Novel Prosthetic Groups for the Radioiodination, Astatination of Biomolecules *via* Disulphide Rebridging

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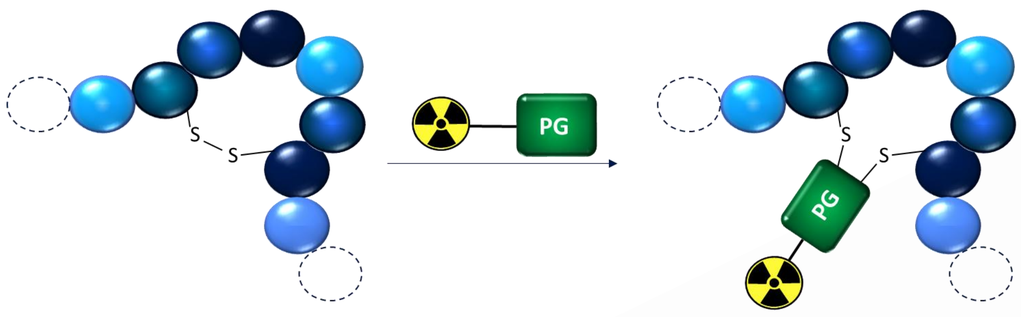
Novel prosthetic groups for radioiodine-131 and astatine-211 labelling were developed to enable biomolecule modification *via* disulphide rebridging. Boronic ester and stannylated precursors were synthesized and evaluated using various labelling strategies. Under Cu-catalyzed conditions, boronic esters afforded high radiochemical yields (87–95%, ^{131}I; 71–85%, ^{211}At). Electrophilic astatination of stannylated precursors using NCS/NIS provided high radiochemical yields (72–85%, ^{131}I; 90–95%, ^{211}At). The optimized precursors offer simple and efficient routes for ^{131}I and ^{211}At labelling and will be applied to octreotide modification through disulphide rebridging.

❖ Labelling of biomolecules *via* disulphide rebridging



- **Site-specific conjugation**
- **Preservation of protein structure**
- **Enhanced stability of the linkage**
- **Compatibility with sensitive biomolecules**

Richard, M. & Kuhnast, B. *Nucl. Med. Biol.* **S4,** 96–97, (2021) Richard, M. & Kuhnast, B.. *EJNMMI*. **47, S1,** S479-S479, (2021)

❖ Radioiodination of prosthetic groups

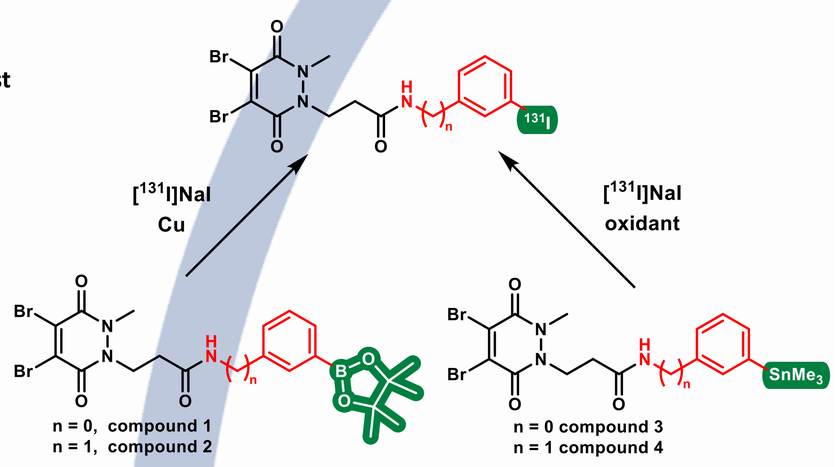
A Reaction with $Cu(py)_4(OTf)_2$ catalyst
$[^{131}I]NaI$, MeOH:MeCN (4:1), RT

B Reaction with $Cu(OCOCF_3)_2$ catalyst
$[^{131}I]NaI$, 1,10-phenantroline, MeOH:H_2O (4:1), 80° C

C Reaction with Cu_2O catalyst
$[^{131}I]NaI$,, 1,10-phenantroline, MeCN, RT

D $[^{131}I]NaI$ with *N*-chlorosuccinimide (NCS), MeCN, AcOH, RT, 20 min

E $[^{131}I]NaI$ with chloramine-T (CAT), MeCN, AcOH, RT, 20 min



Wilston *et al*. Chem. Commun. 2016, 52 (90), 13277. Reilly *et al*. Org. Lett. 2018, 20 (7), 1752. Zhang *et al.* Eur. J. 2016, 22 (47), 16783.

Table 1. Comparison of the labelling results obtained under different reaction conditions. Conditions providing the best results for copper-mediated radioiodination of compounds 1 and 2 are marked in green, and the best conditions for electrophilic radioiodination of compounds 3 and 4 are marked in blue.

Conditions	Precursors	Additives	TLC RCY (%)	HPLC RCY (%)	n
A	1	$Cu(py)_4(OTf)_2$	89 ± 2	95 ± 5	3
A	2	$Cu(py)_4(OTf)_2$	87 ± 2	95 ± 5	3
B	1	$Cu(OCOCF_3)_2$	70 ± 12	80 ± 17	3
B	2	$Cu(OCOCF_3)_2$	58 ± 28	87 ± 3	3
C	1	Cu_2O	-	-	1
C	2	Cu_2O	-	-	1
D	3	NCS	75 ± 20	85 ± 11	3
D	4	NCS	72 ± 15	80 ± 6	3
E	3	CAT	29	26	1
E	4	CAT	37	46	1

