

## AFRICA Application Note

Note Number : 11

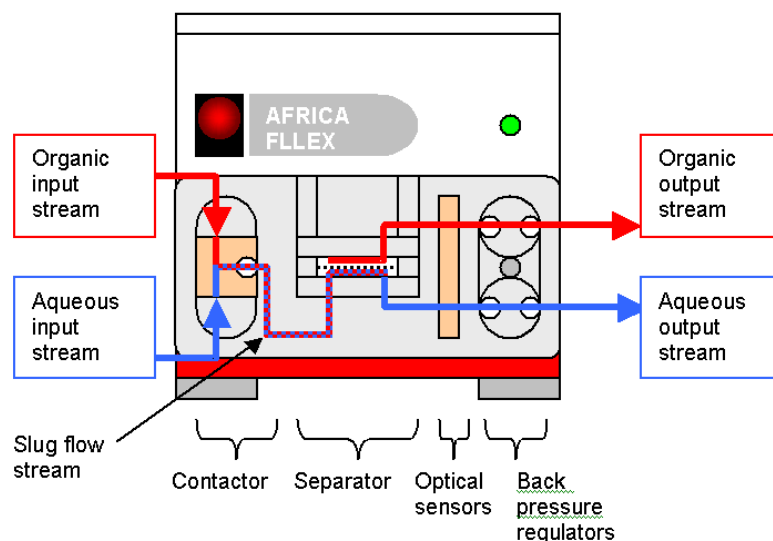
### Flow aqueous work-up using FLLEX

#### 1 Summary

This application note demonstrates the use of the AFRICA FLLEX (Flow Liquid Liquid EXtraction) module for performing post reaction automated liquid-liquid extraction in a standard AFRICA flow system. An amide coupling reaction was performed in the AFRICA system and worked up by extraction with aqueous bicarbonate to remove by-products. The quality of extraction and separation was the same batch.

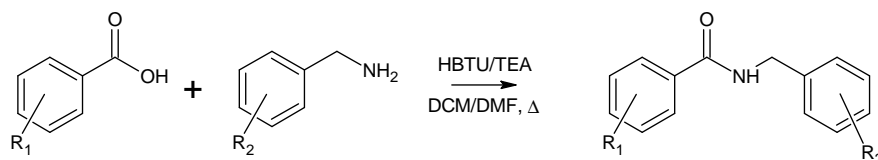
#### 2 FLLEX module

The FLLEX module is a continuous flow contacting and separating system based on a small PTFE membrane separator. By accurately controlling the cross membrane pressure, the organic phase can be forced through the membrane whilst the aqueous phase is retained. An optical sensing system monitors the purity of both output flow streams and can optimise separation conditions. The FLLEX internal volume is 100 microlitres and total flow rates of 0.5mls/min and above are possible.



