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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :		(11) International Publication Number:
A61K 49/04	A1	WO 94/05335
		(43) International Publication Date: 17 March 1994 (17.03.94)

(21) International Application Number: PCT/US92/07431

(22) International Filing Date: 31 August 1992 (31.08.92)

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(81) Designated States: AU, CA, FI, JP, KR, NO, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, SE).

Published
With international search report.
With amended claims.

(54) Title: NEW ORGANIC CONTRAST AGENT ANALOG AND METHOD OF MAKING SAME

(57) Abstract

An organic contrast agent analog is derived to contain fluorine moieties. A method for making the organic contrast agent analog includes the steps of fluorinating the contrast agent analog for increasing the acidity of the analog to increase the choleretic activity of the analog and to render it less toxic.

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NEW ORGANIC CONTRAST AGENT ANALOG AND METHOD OF MAKING SAME

TECHNICAL FIELD

The present invention relates to organic contrast agent analogs and methods of making the analogs. More particularly, the present invention relates to a method of decreasing the toxicity of such agents through chemical modification.

BACKGROUND ART

In general, current cholangiographic agents used as biliary X-ray contrast agents are now considered too toxic to meet risk/benefit criteria for routine use as contrast agents to visualize the biliary system. Because of the relative toxicity of these agents, these agents are being replaced in use by alternative imaging methodologies, such as ultrasound and magnetic resonance imaging (MRI). On the other hand, the resolution achievable with X-ray radiology techniques is superb. Accordingly, biliary contrast agents can still be quite useful.

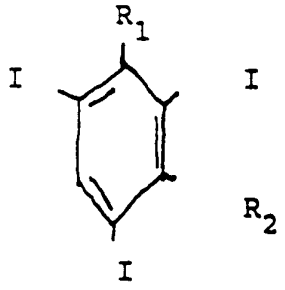
A second issue with regard to these agents is the low rate of choleresis associated with biliary excretion of the agent. The low rate of choleresis increases the biliary concentration and thus increases the toxicity..

Current biliary X-ray contrast agents have amphophilic properties. These agents have a hydrophilic head portion; that is, the $-CO_2H$ terminus, and a hydrophobic tail; that is, triiodo aniline moiety with an unsubstituted 5-position. Because of this property, they are excreted nearly exclusively by the biliary route. Typical of most amphilphilic molecules, these biliary contrast agents tend to self associate. This property is reflected by the low critical micellar concentration and low osmolalities of their aqueous salt solution.

It is therefore desirable to produce a less toxic and more choleretic contrast agent.

SUMMARY OF THE INVENTION

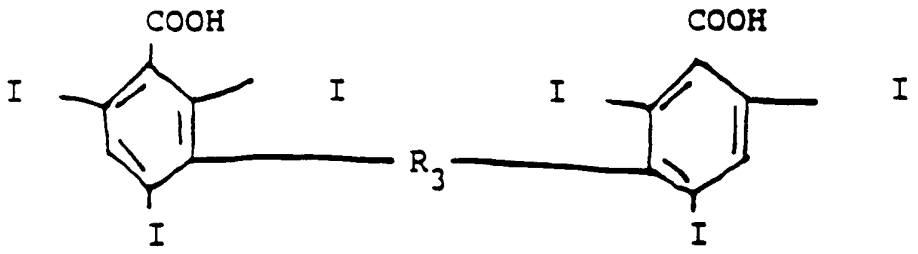
In accordance with the present invention, there is provided an organic contrast agent analog wherein the analog is an oral or intravenous media having the formula I:



and R_1 and R_2 are

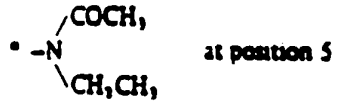
	R_1	R_2
Iopanoic acid	$-CH_2CH(CH_2CH_3)COOH$	$-NH_2$
Ipodatic acid	$-CH_2CH_2COOH$	$-N{=}CHN(CH_3)_2$
Tyropanoic acid	$-CH_2CH(CH_2CH_3)COOH$	$-NHCOCH_2CH_2CH_3$
Iocetamic acid	$-NCH_2CH(COCH_3)CH_2COOH$	$-NH_2$
Iopronic acid	$-OCH_2CH_2OCH_2CH(CH_2CH_3)COOH$	$-NHCOCH_3$
Iosumetic acid	$-N(CH_2CH_3)CH_2CH_2COOH$	$-NHCH_3$

or wherein said analog is an intravenous media having formula II;