❖ Astatination of prosthetic groups

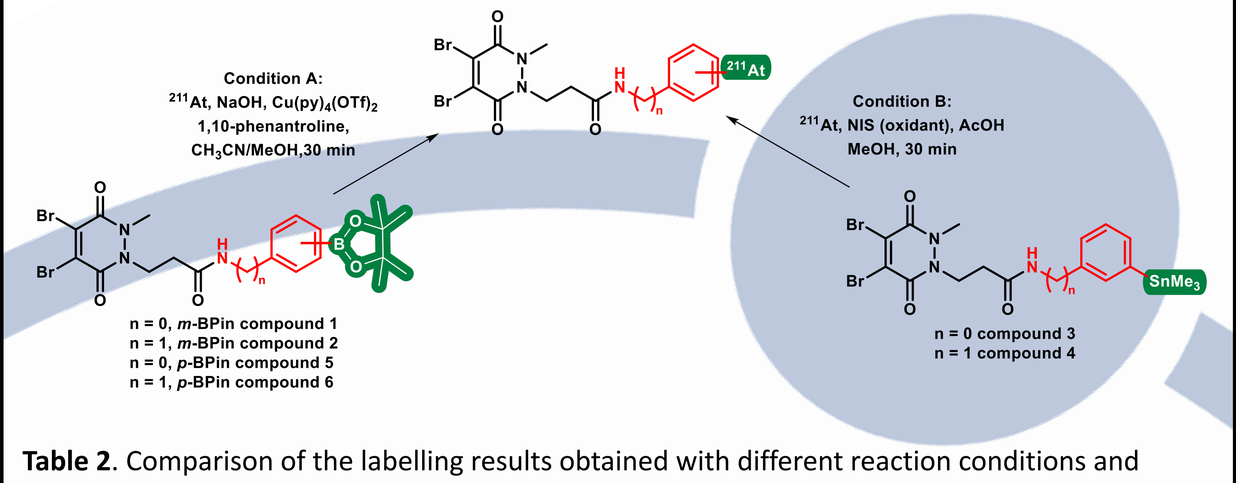
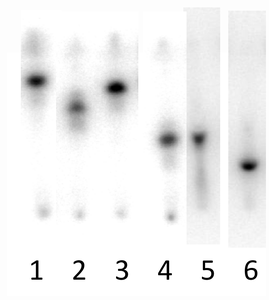
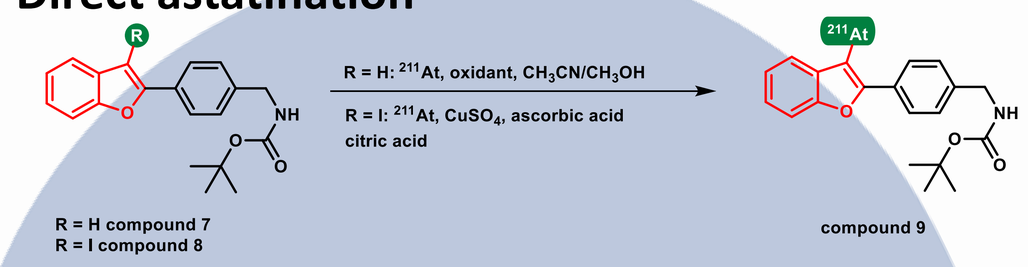


Table 2. Comparison of the labelling results obtained with different reaction conditions and radio-TLC of reaction mixtures with correponding precursors.

Conditions	Precursors	TLC RCY (%)	HPLC RCY (%)
A	1	71	75
A	2	87	82
A	5	82	85
A	6	78	73
B	3	94	92
B	4	95	90



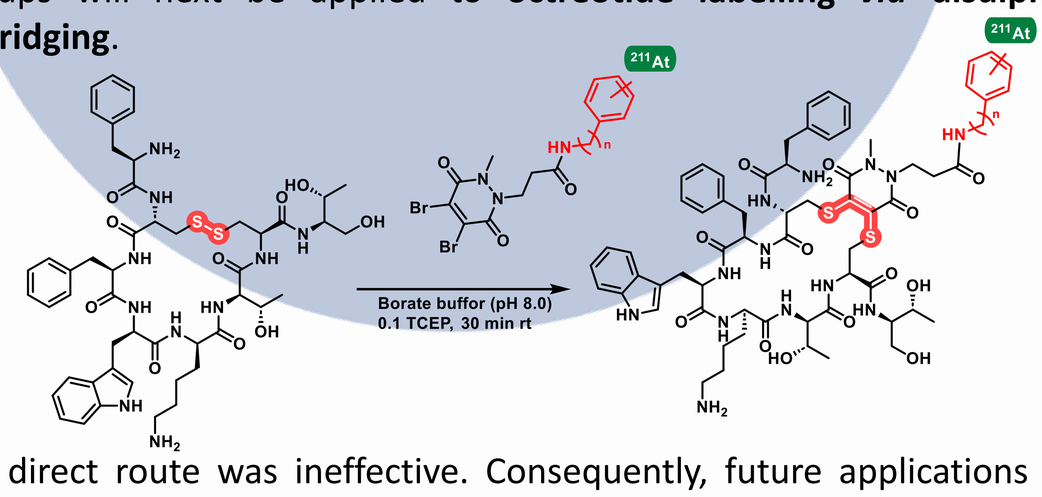
❖ Direct astatination



Direct astatination of the compound 7 showed only slight conversion with hydrogen peroxide and with different oxidants such as: NCS, NIS, Iodogen were unsuccessful and in Cu-catalyzed halogen exchange at high temperature.

❖ Conclusion and Future plans

Efficient radioiodination (^{131}I) and ^{211}At-labelling was achieved using boronic ester and stannylated intermediates. The optimized prosthetic groups will next be applied to **octreotide labelling *via* disulphide rebridging**.



The direct route was ineffective. Consequently, future applications will involve the preparation of compounds containing a boronic ester or another appropriate leaving group.

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