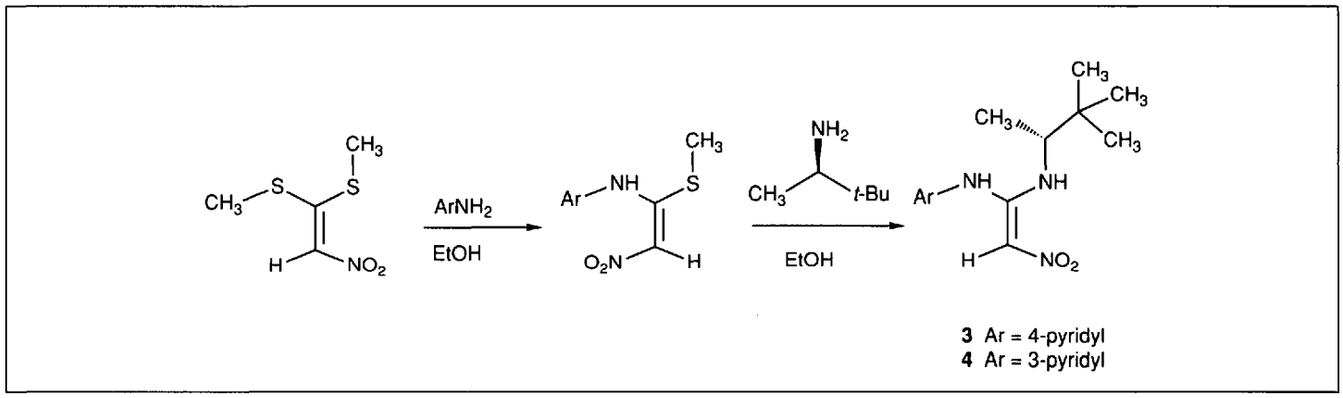
Scheme 1



Scheme 2



bition of spontaneous mechanical activity (pIC_{50}) and stimulation of ^{86}Rb-efflux (pEC_{15}) in rat portal veins [6], and revealed that K-channel opening activity was stereoselective with (*R*)-pinacidil (pIC_{50} = 7.6) being 12 times more potent than (*S*)-pinacidil (pIC_{50} = 6.1). Similar stereoselectivity was found for the 3-pyridyl analogues of pinacidil (**2**). Paradoxically, however, with the nitroethenediamines, as illustrated for the 3-pyridyl analogue **4**, the stereoselectivity for K-channel opening was reversed, with the (*S*)-enantiomer (pIC_{50} = 8.0) being 100-fold more active than its corresponding (*R*)-enantiomer (pIC_{50} = 6.0).

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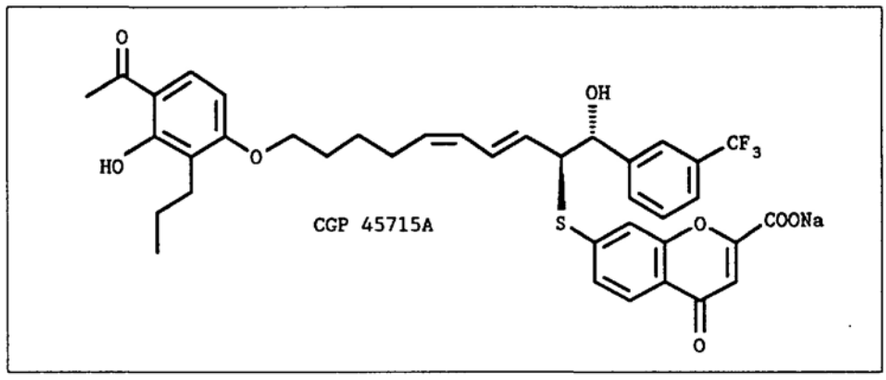
described. These LT antagonists belong to different structural classes: *1*) Indazoles and Indoles: *ICI198615* and *ICI204219*. *2*) Quinolines: *MK-571*, *Wy48252*, *RG12525*, and *SR2640*. *3*) Miscellaneous structures: *ONO-1078*. *4*) LT analogs: *SKF104353*, *LY170680*, and *CGP45715A*. *CGP45715A* is the most potent and longest acting antagonist of the LT analog type known to us. *In vitro*, *CGP45715A* is a potent antagonist of LTD_4 induced smooth muscle contractions (guinea pig ileum and lung parenchyma) and shows similar affinity for the guinea pig lung LTD_4 receptor as the known industry leaders (*ICI204219*, *MK-571*, and *SKF104353*). *In vivo*, *CGP45715A* is an extremely potent and long acting antagonist of LTD_4 mediated bronchoconstriction in guinea pigs, when given by aerosol, intravenous, or oral routes of administration. Applied as an aerosol 1 h prior to LTD_4 (aerosol) challenge the ED_{50} is 0.000045% (concentration of aerosol solution) corresponding to ~30 ng/kg (*SKF104353* ED_{50} > 0.01%; *ICI204219* ED_{50} = 0.0013%). *CGP45715A* is also a potent inhibitor of antigen induced, LT-dependent bronchoconstriction in sensitized guinea pigs. In this model, as well as in the LTD_4 challenge model, the duration of action of p.o. administered *CGP45715A* is at least 24 h.

