VANCOUVER TARGETRY WORKSHOP

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INTRODUCTION

At the time of the previous Workshop in this series (September 1987) our new (Scanditronix MC 40 MkII) cyclotron had been in operation for about a year, but its performance was somewhat "below par" and so early in 1988 considerable effort was put into realigning the beam extraction elements and beam transport system and this had a markedly beneficial effect.

A typical week's cyclotron operations schedule is shown as Table I, and it will be seen that the machine runs 24 hours/day for about 4-1/2 days/week. (Table II is the corresponding PET schedule). At present we are still only utilizing one beam line, but four others are now potentially available and will be fully commissioned when the appropriate targetry has been finalized. There are two reasons why it has taken us so long to bring other beam lines into operation: firstly, pressure to use the machine for PET studies and radioisotope production for off-site use is so great that it is extremely difficult to schedule time for the necessary engineering development work; and secondly, unfortunately we have suffered from frequent breakdowns, particulary of electronic components of the cyclotron, so that time planned for beam development has often been used for fault-finding and repairs.

Despite these problems, as Table II shows, we are now scheduling up to 19 ECAT studies each week, and this number will doubtless increase when our second ECAT comes into service early in 1990. It can be seen that during normal working hours production of oxygen-15 consumes a high proportion of cyclotron time, and not surprisingly we are keenly interested in the "Oxygen-15 generators" which are currently under development.

Table III lists the materials that were produced regularly for use on and off site during 1988 and the remainder of this report is concerned with developments in targetry and automation that are an essential part of our overall chemistry and engineering programme.

Fluoride-18 and ^{18}FDG Production

Several $H_2{}^{18}O$ targets of various shapes and thicknesses have been tested and two stainless steel (316) targets are now installed for routine use. They are 3 mm thick and hold 1.8 ml of water. Local loading with $H_2{}^{18}O$ is achieved using an air operated syringe pump. Unloading into the hot cell area 45 m distance from the target is carried out down 0.85 mm ID PTFE tube. Earlier attempts to use smaller ID polyethylene tubes were plagued with intermittent blockages or surface tension problems. The valves, syringe drives and pumps necessary for both loading and unloading the targets are controlled by a programmable logic controller (Toshiba EX.40). The 20 mm dia. beam entry window degrades the 19 MeV incident proton beam to 16 MeV and consists of 0.6 mm Al and 0.025 mm Ti foils, the latter being in contact with the water. This combination keeps the entry foil flat, and produces less radionuclidic contamination than would a stainless steel foil.

The production of 2-[^{18}F]fluoro-2-deoxy-D-glucose (FDG), according to the route developed by Hamacher et al.[1] (nucleophilic substitution at the trifyl group of 1,3,4,6-tetra-0-acetyl-2-trifluoromethanesulfonyl-β-D-mannopyranose by [^{18}F]fluoride, followed by acid hydrolysis) is now established, using semi-remotely controlled apparatus built 'in house'. This permits the use of modest starting activities (up to 200 mCi) produced by the irradiation of ^{18}0-enriched water (20 atom %) with protons. The apparatus incorporates a small (20mm x 1mm diam.) carbonate form ion-exchange resin (BioRad AG1-X8) to trap [^{18}F]fluoride from irradiated water and to recover enriched water, and HPLC for the purification of product for human PET studies. FDG is prepared on a regular basis for 'in house' animal and human PET studies.

Work is in progress to fully automate the synthesis, so enabling higher initial activities to be used with safety.

