Improved production of ^{76}Br, ^{77}Br and ^{80m}Br via CoSe cyclotron targets and vertical dry distillation

Paul A Ellison[1*], Aeli P Olson[1], Todd E Barnhart[1], Sabrina LV Hoffman[1], Sean W Reilly[2], Mehran Makvandi[2], Jennifer L Bartels[3], Dhanabalan Murali[1], Onofre T DeJesus[1], Suzanne E Lapi[3], Bryan Bednarz[1,4], Robert J Nickles[1], Robert H Mach[2], and Jonathan W Engle[1,5]

[1]Department of Medical Physics, [4]Department of Engineering Physics, and [5]Department of Radiology, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA

[2]Department of Radiology, Division of Nuclear Medicine and Molecular Imaging, University of Pennsylvania, Perelman School of Medicine, Philadelphia, PA, USA

[3]Department of Radiology, University of Alabama at Birmingham, Birmingham, AL, USA

**Corresponding and first author information*

Paul Ellison

B1152 WIMR

1111 Highland Ave

Madison, WI 53705

Telephone: (608)-262-4396

Fax: (608)-262-2413

paellison@wisc.edu

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Abstract

Introduction: The radioisotopes of bromine are uniquely suitable radiolabels for small molecule theranostic radiopharmaceuticals but are of limited availability due to production challenges. Significantly improved methods were developed for the production and radiochemical isolation of clinical quality ^{76}Br, ^{77}Br, and ^{80m}Br. The radiochemical quality of the radiobromine produced using these methods was tested through the synthesis of a novel ^{77}Br-labeled inhibitor of poly (ADP-ribose) polymerase-1 (PARP-1), a DNA damage response protein. **Methods:** ^{76}Br, ^{77}Br, and ^{80m}Br were produced in high radionuclidic purity via the proton irradiation of novel isotopically-enriched Co^{76}Se, Co^{77}Se, and Co^{80}Se intermetallic targets, respectively. Radiobromine was isolated through thermal chromatographic distillation in a vertical furnace assembly. The ^{77}Br-labeled PARP inhibitor was synthesized via copper-mediated aryl boronic ester radiobromination. **Results:** Cyclotron production yields were 103 ± 10 MBq·μA^{-1}·h^{-1} for ^{76}Br, 88 ± 10 MBq·μA^{-1}·h^{-1} for ^{80m}Br at 16 MeV and 17 ± 1 MBq·μA^{-1}·h^{-1} for ^{77}Br at 13 MeV. Radiobromide isolation yields were 76 ± 11% in a small volume of aqueous solution. The synthesized ^{77}Br-labeled PARP-1 inhibitor had a measured apparent molar activity up to 700 GBq/μmol at end of synthesis. **Conclusions:** A novel selenium alloy target enabled clinical-scale production of ^{76}Br, ^{77}Br, and ^{80m}Br with high apparent molar activities, which was used to for the production of a new ^{77}Br-labeled inhibitor of PARP-1. **Advances in Knowledge:** New methods for the cyclotron production and isolation of radiobromine improved the production capacity of ^{77}Br by a factor of three and ^{76}Br by a factor of six compared with previous methods. **Implications for Patient Care:** Preclinical translational research of ^{77}Br-based Auger electron radiotherapeutics, such as those targeting PARP-1, will require the production of GBq-scale ^{77}Br, which necessitates next-generation, high-yielding, isotopically-enriched cyclotron targets, such as the novel intermetallic Co^{77}Se.