CGP45715A is the result of extensive structure activity studies in the course of which around 600 LT analogs have been synthesized. *CGP45715A* is a structural analog of LTD_4. The carboxylic group in the eicosanoid chain of LTD_4 is replaced by a CF_3 group and the dipeptide sulfur side chain by a chromonecarboxylic acid. The eicosanoid backbone could be stabilized by the integration of two Ph rings: one in the polar region and the other at the lipophilic end of the molecule. The (1*R*,2*S*)-configuration of *CGP45715A* does not correspond to the (5*S*,6*R*)-configuration of the natural LT's. The (1*S*,2*R*)-enantiomer displaying the absolute configuration of LTD_4 shows only weak LTD_4 antagonist activity. Besides the configuration, other structural parameters, such as the length of the backbone, the substitution pattern of the Ph nuclei, the number of double bonds, and the nature of the sulfur side chain, are critical for optimal LTD_4 antagonism.

The clinical evaluation of 'second generation' antagonists will clarify, whether LT antagonists are to be of value in the treatment of allergic asthma and other diseases with possible LT involvement.

(Abstract by the authors)

Received: December 11, 1990



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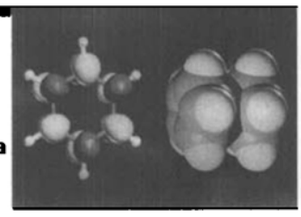

Chimia 45 (1991) 90–92

When *Schrödinger* and *Newton* work together...

'Man can believe the impossible, but man can never believe the improbable'
(Oscar Wilde)

As the invited speaker *H. Berendsen* recently stated in Geneva, the future of molecular simulations lies undoubtedly in mixing more and more *Schrödinger* with *Newton*. In other words, realistic simulations of many-particle systems are going to be more and more performed by using *Newton*ian mechanics with interaction potentials parametrized in part by solving the *Schrödinger* equation. For quantum chemists proud of *Dirac* heritage ('the underlying physical laws...'), the pill could seem in a first sight somewhat bitter: why should they struggle hard to devise intricate methodological and computational strategies to solve $H\Psi = E\Psi$, if the outcome of their efforts is merely used as an ingredient of the old-fashioned, classical *Newton*ian mechanics? It is something like asking F1 pilots to run races in order to help car manufacturers to design 2 CV engines...

The impatient reader should not be confused here with our intention: we are in no case suggesting that quantum mechanics is of no practical use in modeling and understanding the behavior of chemical systems. On the contrary, quantum chemistry is probably one of the most successful theories among the whole range of molecular sciences. Clearly, there are numerous examples in the literature where quantum chemistry, often through its simplest models, has brought a decisive contribution to the rationalization of important chemical phenomena, such as the pericyclic reactions (remember the *Woodward-Hoffmann* rules) or the spectroscopic properties of transition-metal complexes (remember the modern ligand field theory). However, quantum mechanical techniques are notoriously inadequate for modeling macromolecules or solvated systems, but the problem is here to select a theoretical approach appropriate to the case under study.

Undoubtedly, due to their scaling varying from N^3 (semiempirical models) to N^6 (post *Hartree-Fock* models), where N is the number of basis functions, quantum chemical methods are the solution of choice for gas phase systems comprising up to 10^2–10^3 electrons. Some extensions of quantum chemistry techniques, taking account of periodicity conditions, have been suggested for solids such as crystals and polymers, and this is an extremely interesting development for solid-state chemists. It allows to calculate