CYCLOTRON OPERATIONS SCHEDULE WEEK 19

8 - 12 May 1989

Date/time	Beam/Foam	Particle/Energy	Target/Nuclide	User/Ericom
Sunday 7 May				
22:00 - 24:00	Maintenance, select 33 MeV He4			DBM/124
Monday 8 May				
00:00 - 00:45	5/12	He4/33	As_2O_3/Br77	DJB/151
00:45 - 01:00	Change targets			
01:00 - 06:30	5/12	He4/33	NaBr/Rb81	CMN/MJM/150
06:30 - 07:00	Select 25.5 MeV He4			
07:00 - 07:30	5/10	He4/25.5	A/K43	MJM/151
07:30 - 12:00	Maintenance/Engineering			
12:00 - 12:30	Select 9.5 MeV d			
12:30 - 13:30	Radioactive gas development			CJS/170
13:30 - 15:30	PET Neurology Study KF/168	00:00 = 14:00		MJM/170
15:30 - 16:00	Gas development			
16:00 - 18:00	PET Neurology Study CL/168	00:00 = 16:00		NS/170
18:00 - 18:30				
18:30 - 20:00	PET Cardiology Study LA/189	00:00 = 19:00		NS/170
20:00 - 22:30	Maintenance, selected 16.5 MeV d			
22:30 - 23:30	5/1	d/16.5	Ne/F18 (Burn in)	AZS/150
23:30 - 24:00	Select 33 MeV He4			
Tuesday 9 May				
00:00 - 00:45	5/12	He4/33	As_2O_3/Br77	CMN/FB/150
00:45 - 01:00	Change Targets			
01:00 - 05:45	5/12	He4/33	NaBr/Rb81	NS/MJM/150
05:45 - 06:15	Select 19 MeV p			
06:15 - 06:30	5/8	p/19	H_2O/F18	CJS/151
06:30 - 07:00	Select 16;5 MeV d			
07:00 - 09:00**	5/1	d/16.5	Ne/F18 (DOPA)	AZS/NS/151
09:00 - 11:45	Maintenance/Beam Development			
11:45 - 12:15	Select 19 MeV p			
12:15 - 12:30	5/4	p/19	N_2/C11	CP/168
12:30 - 13:00*	5/4	p/19	N_2/C11 (RCP)	DRT/168
13:00 - 13:30	Select 9.5 MeV d			
13:30 - 14:00*	5/6	d/9.5	N_2/O15 ($C15O_2$)	NS/170
14:00 - 14:30	Select 19 MeV p			
14:30 - 15:30***	5/9	p/19	H_2O/F18 (FDG)	DJB/151
15:30 - 17:30	PET Cardiology Study ER/189	00:00 = 16:30		CMN/170
17:30 - 18:00				
18:00 - 20:00	PET Cardiology Study ER/189	00:00 = 18:30		CMN/170
20:00 - 20:30	Study Overrun			
20:30 - 24:00	Maintenance			
Wednesday 10 May				
00:00 - 00:30	Select 33 MeV He4			
00:30 - 05:45	5/12	He4/33	NaBr/Rb81	NS/AZS/150
05:45 - 06:15	Select 19 MeV p			
06:15 - 06:30	5/8	p/19	H_2O/F18	CJS/151
06:30 - 07:00	Select 16.5 MeV d			
07:00 - 09:00**	5/1	d/16.5	Ne/F18 (DOPA)	AZS/NS/151
09:00 - 11:30	PET Neurology Study PT/189	00:00 = 10:00		NS/170
11:30 - 13:00				
13:00 - 15:30	PET Neurology Study VP/183	00:00 = 14:00		DJB/170
15:30 - 16:00				
16:00 - 18:00	PET Neurology study DJB/210	00:00 = 16:30		DJXB/170
18:00 - 18:30	Study overrun			
18:30 - 23:30	Engineering/maintenance			PJNA/123
23:30 - 24:00	Select 33 MeV He4			
Thursday 11 May				
00:00 - 04:45	5/12	He4/33	NaBr/Rb81	DJB/CMN/150
04:45 - 05:00	Change Targets			
05:00 - 05:45+	5/12	He4/33	NaBr/Rb81	IAW/156
05:45 - 06:10	Select 19 MeV p			
06:10 - 06:30	5/8	p/19	H_2O/F18	CJS/150
06:30 - 07:00	Select 16.5 MeV d			
07:00 - 09:00**	5/1	d/16.5	Ne/F18 (DOPA)	AZS/151
09:00 - 11:30	PET Neurology study VP/183	00:00 = 10:00		CMN/170
11:30 - 12:00	Select 19 MeV p			
12:00 - 12:15	5/4	p/19	N_2/C11	SKL/155
12:15 - 12:30	5/4	p/19	N_2/C11	CP/168
12:30 - 13:00				
13:00 - 15:00	PET Cardiology study ER/189	00:00 = 14:00		MJM/170
15:00 - 15:30	Select 19 MeV p			
15:30 - 16:00++	5/11	p/19	N_2/C11 (CH_4)	PGL/155
16:00 - 18:00	PET Cardiology K9 Study ER/189	00:00 = 17.00		MJM/170
18:00 - 18:30	Study Overrun			
18:30 - 22:00	Maintenance			
22:00 - 24:00	No shift			
Friday 12 May				
00:00 - 05:00	No shift			
05:00 - 05:30	Select 33 MeV He4			
05:30 - 06:45	5/12	He4/33	NaBr/Rb81	CMN/DJB/150
06:45 - 07:30				
07:30 - 08:00	Select 19 MeV p			
08:00 - 08:30***	5/9	p/19	H_2O/F18 (FDG)	DJB/151
08:30 - 11:00	PET Oncology Study CW/168	00:00 = 09:30		NS/170
11:00 - 11:30	Select 19 MeV p			
11:30 - 12:00	5/4	p/19	N_2/C11	SKL/CP/168
12:00 - 12:30*	5/4	p/19	N_2/C11 (RCP)	DRT/168
12:30 - 13:00	Select 9.5 MeV d			
13:00 - 13:30*	5/6	d/9.5	N_2/O15 ($C15O_2$)	AZS/170
13:30 - 14:00				
14:00 - 17:00	PET Neurology Study RW/	00:00 = 15:00		AZS/170
17:00 - 17:30	Study overrun			
17:30 - 19:45	Maintenance			DBM/124
19:45 - 24:00	No shift			