Key Words: bromine-77, bromine-76, bromine-80m, Auger radionuclide therapy, positron emission tomography, PARP-1 inhibitor

INTRODUCTION

The radioisotopes of bromine with medical relevance include the diagnostic positron-emitter ^{76}Br ($t_{1/2}$ = 16.2 h) and therapeutic Auger-emitters ^{77}Br ($t_{1/2}$ = 57.0 h) and ^{80m}Br ($t_{1/2}$ = 4.42 h). Radiobromine is organochemically versatile, participating in labeling reactions including oxidative electrophilic radiobrominations using alkyl tin precursors [*1*] and nucleophilic aromatic radiobrominations using diaryliodonium salt [*2*] and aryl boron [*3*] precursors. Many radiobrominated compounds have been investigated, including thymidine analogues bromodeoxyuridine ([^{77}Br]BrUdR) [*4*] and fluoro-bromo-arabanofurosyl-uracil ([^{76}Br]FBAU) [*5*], steroid receptor ligand methoxybromoestradiol ([^{77}Br]MBE) [*6*], peptides [*7*] and proteins [*8*]. Additionally, radiobromine has an advantage over the radioisotopes of iodine in that the C–Br bond is more stable than C–I bond resulting in less dehalogenation of radiolabeled compounds *in vivo.* Rather than accumulate in the thyroid like iodide, radiobromide ions liberated due to *in vivo* dehalogenation remain distributed primarily in the blood pool, with an excretion rate of ~10 days in humans [*9*], resulting in a more diffuse dosimetric burden. These properties make bromine radioisotopes uniquely suited for incorporation into small molecule theranostic agents.

Small biomedical cyclotrons produce the medical radioisotopes of bromine via the ^{77}Se(p,n)^{77}Br, ^{76}Se(p,n)^{76}Br, and ^{80}Se(p,n)^{80m}Br nuclear reactions. However, selenium's low electrical and thermal conductivity, boiling point, and high vapor pressure significantly limit its tolerance to irradiation, even with modest proton intensities. The cyclotron irradiation of binary intermetallic compounds of transition metals and selenium was pioneered in Groningen [*10*] using Cu_2Se. The use of Cu_2Se was later adapted for use with isotopically enriched $Cu_2{}^{76}Se$ [*11,12*] and $Cu_2{}^{77}Se$ [*12*] for the production of radionuclidically pure ^{76}Br and ^{77}Br, respectively. More recently, investigations of the intermetallic compounds NiSe [*13,14*] and ZnSe [*15*] are reported, but only with selenium of natural isotopic composition. Despite this progress, ^{76}Br production capacity remains limited to ~2 GBq and ^{77}Br to ~0.7 GBq per three hour irradiation, dramatically less than the amounts needed for clinical studies. This low ^{76,77}Br yield is primarily due to the thermal limitations of the selenium target resulting in a maximum proton irradiation intensity of 15 – 20 μA [*11,12*], a fraction of modern medical cyclotrons' >100 μA capabilities. Cu_2Se and NiSe cyclotron

targets are also problematic because of co-production of large quantities of gamma-emitting ^{63}Zn ($t_{1/2}$ = 38.1 m) and ^{60}Cu ($t_{1/2}$ = 23.7 m), respectively. The proton activation of naturally monoisotopic cobalt is dosimetrically advantageous, producing small amounts of low radiation dose-emitting ^{59}Ni ($t_{1/2}$ = 76,000 y) and ^{58g}Co ($t_{1/2}$ = 70.9 d). This work aims to mitigate the thermal and dosimetric limitations of radiobromine production targets through the use of a previously unexplored intermetallic, cobalt selenide (CoSe).

Selenium intermetallics release radiobromine when heated, enabling radiobromine recovery via thermal chromatographic distillation and avoiding time consuming target dissolution and recycling of costly enriched materials. So-called "dry distillation" isolates ^{124}I [*16,17*] and ^{211}At [*18-21*] from tellurium and bismuth targets, respectively, with horizontal distillation assemblies that cool slowly after distillation. A compact, easily-assembled vertical distillation assembly that cools rapidly, such as that used for isolating ^{94m}Tc [*22*], is reported here for the isolation of $^{77/76/80m}$Br.