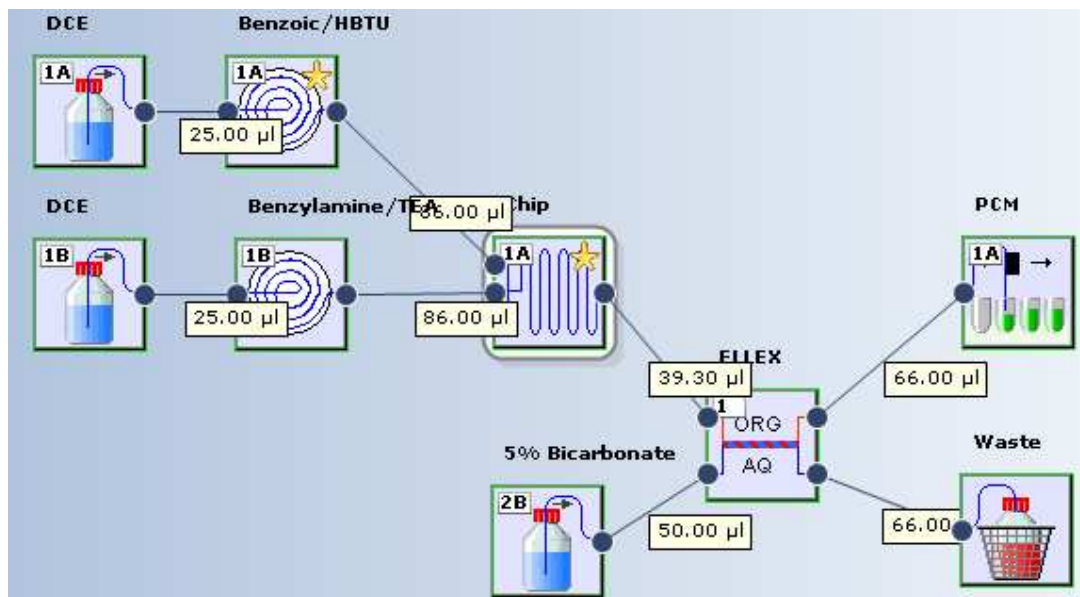
## 3 Reaction

The reaction chosen was a standard amide coupling using HBTU. This had previously been optimised in flow to give quantitative yield. The optimised conditions are 1 equivalent of aryl acid and 1.1 equivalents each of aryl amine, HBTU and triethylamine at 50°C in 20% dimethylformamide<sup>1</sup> in dichloromethane. The reaction was performed in an AFRICA flow reactor chip with a residence time of 10mins.



After the organic reaction mixture exited the reactor it was extracted in the FLLEX with an equal volume of 5% aqueous sodium bicarbonate and the organic phase collected before analysis by HPLC.

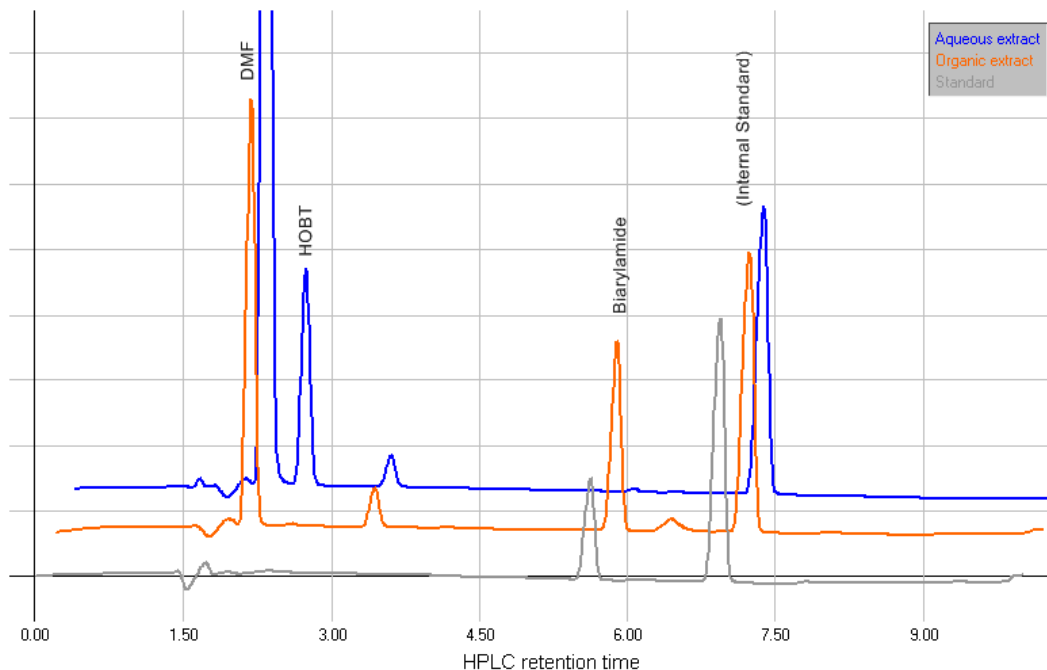
The fluidics layout used in the Reaction Manager software, which controls both the standard AFRICA modules and the FLLEX, is shown below.



<sup>1</sup> To solubilise the HBTU.

## 4 Results

Reverse phase HPLC of the collected product fractions (below) shows much of the DMF and all the HOBT by-product has been extracted into the aqueous phase whilst a negligible quantity of the biaryl amide has been lost.



Quantitative analysis of the AFRICA flow reactions and an analogous batch reaction with batch extraction work-up gave the following results.

Reaction	Organic phase yield	Aqueous phase yield	Total yield
Batch	98.7%	2.4%	101.1%
Flow #1	98.5%	3.2%	101.7%
Flow #2	104.0%	1.8%	105.8%

## 5 Conclusion

The FLLEX extraction system provides a extraction performance equivalent to a normal batch extraction that can be used either as a final work-up stage or between reaction stages in a normal AFRICA system.