TABLE 1.

Duty Engineer: MLR

Operators: Nights DWA/SS Early CRC/JA Late RGH/GCT

* C11 Raclopride studies Tues GS 00:00 = 13:45 (CO_2) 14:00 (RCP)
Fri GS 00:00 = 15:45 (CO_2) 16:00 (RCP)

** F18 for PET 6F DOPA Studies Tuesday DJB, Wednesday GS, Thursday GS
00:00 = EOB + 2½ hours

*** F18 for PET FDG Cardiology and Oncology studies
Tues 00:00 = 16:30 (Gases) 17:30 (FDG)
00:00 = 18:30 (Gases) 19:30 (FDG)
Fri 00:00 = 09:30 (Gases) 11:00 (FDG)

\+ Rb81 for PET Cardiology Study 00:00 = 14:00 (Gases) 15:00 (Rb81)

++ C11 (CH_4) for PET Cardiology K9 Study

Circulation KIG, Bio NB, CJP, RSJF, TJ, AAL, TJS, LA, 114 NB, PET NB, CT, ASOR, 112M, DBM, ENG.NB. MLR, MLS, C.ROOM, 15 X 2, JCC, SO, MJK, FB, Chem NB, KD, CJS, DJS, SLW, AJP, WP, PGL, SKL, DRT.