Radiolabeled inhibitors of the DNA damage response protein, poly ADP ribose polymerase 1 (PARP-1) have been evaluated for non-invasive quantification of PARP-1 expression for patient stratification and treatment response monitoring of PARP inhibitor chemotherapy [*23,24*]. Additionally, the pharmacological mechanism of action brings PARP inhibitors in close proximity to cancer cell DNA [*25*], enabling targeted Auger-electron radiotherapy. Recent radiochemistry reports of ^{77}Br-labeled PARP inhibitors [*2,3*] demonstrate the field is moving in this direction. The radiochemical quality of the radiobromine produced in this work was evaluated by copper-mediated aryl boronic ester bromination, synthesizing a novel ^{77}Br-labeled derivative of the PARP-1 inhibitor, rucaparib.

MATERIALS AND METHODS

Materials

Cobalt powder (Alfa Aesar, 1.6 μm, 99.8%), natural enrichment selenium powder (Acros Organics, 200 mesh, 99.5%), and >99.6% isotopically enriched ^{76}Se, ^{77}Se, and ^{80}Se powders (Isoflex USA) of isotopic

abundance summarized in Table S1 were used for the synthesis of intermetallic CoSe. 1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-8,9-dihydro-2,7,9a-triazabenzo[cd]azulen-6(7H)-one (pre-KX1-Bpin) and 1-(4-iodophenyl)-8,9-dihydro-2,7,9a-triazabenzo[cd]azulen-6(7H)-one (KX-1) were synthesized as previously described [*26*]. Copper catalyst (tetrakis(pyridine)copper (II) triflate; $Cu(py)_4(OTf)_2$) and ligand (3,4,7,8-tetramethyl-1,10-phenanthroline; Lig) were obtained from Sigma Aldrich. Sep-Pak QMA Plus Light (Waters, QMA light) cartridges were prepared with 10 mL of 1 M $KHCO_3$ or 0.5 M Na_2SO_4 and 10 mL water, and Sep-Pak C18 Plus light (Waters, C18 light) cartridges were prepared with 5 mL ethanol and 10 mL water prior to use. All other chemicals were purchased from Sigma Aldrich and used as received.

Production of CoSe cyclotron targets

Cobalt selenide was formed from equal parts elemental cobalt and selenium by heating to 1200 °C in an evacuated quartz ampule. CoSe cyclotron targets were formed by hot pressing CoSe at ~1100 °C into a pocketed (⌀ = 9.5 mm, 1 mm deep) niobium disc (⌀ = 19 mm, 2 mm thick) using the vertical furnace assembly shown in Figure 1. Detailed descriptions of these metallurgical processes are given in the supplementary material. A prepared CoSe cyclotron target was analyzed by X-ray diffraction using a Bruker D8 Discovery X-ray Diffractometer with a Cu Kα X-ray source (1.54 Å, 2 mm cone diameter) and a Vantec-500 detector at 0.6 sample rotations per minute.

Cyclotron production of radiobromine

CoSe with ^{nat}Se, ^{80}Se, ^{76}Se, or ^{77}Se constituents on niobium backings was irradiated with 5 – 40 μA of 11 – 16 MeV protons on the University of Wisconsin GE PETtrace cyclotron. A water jet cooled the back of the niobium disc using an ARTMS QIS solid target system (Vancouver, Canada). Radiobromine production yields and radionuclidic purities were measured at four proton energies by employing a water-cooled degrader foil positioned 3.6 cm away from the face of the CoSe target. Molybdenum and tungsten foils (Alfa Aesar) degraded the 16 MeV primary beam to 13, 12, or 11 MeV proton energy with a 0.10 mm W

foil, a 0.20 mm Mo foil, or a 0.25 mm Mo foil, respectively, based on calculations performed with SRIM-2013.00 [*27*]. High purity germanium (HPGe) spectrometry quantified radioactivity in mixed radionuclide sources and dose calibrator measurements (Capintec CRC 15R, setting #690÷2 for ^{76}Br, #121 for ^{77}Br, and #170 for ^{80m}Br) quantified activity in fractions following radiochemical separation.

