

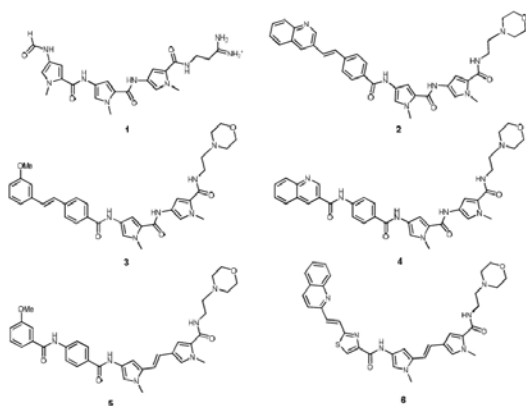
## OL – 13 – R

### Essential hydrogen bonding and hydrophobic interactions in highly potent antibacterial minor groove binders

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Minor groove binders (MGBs) related to the natural product distamycin (**1**) have attracted much attention. A wide range of analogues has been prepared at Strathclyde with many structural variations aimed at increasing hydrophobicity. These include *N*-alkyl substituents larger than methyl and more lipophilic head groups than formyl; a low pK<sub>a</sub> tail group has also been found important for antibacterial activity. Extending this strategy, we have also shown that the substitution of the polar, hydrogen bonding amide linkage between the head group and the first heterocyclic monomer with the non-polar, non-hydrogen bonding alkene isostere led to a series of highly active anti-bacterial MGBs such as (**2**) and (**3**) with activity of less than 1 µg/ml MIC. These compounds are approximately 100 times more active compared to their all amide analogues such as (**4**). This raised the question of whether the alkene's position is important, or whether the simply increased lipophilicity is responsible for the increased activity. To investigate this, a series of MGBs containing internal alkene linkages such as (**5**) or combinations of both internal and terminal alkene linkages such as (**6**) were prepared using newly developed synthetic methodologies. Further antibacterial testing, T<sub>m</sub> measurements, NMR studies and molecular modelling, have suggested that specific hydrogen bonding is essential both for binding to DNA and antibacterial activity (*Org. Biomol. Chem.* 2009, DOI: 10.1039/b901898k).



## PO – 52- A

### Synthesis of 5-membered heterocycles by SmI<sub>2</sub>-promoted intramolecular coupling reaction of alkynes with $\alpha,\beta$ -unsaturated ester

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An intramolecular carbon-carbon bond forming reaction of  $\alpha,\beta$ -unsaturated carbonyl compounds having an alkene or alkyne function in the same molecules would be one of the most useful synthetic methods for constructing carbocyclic and/or heterocyclic compounds. For this purpose, a radical cyclization have usually been employed by using the reagents; such as 1) tributyltin hydride and AIBN, 2) nickel dicyclooctadiene, 3) rhodium complex, 5) palladium complex etc.

However, the exploitation of samarium diiodide for an intramolecular coupling of  $\alpha,\beta$ -unsaturated carbonyl compounds with alkenes or alkynes has not been reported to date, to the best of our knowledge. Thus, we investigated a samarium diiodide-promoted intramolecular coupling of alkynes with  $\alpha,\beta$ -unsaturated esters to form pyrrolidine and tetrahydrofuran derivatives. The reaction of ethyl (2*E*)-{(3-bromoprop-2-yn-1-yl) [(4-methylphenyl)sulfonyl]amino}but-2-enoate with 2.0 equivalents of samarium diiodide in THF-HMPA gave the cyclization product in good yield. Similar reaction of oxygen analogue also provided the tetrahydrofuran derivative in moderate yield. Further application of this strategy to the synthesis of other types of heterocyclic compounds will also be discussed.

## PO – 52 – B

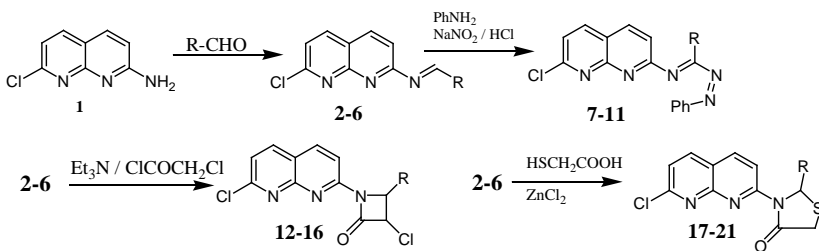
### Synthesis of 3-chloro-1-(2-chloro-1,8-naphthyridin-7-yl)-4-arylazetidion-2-ones and 3-(2-chloro-1,8-naphthyridin-7-yl)-2-arythiazolidin-4-ones as antimicrobial agents.