I A Watson 5 May 1989

TABLE 2

ECAT SCHEDULE

Day/Date	ECAT Time	Investigation	Labelled Substrate	Zero Time	Chemist	Clinician
		C Y C L O T R O N M A I N T E N A N C E				
Monday 8	13:30-15:30	Schizophrenia	$C^{15}O_0$, $^{15}O_2$, $C^{15}O$	14:00	MJM	KF
	15:30-18:15	Visual Activation	$C^{15}O_2$	16:00	NS	CL
	18:15	Cardiac volunteer	$C^{15}O$, $C^{15}O_2$	19:00	NS	LA & Co
Tuesday 9	10:30-12:45	Neuro (Movement disorder)	^{18}F-DOPA	11:00	AZS/NS	DB
	13:15-15:15	Neuro (? C.B.D)	$C^{15}O_2$	13:45	NS	GS
			^{11}C-Raclopride	14:00	DRT	
	15:45-18:30	Cardiac (Transplant)	$C^{15}O$, $C^{15}O_2$	16:30	CMN	
			^{15}FDG	17:30	DJB	LA/ER
	18:30-	Cardiac	$C^{15}O$, $C^{15}O_2$	19:00	CMN	
			^{18}FDG	20:00	DJB	LA/ER
Wednesday 10	09:30-11:15	Neuro (C.V.D)	$C^{15}O_2$, $^{15}O_2$, $C^{15}O$	10:00	NS	V di P
	11:15-13:30	Neuro (?C.B.D)	^{18}F-DOPA	11:30	AZS	GS
	13:30-16:00	Neuro (C.V.D)	$C^{15}O_2$, $^{15}O_2$, $C^{15}O$	14:00	DJB	V di P
	16:00 -	Tremor Activation	$C^{15}O_2$	16:30	DJB	JC
Thursday 11	09:30-11:15	Neuro (C.V.D)	$C^{15}O_2$, $^{15}O_2$, $C^{15}O$	10:00	CMN	V di P
	11:15-13:30	Neuro (?C.B.D)	^{18}F-DOPA	11:30	AZS	GS
	13:30-16:30	Cardiac	$C^{15}O$, $C^{15}O_2$	14:00	MJM	ER
			^{81}RbCl	15:00	IAW	
	16:30-	Cardiac K9	$C^{15}O$, $C^{15}O_2$	17:00	MJM	LA & Co
			$C^{11}H_4$	18:00	PGL	
Friday 12	09:00-10:30	Oncology (flow)	$C^{15}O_2$	09:30	NS	CW
			^{18}FDG	11:00	DJB	CW
	10:30-13:00	Oncology	$C^{15}O_2$	13:15	AZS	GS
	13:00-14:45	Neuro (?C.B.D)	^{11}C-Raclopride	13:30	DRT	
	14:45-	Aphasion stimulation	$C^{15}O_2$	15:00	AZS	RW

TABLE 3

ROUTINE RADIONUCLIDE CLINICAL PRODUCTIONS
JANUARY - DECEMBER 1988

PRODUCTIONS FOR PET

Nuclide	Chemical Form	No. of Production runs	Cyclotron Time (hours)	Samples/ MBq (on site)	Samples/ MBq (off site	Total Activity MBq (mCi)	No of patients
O15	$O_2/CO_2/CO$	1310₂ 89 CO_2 75CO	500(approx)	on line	-	on line	289
C-11	Nomifensine	54	27	50/20550	-	20050 (555mCi)	46 +
F-18	Fluoride (aq.soln.)	18	9	-	18/17754	17754 (657mCi)	18
F-18	Fluorodeoxy uridine	20	36	20/5786		5786 (156mCi)	26
F-18	6-Fluoro DOPA	128	256	116/26216	-	26216 (970mCi)	116
F-18	2Fluoro-2-Deoxy -D-glucose	93	63	45/15330	1/916	16216	44 +
Rb-81	Chloride	45	45	35/9130	12/2181	11611	49

PRODUCTIONS FOR OFF-SITE USE

Nuclide	Chemical Form	No. of Production runs	Cyclotron Time ** (hours)	Samples/ MBq (on site)	Samples/ MBq (off site	Total Activity MBq (mCi)	No of patients
Kr-81m	Gas generator	293	941	138/118 GBq	1631/ 1391 GBq	1509 GBq (40.8Ci)	10967 *
Kr-81m	Solution generator	33	70	-	33/33350	33350 (901mCi)	76
Fe-52	Citrate	29 (ex UOB)	(58)	29/134	-	134 (3.6mCi)	29
K-43	Chloride	34 (ex UOB)	(68)	3/27.1	69/4447	4474 (121mCi)	8+
Pb-203	Chloride	4	5	-	4/74.4	74.4	+
Br-77	Bromide	42	21	-	45/298	(8.05mCi)	10

Total programmed cyclotron time for the period = 5324 hours
UOB = Nuffield Cyclotron, University of Birmingham
* Number of patients is an estimate based on the activity supplied
** 1047 hours (≈ 20%) of programmed time used to supply materials off site
+ materials also used for non clinical research and development work

Fluorine Gas Targets, [^{18}F]6-Fluoro DOPA and [^{18}F] 5-Fluorodeoxyuridine Production

