# New Drug Monitor

*New Drug Monitor provides an insight into the latest developments in drug discovery through brief synopses of recent presentations and publications.*

## Angiotensin II receptor antagonists

Pharmacological approaches to modulate the renin angiotensin system for hypertensive therapy have included attempts to inhibit *I*) release of renin by the kidneys in response to a fall in blood pressure; *II*) conversion of angiotensinogen I by renin; *III*) conversion of angiotensin I to angiotensin II by angiotensin-converting enzyme (ACE). Some renin inhibitors have reached clinical trials, but further development has been limited by poor bioavailability. Although ACE inhibitors, such as captopril and enalapril, are used effectively in the treatment of hypertension and congestive heart failure, recent efforts have been focused on the development of effective angiotensin II receptor antagonists. Such agents would be more specifie as inhibitors of the renin-angiotensin system than are ACE inhibitors, and would inhibit the action of angiotensin II produced via ACE-independent pathways.

The potential benefit of angiotensin II antagonists has been demonstrated using the peptide saralasin, which is specific angiotensin II inhibitor. However, the poor hioavailability of this agent has driven a search for orally active nonpeptide compounds. In consequence, losartan was recently marketed for the treatment of hypertension. However, this compound is selective only for one of the two major subtypes of angiotensin II receptor ($AT_1$) . Although $AT_1$ receptors are known to mediate most of the physiological effects of angiotensin II, the effects of the raised levels of circulating angiotensin II observed on administration of $AT_1$ - specific inhibitors on the other receptor are unknown. Recent research has therefore focused on the identification of orally active angiotensin II antagonists that exhibit potent and equal affinity for both receptor subtypes. Some of these new drugs are:

1. The agents based on the modification of the trisubstituted 1,2,4-triazolinone biphenyl-sulphonamides. These compounds showed subnanomolar potency at both the $AT_1$ (rabbit aorta) and $AT_2$ (rat midbrain) receptors and was orally active at a dose of 3 mg/kg . (Chang and coworkers. *J.Med Chem* 1995;**38:**3741-3758)

2. A series of 5-[[ 1-(4'-carboxybenzyl)-imidazolyl] methylidene] hydantoins. These compounds reduced the mean arterial blood pressure of renal hypertensive rats by 40% at 30 mg/kg and by 25% at 10 mg/kg. ( Edmunds and coworkers. *J Med Chem* 1995; **38**:3759-3771)

3. A novel series of benzimidazole-7-carboxylic acid bearing a 5-oxo-1,2,4-oxadiazole ring as an acidic bio-isosteric replacement for the tetrazole group. The structure-activity relationships of the benzimidazole derivatives bearing the 5-oxo-1,2,4-oxadiazole group were found to be similar to those of the tetrazole derivative. However, These compounds were found to have improved oral bioavailability in comparison to the original tetrazole compounds. ( Kohara and coworkers. *Bioorg Med Chem Lett* 1995; **5**: 1903-1908)

4. The replacement of the imidazole group of losartan with 1,2,3,4-tetrahydro-2,4- pyrimidinedione (uracil). (Dorsch et al, *Bioorg Med Chem Lett* 1995;**5**: 2071-2076)

5. Modification of the N-$^3$nitrogen with a *N,N*-dimethyl-acetamide residue afforded a compound with enhanced affinity at the $AT_1$ receptor. The studies showed these compounds were particularly potent orally active angiotensin II antagonists in animal models. ( Dina and coworkers. Abstract presentation (Medi 063) at the ACS Fall Meeting 1995, Chicago, USA)

***Pravit Akarasereenont***

Department of Pharmacology,
Faculty of Medicine Siriraj Hospital,
Mahidol University, Bangkok 11000,