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Literature survey showed that 4-thiazolidinones and azetidionones are associated with a wide range of biological properties. Various 1,8-naphthyridines are reported to be potential antibacterial, antimalarial and diuretic agents. Hence it is thought interesting to undertake the synthesis of 1,8-naphthyridines having thiazolidinone and azetidionone moieties as substituent. 2-Amino-7-chloro-1,8-naphthyridine (1) undergoes condensation with different aromatic aldehydes to form 2-aryledineamino-7-chloro-1,8-naphthyridines(2-6). These imines when treated with aniline and sodium nitrite yields formazans (7-11). Azetidionones (12-16) are obtained by the reaction of imines with chloroacetylchloride. These imines are converted to thiazolidinones (17-21) by treating them with thioglycolic acid.



## **PO – 52 – C**

**Formal synthesis of (-)-haouamine A using a tandem Prins/Friedel-Crafts sequence.**

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A formal synthesis of (-)-Haouamine A has been achieved originating from the amino acid chiral pool. The synthesis features the construction of an atypical L-m-tyrosine derivative from L-serine using a Negishi cross-coupling procedure. The indeno-tetrahydropyridine ring system was assembled using a tandem Prins cyclization coupled with a Friedel-Crafts alkylation. The feasibility of this methodology was explored in the preparation of a variety of tricycles.

## PO – 52 – D

### New syntheses of antiparasitic compounds and their biological activity

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Diversity oriented syntheses of some furo[2,3-*d*]pyrimidines (**1**) and pyrrolo[2,3-*d*]pyrimidines (**2-4**) related to folate, guanine, and diaminopyrimidine-containing drugs have been developed for the preparation of potential anti-infective and anticancer compounds. Amide couplings and Suzuki couplings on the basic heterocyclic templates were used, in the latter case yields being especially high using aromatic trifluoroborates as the coupling partner leading for example to (**2**). A new ring synthesis of 6-aryl-substituted deazaguanines bearing 2-alkylthio groups has been developed using Michael addition of substituted nitrostyrenes (for **3** and **4**). Diversity at C-2 has been introduced by oxidation and substitution with a range of amino nucleophiles leading to compounds such as (**3**). This has been a difficult transformation before this study and the chemical reactivity of these pyrrolopyrimidines with respect to both electrophilic substitution in ring synthesis and nucleophilic substitution for diversity will be discussed. Several compounds were found to inhibit pteridine reductases from the protozoan parasites *Trypanosoma brucei* and *Leishmania major* at the micromolar level and to inhibit the growth of *Trypanosoma brucei brucei* in cell culture at higher concentrations (*Org. Biomol. Chem.* 2009, DOI: 10.1039/b818339b). From these results, significant structural features required for inhibition of this important drug target enzyme have been identified and correlated with X-ray crystallographic studies of the binding of several compounds to pteridine reductase 1 of *T. brucei*. The structural features necessary include specific hydrogen bonds and hydrophobic interactions. Evidence that pteridine reductases are significant targets for drug discovery has accrued from the fact that the antitrypanosomal activity of some pyrrolopyrimidines prepared is synergised by methotrexate.

## OL – 45 – A

Synthesis and antimicrobial activity of 2-cyclopropyl-[1,8]-naphthyridine-3- carboxylic acid - (4-phenyl-2-thioxo-thiazol-3-yl)-amides, [1,3,5]-triazine, [1,3,4]-thiadiazole-2-thiol, [1,2,4]-triazole-3-thiol and coumarin derivatives.

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2-Cyclopropyl-[1,8] naphthyridine-3-carboxylic acid ethyl ester (**1**) reacts with 99% hydrazine hydrate, to yield 2-cyclopropyl-[1,8]-naphthyridine-3-carboxylic acid hydrazide (**2**), further which reacts with carbon disulphide in presence of potassium hydroxide to yield (**3**). Compound **3** on reaction with 99% hydrazine hydrate yields 4-amino-5-(2-cyclopropyl-[1,8]-naphthyridin-3-yl)-4H-[1,2,4]-triazole-3-thiol(**4**). This reacts with phenacyl bromide to give rise to 4-Amino-5-(2-cyclopropyl-[1,8]-naphthyridin-3-yl)-4H-[1,2,4]triazole-3-thiol(**5**). On other hand compound (**4**) on treatment with oxalyl chloride in presence of triethylamine provides coumarin derivative (**6**). Compound (**3**) on treatment with acetic acid affords 5-(2-cyclopropyl-[1,8]-naphthyridin-3-yl)-[1,3,4]-thiadiazole-2-thiol (**7**). Compound (**3**) reacts with phenacyl bromide in resulting 2-cyclopropyl-[1,8]-naphthyridine-3-carboxylic acid (4-phenyl-2-thioxo-thiazol-3-yl)-amide(**8**). Compound (**1**) reacts with guanidine hydrochloride to yields (**9**) which reacts with aromatic nitriles to afford (**10**).