Radiochemical isolation of radiobromine

Radiobromine thermal chromatographic distillation from irradiated CoSe targets occurred in the same furnace assembly shown in Figure 1, as detailed in the supplementary material. Briefly, the irradiated CoSe was sealed in the assembly and lowered into a tube furnace preheated to 1050 °C. Multiple collimated radiation detectors monitored the progress of the distillation. Following 5 – 15 minutes of heating, the tube was removed from the furnace and quenched in water. After cooling and venting, warm water rinsed the outlet gas flow path into the H_2O trap. The water was passed through a prepared QMA light cartridge, trapping the radiobromide, followed by its elution with 700 µL of 20 mM K_2SO_4 or 0.1 M NH_4OH in 1:1::MeCN:H_2O. HPGe spectrometry and dose calibrator measurements assessed the radiochemical yield of the distillation process.

Radiosynthesis of ^{77}Br-labeled PARP inhibitor

The copper-mediated aryl boronic ester bromination reaction shown in Figure 2 evaluated the radiochemical quality of the [^{77}Br]bromide by using 1 µmol pre-KX1-Bpin with varying solvent volume and composition, K_2SO_4 concentration, and temperature. Reactions were purified by diluting in 15 mL water, loading on a prepared C18 light cartridge, rinsing with 10 mL water, and eluting crude product in 700 µL ethanol. Following a 1:1 dilution with water, preparative HPLC purified the product (Kinetix XB-C18, 5 µm, 100 Å, 10x250 mm, 4 mL/min 40:60 :: MeCN:0.1 M ammonium formate, pH 4.5). A final C18 light cartridge purification formulated the product in a small volume ethanol solution. Dose calibrator measurements of purified fractions determined the radiochemical conversion. Preparative HPLC injections of

100 – 500 pmol of stable, iodinated KX1 estimated the ^{77}Br-labeled PARP inhibitor (^{77}Br-PARPi) mass versus 254 nm absorbance calibration curve.

RESULTS

Production of CoSe cyclotron targets

Elemental cobalt and selenium powder readily fused into solid pieces (270 ± 20 mg) in 1 hour at 1200 °C inside a vacuum ampule. Typical mass losses to the ampule walls were 6 ± 4% (n=10). CoSe cyclotron targets contained 180 – 220 mg of CoSe in a 9.5 mm diameter pocket and exhibit the X-ray diffraction pattern shown in Figure S2.

Cyclotron production of radiobromine

Water-cooled CoSe cyclotron targets withstood proton irradiation at all investigated proton energies (11 – 16 MeV) and intensities (5 – 40 μA). The radiobromine production rate was consistent between 10 and 40 μA (Figure S3), indicating that CoSe targets retain radiobromine up to at least 640 W of power deposition (at 40 μA). Radiobromine yields [*28*] from CoSe targets are shown in Table 1 and Figure 3 with end of bombardment (EoB) radionuclidic purities in Table 2. ^{58g}Co was co-produced at 140 ± 50 kBq·μA^{-1}·h^{-1} at 16 MeV (n=4) and 20 ± 10 kBq·μA^{-1}·h^{-1} at 13 MeV (n=3).

Radiochemical isolation of radiobromine

Thermochromatographic distillation of radiobromine readily occurred within 5 – 10 minutes in a 1050 °C furnace. Typical traces from detectors collimated on the CoSe (Fig. 1, left) and H_2O trap (Fig. 1, right) are shown in Figure 4 with detailed explanation in the supplementary material. 96 ± 4% (n=8) of the QMA-loaded $^{76/77/80m}$Br was recovered in the K_2SO_4/NH_4OH eluant. Optimized yields of the combined dry distillation and radiobromide recovery process were 76 ± 11% (n=6). The CoSe cyclotron targets lost 0.9 ± 0.5% (n = 20) of their mass with each irradiation/distillation cycle.