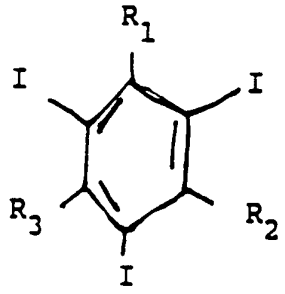
and R_3 is

	R_3
Iodipamide	$-NHCO(CH_2)_4CONH-$
Ioglycamide	$-NHCOCH_2-O-CH_2CONH-$
Iodoxamate	$-NHCO(CH_2CH_2O)_4CH_2CH_2CONH-$
Iotroxamide	$-NHCO(CH_2OCH_2)_2CONH-$
Iosulamide*	$-NHCOCH_2CH_2SO_2CH_2CH_2CONH-$



at position 5

or wherein said analog is an urographic media having formula III;



wherein the analog includes one or more flourine substitutions or additions.

The present invention further provides a method of making the organic contrast agent analog including the steps of forming the organic contrast agent analog having formulas I, II, or III and substituting or adding at least one flourine moiety to the analog.

FIGURES IN THE DRAWINGS

Other advantages of the present invention will be readily appreciated as the same becomes better understood by reference to the following detailed description when considered in connection with the accompanying drawings wherein:

Figures 1 and 2 are high resolution NMR proton spectrums;

Figure 3 is a high resolution NMR fluorine spectrum;

Figures 4 and 5 are mass spectrum analyses performed on TFA-IOP made in accordance with the present invention;

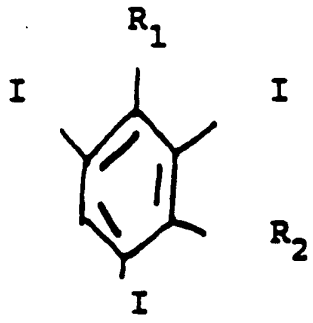
Figure 6 is a plotted curve comparing biliary concentration over time of IOP versus TFA-IOP;

Figure 7 is comparitive data of TFA-IOP and IOP plasma concentration versus time; and

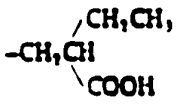
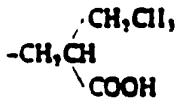
Figure 8 is comparative date of TFA-IOP and IOP biliary excretion concentration versus time.

DESCRIPTION OF THE INVENTION

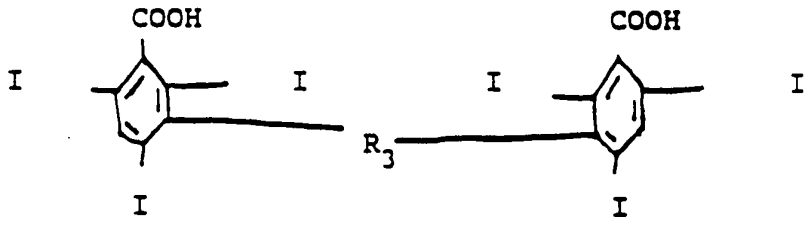
Generally, an organic contrast agent analog made in accordance with the present invention has the following general formula I:



and R_1 and R_2 are

	R_1	R_2
Iopanoic acid		$-NH_2$
Ipodatic acid	$-CH_2CH_2COOH$	$-N{=}CHN(CH_3)_2$
Tyropanoic acid		$-NHCOCH_2CH_2CH_3$
Iocetamic acid		$-NH_2$
Iopronic acid		$-NHCOCH_3$

or wherein said analog is an intravenous media having the formula II;

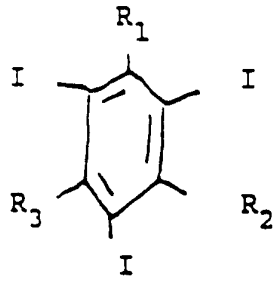


and R_3 is

	R_2
Iodipamide	$-NHCO(CH_2)_4CONH-$
Iodiglycamide	$-NHCOCH_2-O-CH_2CONH-$
Iodoxamate	$-NHCO(CH_2CH_2O)_4CH_2CH_2CONH-$
Iotroxamide	$-NHCO(CH_2OCH_2)_2CONH-$
Iosulamide*	$-NHCOCH_2CH_2SO_2CH_2CH_2CONH-$

* $-N(COCH_3)(CH_2CH_3)$ at position 5

or wherein said analog is an urographic media having the formula III;



The agent includes a hydrophilic head (side chain) and a hydrophilic tail (benzine ring). The flourine addition or substitution provides means for increasing the acidity of the agent and increasing the choleretic activity of the agent to render the agent less toxic.

