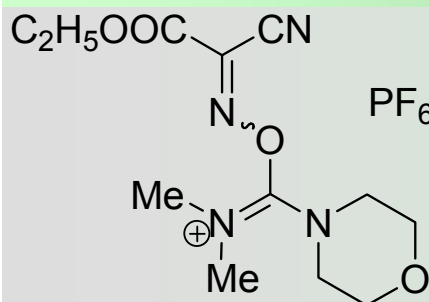


## COMU ....The Ultimate Coupling Reagent !

*The best ever - superior to HBTU, TBTU, TOTU, HCTU, TCTU and other known coupling reagents - A safe, efficient and better alternative to HATU!*



Luxembourg Biotechnologies Ltd. and its associates are proud to present the new generation of coupling reagents designed in response to growing safety concerns with currently available industrial scale coupling reagents.

**(COMU)**

**1-[(1-(Cyano-2-ethoxy-2-oxoethylideneaminoxy)-dimethylamino-morpholino)]uronium hexafluorophosphate (Patent pending). (1)**

### INTRODUCTION

Peptide production in either solid or liquid phase technologies consume vast amounts of coupling reagents.

Some are allergenic, some are suspected as flammable, some possess an explosive nature (facts which influence both transportation and use).

Luxembourg Biotechnologies Ltd. sought for "the ultimate product", one which would serve in most peptide production modes while having favourable "cost-effectiveness", being applicable for industrial use, and exposing coupling reagent users with minimal negative side effects.

In the light of the above, and in close collaboration with the research groups of **Professor Fernando Albericio** (Barcelona, Spain (2)) and **Professor.**

**Ayman El-Faham** (Alexandria, Egypt), Luxembourg Biotechnologies Ltd. (Rehovot, Israel) has been continuously promoting and supporting the development of new reagents, aimed at eliminating the problems described above. Differential thermal analysis and ARC studies recently carried out, have shown that the new class of reagents, including **COMU**, are not explosive under normal operating conditions and, importantly, allergic reactions such as contact dermatitis or asthma are drastically reduced or eliminated.

Apart from the obvious health and production benefits associated with the new reagents, their chemical benefits are most impressive, exceeding expectations.

The introduction of a proton accepting moiety (the morpholino group) into the structure of **COMU** allows the use of one equivalent of base during the coupling protocol, thus contributing to reduction of racemization in the growing peptide chain without impairing the reaction rate or the overall yield of the coupling process.

Even in the presence of one equivalent of base, reaction times and overall yields are superior or at least equal to HATU including "difficult" couplings, as shown in the following tables:

**Table 1: Extent of coupling of Fmoc-Val-Val-NH<sub>2</sub> in DMF solution using different equivalents of base (3)**

Time (min.)	HATU (yield %)		COMU (yield %)	
	2 eq. base	1 eq. base	2 eq. base	1 eq. base
5	83%	70.0	95.1	82.0
10	87.6	76.0	96.0	86.0
20	90.5	80.0	98.0	90.1
30	92.5	82.0	98.5	94.5
60	93.0	82.0	100.0	96.0
120	94.0	83.0	100.0	98.0

**Table 3: Racemization tests with various coupling reagents (3) and bases in DMF solvent**

Coupling Reagent	Base (Equivalents)	Yield (%)	DL (%)
HBTU	DIEA (2)	80.2	8.2
	TMP (2)	81.2	6.4
	DIEA (1)	75.0	5.3
HATU	DIEA (2)	78.4	3.1
	TMP (2)	77.9	2.1
	DIEA (1)	74.8	2.4
COMU	DIEA (2)	88.2	0.12
	TMP (2)	91.0	0.90

### ADVANTAGES OF THE COMU

- Applicable in solid and solution phase synthesis
- Better, faster coupling in high yields.
- Drastically reducing extent of racemization
- Higher solubility in most usual solvents (higher DMF and NMP solubility: more concentrated solutions thus better volumetric yields, less solvent waste).

**Table 2: Extent of coupling of Z-Aib-Val-OMe using different coupling agents, equivalents of base in DMF as solvent .**

Time (min.)	HBTU (Yield%)	HATU (Yield%)	COMU (Yield %)	
	2 eq. base	2 eq. base	2 eq. base	1 eq. base
2	70.0	80.0	89.0	85.0
5	76.0	85.0	92.0	89.0
10	78.0	87.0	93.0	90.0
20	80.0	89.0	95.0	91.0
30	81.0	90.0	97.0	93.0
60	83.0	91.0	98.0	96.0
120	83.0	92.0	99.0	97.0

**Table 4: Solid-Phase Synthesis of Pentapeptide (Tyr-Aib-Aib-Phe-Leu-NH<sub>2</sub>) vs Tetrapeptide (Tyr-Aib-Phe-Leu-NH<sub>2</sub>, des-Aib (4-mer)) (4)**

Coupling Reagent	Base (equiv.)	Penta (%)	Tetra, Des-Aib (%)
HATU	DIEA (2)	83	17
HBTU	DIEA (2)	47	53
COMU	DIEA (2)	> 99	< 1

- Does not contain hydroxybenzotriazoles. Preliminary DSC studies indicate low to non-existent explosivity.
- Low allergenic potential (if any)
- Colour changes during coupling allows visual or colorimetric reaction monitoring
- Easily removed by-products

For more information, trial samples, protocols and quotes for large quantities then please contact:

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#### Notes and References:

- Patent Application 2008. This compound and derivatives are proprietary products of Luxembourg Biotechnologies Ltd.
- Poster in 30th European Peptide Symposium, September 2008, Helsinki, A Non-Explosive Replacement for Benzotriazole Based Coupling Reagents, A. El-Faham, R. Subiros-Funosas, F. Albericio.
- A. El-Faham, F. Albericio. Morpholine-Based Immonium and Halogenoamidinium Salts as Coupling Reagents in Peptide Synthesis. *J. Org. Chem.*, 73, 2731-2737 (2008).
- a) A. El-Faham, R. Subiros-Funosas, F. Albericio, in press; and  
b) R. Subiros-Funosas, A. El-Faham, F. Albericio, in press.