Radiosynthesis of ^{77}Br-PARPi

The [^{77}Br]bromide QMA eluant was either used directly for radiolabeling or after drying under argon flow at 120 °C. Radiochemical conversions from 4.7 – 95% were observed for the reaction conditions, as summarized in Table S3, with conditions of reactions {1-4,6-12} adapted from Reilly *et al*. [*26*] and reaction {5} from Zhou *et al.* [*3*]. A single radiolabeled peak was eluted from preparative HPLC (see Figure S4), confirmed to be the desired ^{77}Br-PARPi through co-injection with stable iodinated analogue compound (KX1). Based on HPLC absorbance measurements of KX1, the synthesized ^{77}Br-PARPi had an estimated molar activity of up to 700 GBq/μmol (19 Ci/μmol) at the time of analysis.

DISCUSSION

The Co-Se binary phase diagram shows that there exists an intermetallic species with stoichiometric flexibility near $Co_{0.88}Se$ with a melting point of 1078 °C [*30*]. Described high temperature CoSe preparation methods successfully form this compound (Figure S2) [*31*] and are significantly faster than multi-step, low temperature (125 – 530 °C) Cu_2Se sintering methods [*11*]. Final CoSe cyclotron targets were energetically "thick" to effectively maximize the production yield of (*p,n*) nuclear reactions from 13, 12, and 11 MeV protons, but "thin" to 16 MeV protons.

The CoSe targets tolerated higher cyclotron beam intensity (≥40 μA) than Cu_2Se targets (15 – 20 μA) [*11,12*]. Hot pressing wets the niobium backing with the molten CoSe intermetallic, establishing excellent thermal contact with the water-cooled backing allowing for effective removal of the deposited proton beam power. Radiobromine from CoSe is radionuclidically pure (see Table 2) and yields are 1.3 – 2 times greater than those from other selenium alloys [*12,13*] (see Table 1 and Figure 3). The ^{77}Se(*p,2n*)^{76}Br threshold limits the radionuclidic purity of ^{77}Br above 13.3 MeV. Measured ^{77}Br yields from Co^{77}Se targets were compared with theoretical yields calculated from measured cross sections [*32*] and found to be 38% of theoretical at 12 MeV, 43% of theoretical at 13 MeV and 70% of theoretical at 16 MeV. This disagreement was shown (see supplementary material, table S2) to result from a mismatch in proton beam spot and target diameters [*33*]. The degrader foil increases beam spread and therefore lowers radiobromine yield.

The optimized dry distillation process yielded ~75% recovery of cyclotron produced radiobromine and CoSe targets were exceptionally reusable, with ~1% of CoSe mass lost with each production. This is likely due to the metallurgical properties of the CoSe intermetallic, the short time the targets are heated during distillation, and the rapid quenching that prevents hot CoSe from partitioning into less resilient cobalt- and selenium-containing species during cooling.

Large reaction volume and water content negatively affected radiochemical reactivity the copper-mediated aryl boronic ester bromination. Utilization of hot (80°C) dimethylsulfoxide (DMSO) as reaction solvent in {5} improved radiochemical conversion compared with the similar conditions of {2}. The presence of the K_2SO_4 impeded the reaction, likely by coordinating and deactivating the tetrakis(pyridine)copper (II) triflate catalyst. Copper sulfate is a poor catalyst in copper-mediated [^{18}F]fluorination of boronic acids [*34*]. Potassium sulfate was included in these reactions as it is an effective, non-basic QMA release agent for [^{77}Br]bromide. Bromination reactions using [^{77}Br]bromide released from QMA cartridges in 0.1 M NH_4OH improved radiochemical conversion, as seen in reactions {6-12}. Optimal radiochemical labeling conditions resulted from reacting dried ^{77}Br in 0.1 M NH_4OH eluant with 1 μmol pre-KX1-Bpin, 0.5 μmol $Cu(py)_4(OTf)_2$, and 0.5 μmol Lig in 70 μL MeOH at room temperature for 1 hour. The measured molar activity of the radiolabeled compound was exceptionally high, amounting to ~35% of the theoretical maximum ^{77}Br molar activity of 2000 GBq/μmol (55 Ci/μmol).