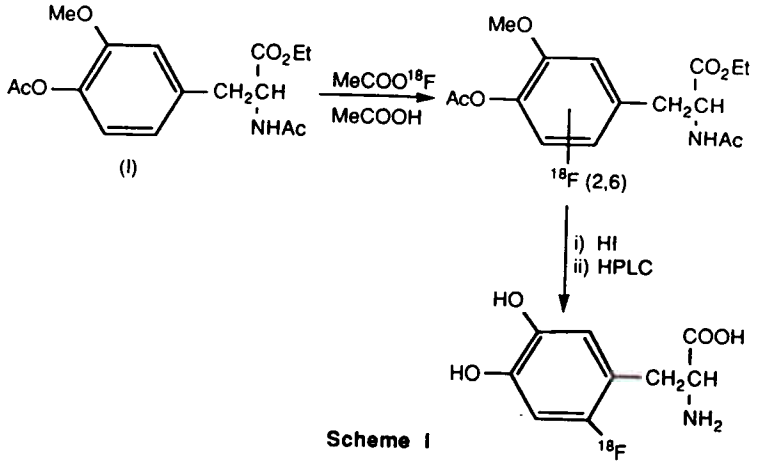
Water cooled nickel targets with 0.050 mm Havar backed by 0.025 mm nickel sandwich window is filled through air operated bellows valves with 0.2% F_2 in Neon to a pressure of 14 bar. This pressure is monitored using a transducer with a digital readout in the cyclotron control room and in the hot cell area. The pressure rises to approximately 24 bar during irradiation with 15-20 micro amps of 16.5 MeV deuterons. The target and vacuum windows are cooled with high velocity helium jets. Production reproducibility has been improved by ensuring adequate supplies of research grade Neon and 2% F_2/Neon with certified analyses. Two targets are currently installed for routine use.

The production of L-6-[^{18}F]fluoro-DOPA is based on the reaction of a protected L-DOPA (I) (Scheme I) with acetyl [^{18}F]hypofluorite in glacial acetic acid, followed by deprotection with hydriodic acid.[2,3]

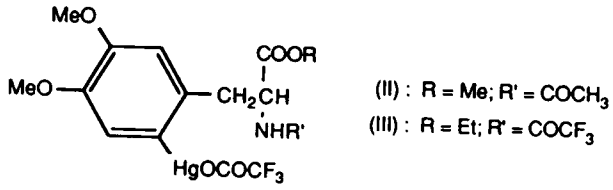
This chemistry produces L-2- and L-6-[^{18}F]fluoro-DOPA in the ratio 9:11. HPLC (Nucleosil 5 C18 column : 5 μm, 25 cm x 20 mm i.d.; Technicol Ltd.) provides L-6-[^{18}F]fluoro-DOPA in greater than 95% radiochemical purity as assessed by ^{19}F-NMR spectroscopy and analytical HPLC. Chiral purity is found to be greater than 98% by TLC.

To minimise radiation exposure to the operator the method is now semi-automated. Typically the overall radiochemical yield is 6-8% providing 5-15 mCi of L-6-[^{18}F]fluoro-DOPA for i.v. injection. Each sample is checked for chemical and radiochemical purity by analytical HPLC. Generally radiochemical purity exceeds 97% with the L-2-[^{18}F]fluoro-isomer as major contaminant. Small levels of the neurotoxin, L-6-hydroxy-DOPA, have been detected in the product. (Only samples that contain less than 50 ug of L-6-hydroxy-DOPA are approved for PET studies). Approximately 160 clinical samples have now been supplied using this method.

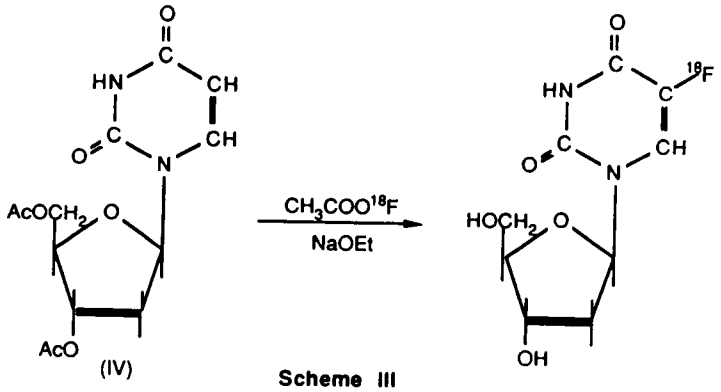
The major disadvantage with the method is the isomer separation which requires careful judgement on fraction collection (the isomer peaks partially overlap). This makes full automation difficult. The preparation of L-6-[^{18}F]fluoro-DOPA by a regioselective method of fluorination has recently been the subject of two publications.[4,5] The precursors (II and III) (Scheme II) react at the 6-position with labelled acetyl hypofluorite (demercuration) to yield a protected intermediate as before. This is hydrolysed and the resultant L-6-[^{18}F]fluoro-DOPA is purified by HPLC.



