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

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A convenient pathway for synthesis of trans-metanicotine analogues was developed. trans-Metanicotine, a subtype(alpha4beta2)-selective ligand for neuronal nicotinic acetylcholine receptor, is under clinical phase for Alzheimer's disease. Allylation of N-methyl aldimines with allylmagnesium bromide yielded methyl-(1-aryl-but-3-enyl)amines. Protection of the amines with Boc group and followed by Heck reaction with 3-bromopyridine gave methyl-(1-aryl-4-pyridin-3-yl-but-3-enyl) carbamic acid tert-butyl esters. Following deprotection of N-Boc group provided methyl-(1-aryl-4-pyridin-3-yl-but-3-enyl)amines in good yields. Thus, trans-metanicotine analogues modified at the α-position of the methylamino group with various aryl groups can be obtained in 5 steps.

[PD1-11] [10/19/2001 (Fri) 14:00 - 17:00 / Hall D]

Synthesis of Novel TNF-α Production Inhibitors. 2-[3-(Cyclopentyloxy)-4-methoxyphenyl]-substituted-1-isoindolinone derivatives

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This study describes the synthesis and in vitro evaluation of 2-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-isoindolinone derivatives substituted on benzene moiety of isoindoline ring for the inhibition of TNF-α production. From this study, we have found the 6-C position on isoindolinone ring is an optimal derivatization site. Among the compounds synthesized, 6-amino-2-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-isoindolinone (6) was the most potent in inhibitory activity of TNF-α production in LPS-stimulated RAW264.7 cells.

[PD1-12] [10/19/2001 (Fri) 14:00 - 17:00 / Hall D]

Synthesis of Chelerythrine, Natural Benzo[c]phenanthridine Alkaloid

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Benzo[c]phenanthridines are naturally occurring alkaloids which have demonstrated numerous biological activities. Among these structures, fagaridine, nitidine and fagaronine have solicited much attention as antitumor drugs. Many synthetic approaches to benzo[c]phenanthridine alkaloids leading to natural products have been reported, but relatively few studies of synthetic analogues have been described. These alkaloids have also demonstrated binding affinities to DNA, have been presumed to be intercalators and have been shown to be inhibitors of DNA topoisomerase I and II, the well known targets for clinically important and emerging antitumor drugs.
As part of our endeavor to develop potential antitumor agents, we have tried to synthesize benzo[c] phenanthridine alkaloids. Our strategy is based on the synthesis of substituted 3-arylisoquinolines which is a crucial intermediates for the formation of C ring of these alkaloids. The synthesis of chelerythrine and other derivatives will be described.

[PD1-13] [10/19/2001 (Fri) 14:00 - 17:00 / Hall D]

Pimarane Cyclooxygenase 2 (COX-2) Inhibitor and its Structure-Activity Relationship