CONCLUSION

This work presents new methods for cyclotron production and radiochemical isolation of theranostic radionuclides of bromine, including ^{77}Br, ^{76}Br, and ^{80m}Br. Novel accelerator targets of the intermetallic compound CoSe tolerate higher intensity proton irradiations and produce ^{77}Br at three times the rate of previously reported methods. Radiobromine is isolated using a vertical dry distillation assembly that offers several key advantages over horizontal assemblies, including better hot cell compatibility, more rapid heating, and quench cooling of CoSe targets during fabrication and distillation. CoSe targets are resilient to the irradiation/distillation process and individual targets have been reused in 20+ radiobromine

productions. Produced [^{77}Br]bromide is radiochemically reactive and has been used to synthesize $^{76/77}$Br-based theranostic radiopharmaceuticals with high apparent molar activities.

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Disclosure

No potential conflicts of interest relevant to this article exist.

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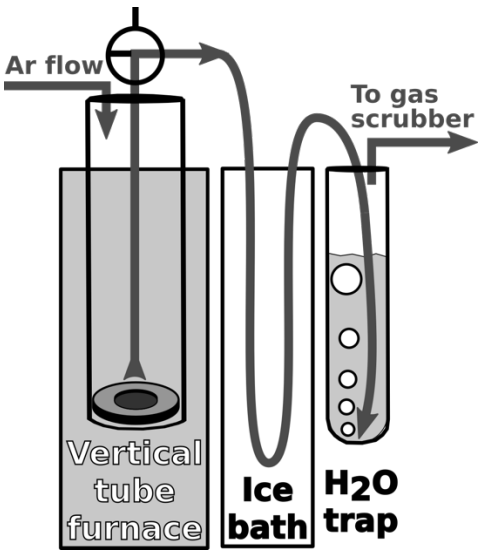

Figure 1. Radiobromine furnace assembly with CoSe heated inside quartz tube (left).

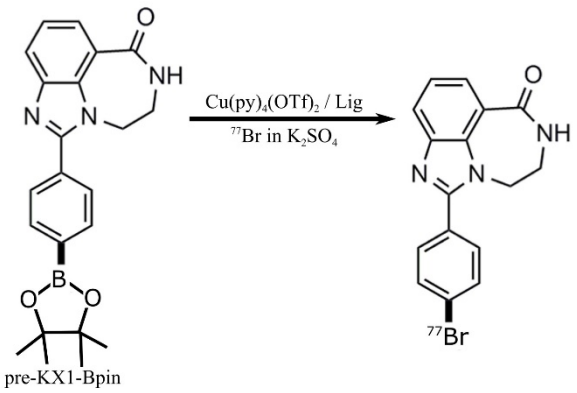

Figure 2. Radiosynthesis of ^{77}Br-labeled PARP-1 inhibitor.

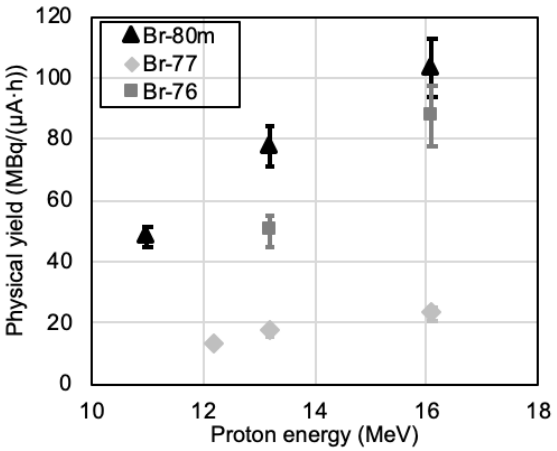

Figure 3. Production yield of ^{80m}Br, ^{77}Br, and ^{76}Br from irradiation of Co^{80}Se, Co^{77}Se, and Co^{76}Se, respectively. Error bars represent standard deviations of measurements from multiple irradiations (see Table 1 for details).