Scheme I



Scheme II



Scheme III

The chemical purity of the product is almost identical to that from the previous method, but the mercury by-products must be removed by a thiol column during the chemistry. The method has yielded

comparable activities of L-6-[^{18}F]fluoro-DOPA but with higher radiochemical purity. Because the HPLC is essentially a "clean up" with one major peak this method is much more amenable to full automation. Although levels of mercury in the product have so far been below the limit (< 0.02 ug/mL) detectable by atomic absorption spectroscopy, we are still concerned about the fate of mercury in this procedure and so have not yet adopted it for routine use.

5-[^{18}F]Fluoro-2^{1}-deoxy-uridine is useful for the delineation of brain and lung tumours in man.[6-10] It has been requested for PET oncology studies and has now been synthesised essentially according to a reported procedure,[10,11] but with remote control and a modified purification procedure incorporating HPLC.

Thus the acetylated deoxyuridine derivative IV (Scheme III) is dissolved in acetic acid and fluorinated by passing acetyl [^{18}F]hypofluorite into the solution at room temperature. After the evaporation of solvent, the acetyl groups are removed by hydrolysis with sodium ethoxide in ethanol at 95° C. The ethanol is then removed and the residue dissolved in water and neutralised by passage through ion exchange columns. Preparative HPLC purification is then carried out on a reverse phase (C18) column eluted with a solution of KH_2PO_4 (0.07 M). The pH is adjusted to 7 with sodium bicarbonate solution before millipore filtration.

The synthesis takes 2 h and typically the product is obtained in ca 25% radiochemical yield (decay-corrected). Radiochemical and chemical purity exceeds 97% as measured by HPLC. Preparations contain less than 10 mg of stable material. Twenty patient doses have been supplied for PET studies to date.

11C-Methylations: Production of S-[N-methyl-^{11}C] Nomifensine, [O-methyl-^{11}C] Raclopride

A hot cell has been equipped with a $^{11}CO_2$ cryotrapping system (liquid argon), a $^{11}CH_3I$ production and precursor methylation system. HPLC purification and product formulation are also accomplished in the cell. A high degree of flexibility has been retained in this system by controlling the valves, heaters, syringe drives, vial penetrator, HPLC loop injectors and rotary evaporator using a programmable logic controller (Toshiba EX 40).

The precursor, nor-nomifensine, has been successfully resolved, essentially by a published procedure[12] to give the S-isomer, so enabling S-[N-methyl-^{11}C]nomifensine rather than the racemate to be produced. Biological studies performed 'in house' have confirmed the advantages of using the S-isomer for PET studies. Preparations are now carried out in the fully automated apparatus described above. Fifty-four preparations have been supplied for PET studies during 1988.

We are grateful to Drs. Urbach and Grome (Hoechst, FRG) for helpful discussions and the supply of materials, and also to Dr. B. Langstrom for advice on the separation of S-nornomifensine and the supply of reference S-nornomifensine.

The development of the production of [O-methyl-^{11}C]raclopride[13] was undertaken, aided by a short working visit from Dr. C. Halldin (Karolinska Institute, Stockholm). This development is now complete and permits [^{11}C] raclopride to be produced in the same fully automated hot cell as [^{11}C]nomifensine. HPLC purification is facilitated by means of a sample enrichment system using two independent injection valves (Rheodyne 7010P) (Figure 1).

We are grateful to Dr. Hall of Astra Lakemedel AB for providing desmethylraclopride and raclopride tartrate for these studies.

