Karl Hansen Weekly Report 7 Jan 2002

### L-859,016

Material produced in the prep lab was front run. Due to the termination of the project, only one 2 kg batch will be processed and responsibility for coupling will be transferred to M. Kubryk.

### L-224,715

In order to support the delivery timeline, readily available starting materials needed to be identified. An analog of carboxylic acid **2** has been used to make the structurally similar L-822,869. This material is not readily available, however 500 g have been ordered by the medicinal scale-up group. Steps were taken to find this material and also purchase an additional 115g from the same lot from the supplier. This material will support the first 200g delivery of 715.

For the second delivery, the most readily available starting point is arylbromide **3**. 25kg of this compound were purchased at 130%/kg from interchem for a delivery in 3weeks. An additional 1kg was purchased from aldrich at ~2000%kg to support research for the next three weeks.



#### Salt Form:

Salt studies have been performed by V. Vydra in Automation. The study has identified the phosphate, tartrate, sulfate and benzensulfonate as providing crystalline solids by powder diffraction. The bezylate and tartrate will probably be pursued first.

### Coupling:

Initial experiments show the coupling of boc amino acid intermediate 4 to triazolopyrazine 5 to proceed in the absence of HOBT with isolation without chromatography.



**70130-309** 100mg of **4** was mixed with 1.0 equiv of **5** and 1.2 equiv. of EDC in 20ml/g DMF. After 18h 75% conversion was observed to a later eluting peak. 1.0 equiv. of  $Cs_2CO_3$  was charged, but no further conversion was observed. An additional 0.3 equiv of EDC was charged and 95% of **4** was observed after 2h. The material was isolated by diluting with 10% NaCl (roughly 30ml/g). Solids present in the reaction mixture dissolved then new crystals formed. These were isolated at RT and washed with 10% NaCl and water. 84 mg (55%) of white solids were isolated. <sup>1</sup>H-NMR was difficult to interpret due to Boc group,

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but LCMS of the isolated solids gave m/z = 451 (M-tBu+1) for the major peak. Sample given to Dormer for confirmation. ML's contained product in comparable LCAP to unreacted starting material. Several impurities are present in both the MLs and product in the 1-5% range. One elutes very closely to the product with m/z = 530.

**70130-311** Coupling was performed as above with EDC and HOBT. Reaction stopped at 80% conversion and required a second charge of EDC. Solids were isolated as above (90% physical yield), but two major impurities were present one eluting early (3.4 min) and one at 14 min. LCMS is being performed to confirm identity. These impurities are the majority of the LCAP for this sample.

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L-859,016

2 kg of pyrrazolotriazine was coupled by M. Kubryk in prep lab. Material will be analyzed and then bagged next week.

L-224,715

**Raw materials:** 

615g of the trifluorophenyl acetic acid have been received.

Salt Form:

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### Besylate salt evaluated by Phys. Meas. Tartrate may have been prepares

**70130-321** Solutions of **715** and benzensulfonic acid in DCM were combined in 1:1 stoichiometry in 3 vials giving ~35mg of salt in each. The DCM was removed in vacuo to give a white solidthat was amorphous under the microscope. The solids were then suspended in the crystallization solvents toluene, IPA and IPAC. The IPAC and toluene did not dissolve completely in 2ml while the IPA required 2 volumes of Hexanes to afford solids. These were heated at 80C for 0.5h and then cooled to RT only IPA expt. dissolved completely. Of the three expts only the IPAC was judged to have crystals. These were isolated and then given to Physical Measurements along with a sample of besylate salt prepared by M. Palucki (72061-046). Both of these samples had identical HPLC traces, supporting a 1:1 salt formation. Physical measurements indicated that btoh samples had a MP of 179°C, identical x-ray powder patterns and no appreciable loss oin the tg. Yield was 27mg (77%) for the IPAC conditions.

**70130-323** Dissolved 92mg of L224,715 in 4ml of IPA containing 1 equiv of  $H_3PO_4$ . Solids forme immediately and did not dissolve upon reheating. Removed IPA and was able to get solids to redissolve in MeOH. Held onto solution.

**70130-325** Attempted to make HBr salt of 715 as above. Only oily precitpitates formed in a variety of solvents.

**70130-327** Dissolved 50mg of 715 in 2ml of IPA. Added 1 equiv of (L)-tartaric acid dissolved in 0.2ml IPA. Solution was clear but after 10 minutes crystals began to form. The slurry was heated at 77°C for 30min but solids did not dissolve completely and appeared microcrystalline under scope before and after age. DSC gave an exothermic peak at 207°C.

**70130-329** Repeated above expt with ethanol. Crystals formed quickly at RT in 2.2 ml of solvent. Diluted with 4ml of EtOH and achieved a clear soln at 75°C. Temp was slowly lowered to RT and xtals formed at 40°C. Crystals looked much larger under scope. They were isolated at RT with an ethanol wash. <sup>1</sup>H-NMR shows definite presence of 715 with shifting of peaks realtive to free base, although the tartrate peaks were buried. 58% recovery. Solids given to phys meas. For evaluation.

**70130-331** Attempted to form crystals as above in 2.2ml of MeOH-did not ppt even at 0C. Added 2ml of IPA and solids formed. Heated to clear soln and then cooled-gacve xtals similar to ethanol expt.

**70130-333** Performed crystallization in 1.2ml of MeOH (40mg scale, 25ml/g) Clear soln was aged over weekend and gave good size crystals. These were isolated and will be analyzed and compared to **329**.

Coupling:



**70130-315** Scale-up to 500mg of the coupling (70130-313) gave 100% conv to the desired product however, two earlier eluting impurities are isolated with desired product. Samples of the ML's and product have been given to analytical for identification

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L-859,016

2 kg of L859,016 was prepared in the prep lab. This material was 99.9% pure with one impurity at 0.06%. Material will be sent to chem data on an a-sheet unmilled

### L224,715:

**Balsells:** Racemic material has been brought through the beta-lactam intermediate. Noyori reduction of keto ester gave 89% ee material. This was brought through to beta lactam and then upgraded to 99% ee in one crystallization.



**Salt Form:** Two salts (besylate and tartrate)have been scaled up and given to PR&D and Phy. Meas. Tartrate appears to form a hemi-hydrate while besylate forms a hemihydrate, only under very humid conditions. HCl salt appears to be crystalline as well

### Besylate salt

**70130-337, 339** Benzenesulfonic acid (0.2ml, 79mg/ml soln in IPAC, 1 equiv.) was added to solution of 715 in IPAC (50ml/g). Solids did not form until the solution was heated at 55°C. ML's were assayed to contain 1mg/g of 715. Cooled to RT, filtered, washed with IPA. Dried at 40°C in vac oven w/ N2 sweep. 85% isolated yield. Same form as previous samples. Solubility of Besylate salt is ~1.2 mg/g at RT by LC.

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# DOCKET



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