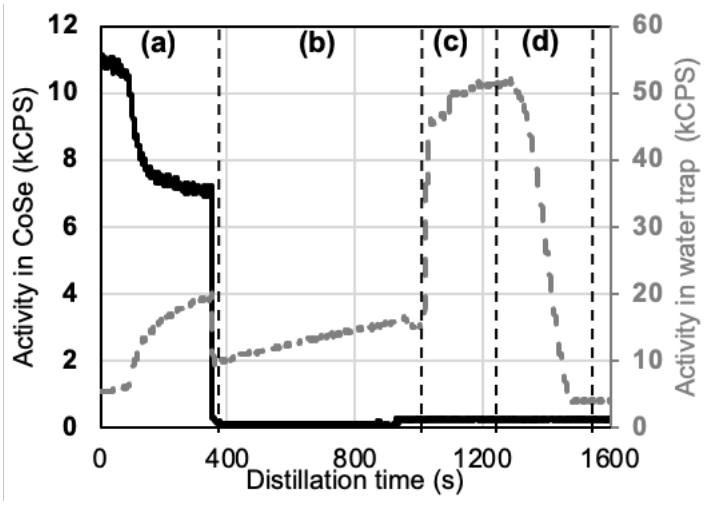

Figure 4. Typical radioactivity profiles in kilocounts per second (kCPS) in the radiobromine distillation assembly. The detector collimated on CoSe (Fig. 1, left) is shown in solid black on the left axis while the detector collimated on the H_2O trap (Fig. 1, right) is shown in dashed grey on right axis. Region (a) spans the duration of heating, region (b) spans the quench/cooling period, region (c) spans the H_2O rinse of outlet quartz and PTFE lines, and region (d) spans the QMA cartridge loading.

E_p (MeV)	Target	n	Physical yield (MBq·μA^{-1}·h^{-1})			
			^{82}Br	^{80m}Br	^{76}Br	^{77}Br
16	Co^{nat}Se	4	2.0 ± 0.3	62 ± 7	9.9 ± 0.9	2.8 ± 0.4
	Co^{80}Se	12	0.0011 ± 0.0001	103 ± 10	0.0072 ± 0.0005	0.006 ± 0.005
	Co^{77}Se	1	<0.07	n/a	12 ± ~1	23 ± ~2
	Co^{76}Se	2	<0.06	n/a	88 ± 10	0.05 ± ~0.005
13	Co^{80}Se	2	0.0015 ± 0.0002	77 ± 7	0.0040 ± 0.0005	<0.002
	Co^{77}Se	3	<0.02	<0.3	0.07 ± 0.01	17 ± 1
	Co^{76}Se	1	<0.004	n/a	50 ± ~5	0.1 ± ~0.01
12	Co^{77}Se	2	<0.002	<0.5	0.048 ± 0.001	13.1 ± 0.5
11	Co^{80}Se	8	0.0015 ± 0.0003	48 ± 3	0.0010 ± 0.0001	<0.002

Table 1. Production yield of ^{82}Br, ^{80m}Br, ^{76}Br, and ^{77}Br from various isotopic compositions of CoSe targets at four proton energies (E_p). Reported uncertainties represent standard deviations of multiple irradiations or are estimated when n=1. Limits of detection calculated from HPGe spectra [*29*] are reported. In some cases (denoted as n/a), HPGe measurements were too late to quantify short-lived ^{80m}Br.

E_p (MeV)	Target	EoB radionuclidic purity	
16	$Co^{80}Se$	99.99%	^{80m}Br
	$Co^{77}Se$	63%	^{77}Br
	$Co^{76}Se$	99.9%	^{76}Br
13	$Co^{80}Se$	99.99%	^{80m}Br
	$Co^{77}Se$	99.6%	^{77}Br
	$Co^{76}Se$	99.8%	^{76}Br
12	$Co^{77}Se$	99.6%	^{77}Br
11	$Co^{80}Se$	99.99%	^{80m}Br

Table 2. End of bombardment (EoB) radionuclidic purity of ^{80m}Br, ^{77}Br, and ^{76}Br produced at various proton energies (E_p).