The preparation of [N-methyl-^{11}C]SCH 23390 can also be carried out in the same fully automated apparatus used for [^{11}C] nomifensine and [^{11}C]Raclopride production. Production for PET studies awaits ethics approval. We are grateful to Dr. Barnett, Scherring-Plough Corp. (USA) for the supply of nor SCH 23390 and SCH 23390.

[^{11}C]-Methane, [^{11}C]-Phosgene and S-[^{11}C]CGP 12177

^{11}C-Methane is produced by 19 MeV proton irradiation of 5% H_2 in N_2 in an Al target fitted with a 0.05 mm havar window. ^{11}C-Methane is converted to ^{11}C-Phosgene by means of a chlorination/

oxidation procedure in a hot cell. Subsequent reaction of $^{11}COCl_2$ with a suitable precursor yields ^{11}C-CGP-12177.

CGP 12177 is an excellent ligand for pulmonary and cardiac β-receptors. It is a selective antagonist with low lipophilicity and high affinity. Primary 'in-house' studies with [^{3}H]CGP 12177 have shown high tissue plasma and specific/non-specific binding ratios in vivo. These studies also confirm that the S-isomer has much higher affinity than the R-isomer. Hence it is intended to prepare S-[^{11}C]CGP 12177 for PET studies.

The labelling of CGP 12177 involves the reaction of [^{11}C]phosgene[14] with an appropriate diamine as already described.[15] In order to prepare S-[^{11}C]CGP 12177 it will be necessary to use the S-diamine. Work is in progress to synthesise an adequate quantity of the R,S-diamine and to attempt its resolution by chiral HPLC. An automated system for the production of [^{11}C]phosgene has been constructed and trials of the radiosynthesis of R,S-[^{11}C]CGP 12177 are in progress.

We are grateful to Dr. K. Jaeggi and Dr. L.J. Browne of Ciba-Geigy AG for the supply of essential materials and for useful discussions and also to Allen and Hanbury Ltd., Glaxo Research Ltd. and Glaxo Laboratories Ltd. for supporting this project.

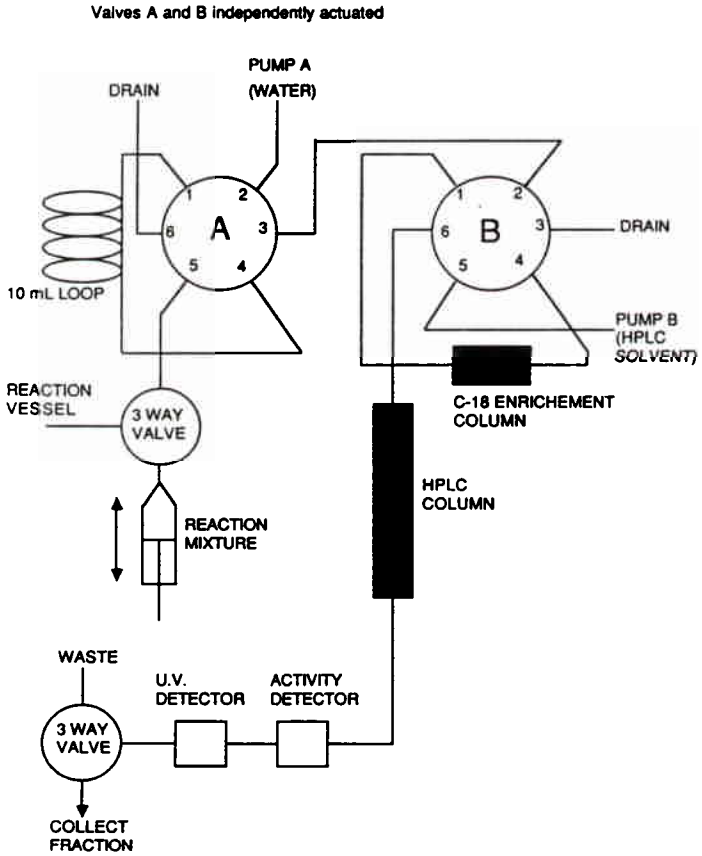


Figure 1 HPLC Sample Enrichment and Purification System

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