diastereomeric mixtures.

[PD1-5] [10/19/2001 (Fri) 14:00 - 17:00 / Hall D]

Synthesis and Antitumor Activity of 4'-O-Aminoacyl-, Carbamate-, and Carbonate Prodrugs of 4'-Demethyl-1-Deoxypodophyllotoxin

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Deoxypodophyllotoxin (DPT), first isolated from *Anthricus sylvestris* is a potent inhibitor of mitosis, and showed a potent cytotoxic activity against a wide variety of cancer cell lines. But, DPT still did not show a potent antitumor activity comparable to its potent cytotoxic activity. This was considered to be due to poor aqueous solubility and bioavailability of DPT. To obtain compounds with pharmaceutically acceptable properties and improved antitumor activity, we designed 4'-demethyl-1-DPT derivatives in which the methyl group at 4'-position was replaced with various aminoacyl, carbamoyl, oxycarbonyl groups. Among them, 4'-demethyl-4'-*O*-(8-aminooctanoyl)-1-DPT, 4'-demethyl-4'-*O*-(2-hyroxyethylcarbamoyl)-1-DPT, and 4'-demethyl-4'-*O*-(2-chloroethylcarbonyl)-1-DPT showed inhibition ratio (IR) of 87%, 95%, and 89%, respectively, much higher than the IR (78%) of etoposide which was used as positive control.

[PD1-6] [10/19/2001 (Fri) 14:00 - 17:00 / Hall D]

Stereoselective synthesis hydroxylated cyclopentane carbocycle for nucleosides via sequential Claisen rearrangement and RCM reaction

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Extensive efforts in the search of chemotherapeutic agents against viral infection and cancers have led to the discovery of a variety of biologically active nucleoside analogs, including carbocyclic nucleosides (i.e. abacavir).
As part of our drug discovery program, we have determined to synthesize carbocyclic nucleosides with hydroxy group at 5'-position. Herein, We would like to introduce synthetic method of cyclopentane carbocycle intermediate for the synthesis of 5'-hydroxy carbocyclic nucleosides using sequential Claisen rearrangement and ring closing metathesis from D-mannitol.

[PD1-7] [10/19/2001 (Fri) 14:00 - 17:00 / Hall D]

Synthetic Approaches to the Generation of New COX-2 Inhibitor through the Modification of Indomethacin

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All nonsteroiddal antiinflammatory drugs(NSAIDs) inhibit coclooxygenase(COX) isoenymes to different extents, which accounts for their antiinflammatory and analgesic activities and their gastrointestinal(GI)

side effects. Recent studies have shown that derivatization of the carboxylate, amide moiety in substrate analogue inhibitors, such as indomethacin, results in the generation of COX-2 selectivity.
In this paper, we will present a facile synthetic method to prepare indole carbamic ester and urea derivatives as target molecules via Curtius Rearrangement of indomethacin followed by quenching the resulting isocynates with alcohols and amines, respectively. The prepared indole carbamic ester and urea derivatives exhibited weak analgesic activities at the acetic acid induced writhing test for ICR male mice. The developed synthetic metholodogy will be further utilized for development of new COX-2 inhibitors.

[PD1-8] [10/19/2001 (Fri) 14:00 - 17:00 / Hall D]

Synthesis of Aminocarbocycles from Glucose

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The addition of O-benzylhydroxylamine hydrochloride to a basic aqueous solution of an unsaturated glycoside triester in the presence of a Pd (II) chloride gave an anticipated aminocyclohexanone and a carbocyclooxime. The Ferrier reaction mechanism forms a carbonyl intermediate that is stable enough to react with amine, which then cyclizes to form the aminocyclo compound. This could offer a direct method of amination of carbocycles from simple sugars through the intermediate intramolecular cyclization reaction.

[PD1-9] [10/19/2001 (Fri) 14:00 - 17:00 / Hall D]

Combretoxazolones: Synthesis, Cytotoxicity and Antitumor Activity

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Combretastatin A-4 (CA-4, 1) is one of the most potent antimitotic agents and binds to tubulin on the colchicine binding site. It shows strong cytotoxicity agaisnt a variety of human cancer cells, including multi-drug resistant cell lines. From a series of SAR studies, it was established that the cis-orientation of two phenyl rings is essential to strong cytotoxicity. However, cis-combretastatin analogues are prone to isomerize to trans-forms during storage and administration. The trans-forms of these compounds show dramatic reduction in both antitubulin activity and cytotoxicity. This prompted the syntheses of a number of cis-restricted 5-membered heterocyclic analogues of CA-4 (5) (Figure 1). In this presentation we report the synthesis and evaluation of cytotoxicity of two series of oxazolone-type compounds (6, 3,4-diaryloxazolones, 7, 4,5-diaryloxazolones), hereafter given a trivial name of combretoxazolone.

The results from this study showed that a 3-(3,4,5-trimethoxyphenyl) group was essential for the cytotoxicity of 3,4-diaryloxazolones (6), meanwhile this moiety at 4-position was indispensable for 4,5-diaryloxazolones (7). Variation of the second aryl groups led to the findings that these oxazolone type compounds share the common feature of combretastatins family. Most compounds exhibited potent cytotoxicity in a variety of tumor cell lines with IC50 values of sub-nanomol, equipotent with CA-4. One compound, compound 6g exhibited a significant antitumor activity in BDF1 mice bearing B16 murine melanoma cells with inhibition rates of 67 and 61% at 100 and 30 mg/kg/day, respectively.

[PD1-10] [10/19/2001 (Fri) 14:00 - 17:00 / Hall D]

Synthesis of trans-Metanicotine Analogues