Examples of oral cholecystographic contrast media which can be modified in accordance with the present invention are

Table I.

Common name	proprietary name	Manufacturer	Molecular weight (m.w.)		Iodine (% m.w.)
			Acid form	Salt form	
Iopanoic acid	Telepaque	Winthrop	571		66.7
Ipodate, calcium	Oragratin, calcium	Squibb	598	1,234	63.7
Ipodate, sodium	Oragratin, sodium	Squibb	598	620	63.7
Tyropanoate, sodium	Bilopaque	Winthrop	641	663	59.4
Iocetamic acid	Cholebrine	Mallinckrodt	614		62.0
Iopronic acid	Oravue	Squibb	673		56.6
Iosumetic acid		Schering	628		60.6

Examples of intravenous cholangiographic media modifiable in accordance with the present invention are

Table 2.

N-Methylglucamine salt of contrast media	Proprietary name	Manufacturer	Molecular weight (m.w.)		Iodine (% m.w.)
			Acid form	Salt form	
Iodipamide	Cholegratin	Squibb	1.140	1.530	66.8
Iogiycamide	Biligram	Schering	1.128	1.518	67.5
Iodoxamate	Cholevue	Winthrop	1.288	1.678	59.1
Iotroxamide		Schering	1.316	1.706	57.9
Iosutamide		Winthrop	1.376	1.764	55.3

More specifically, the starting agent can be a cholangiographic or cholecystographic agent as stated above. The agent can be of the oral or intravenous types. That is, the agent is iodinated such that it can be used as a biliary X-ray contrast agent for routine use to visualize hepatocytes gallbalder and the the biliary system. Unlike previously used cholecystographic agents, such as underivatized iopanoic acid, the present invention is a chemically modified organic contrast agent analog which is rendered less toxic and more choleretic by the modification of the agent including additional fluorine functionalities on the agent, the fluorine functionalities rendering the agent more acidic and more choleretic.

It has been hypothesized that if an amphophilic molecule, such as a common organic contrast agent analog is rendered a stronger acid and is fully or at least more disassociated at physiological pH, it will most likely be excreted unconjugated, without causing choloresis and without being trapped in the intrahepatic shunt pathway (Sawkat, MS. et al; Influence of sid-chain charge on hepatic transport of bile acids and bile acid analogues. American Journal Physiology 249:G479-G488, 1985; Gurantz D., et al; Influence of bile acid

structure on bile flow and biliary lipid secretion in the hamster. American Journal Physiology 247:G738-G748, 1984; Yoon, YB, et al, Effect of side-chain shortening on the physiologic properties of bile acids: hepatic transport and effect on biliary sectetion of 23-nor-ursodeoxycholate in rodents. Gastroenterology 90:837-852, 1986). Even in the presence of choleresis, if the hepatocyte and canalicular transport steps are rapid, the biliary contrast agent is expected to move as a bolus, and anatomical details, such as the intrahepatic ducts, can be visualized in patients with good hepatocyte function.

For example, the agent can be N-trifluoroacetyl-iopanoic acid or alpha-fluoro-N-trifluoroacidic-iopanoic acid.

The present invention further provides a method of making the organic contrast agent analog. The method generally includes the steps of forming the organic contrast agent analog having the formulas I, II, or III and then increasing the acidity of the agent while increasing the choleretic activity of agent to render the agent less toxic by adding or subtituting flourine on the agent.

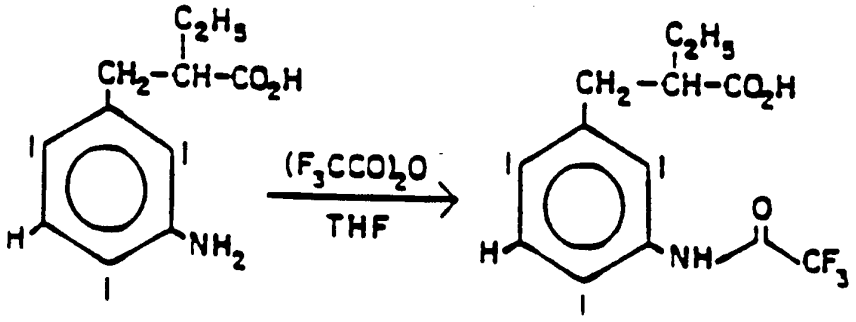
EXPERIMENTS

1. Synthesis of N-trifluoro Derivative of Iopanoic Acid

Three fluorine atoms were attached to the cholecystographic agent iopanoic acid (IOP) so that it could be detected using 19-F magnetic resonance techniques.

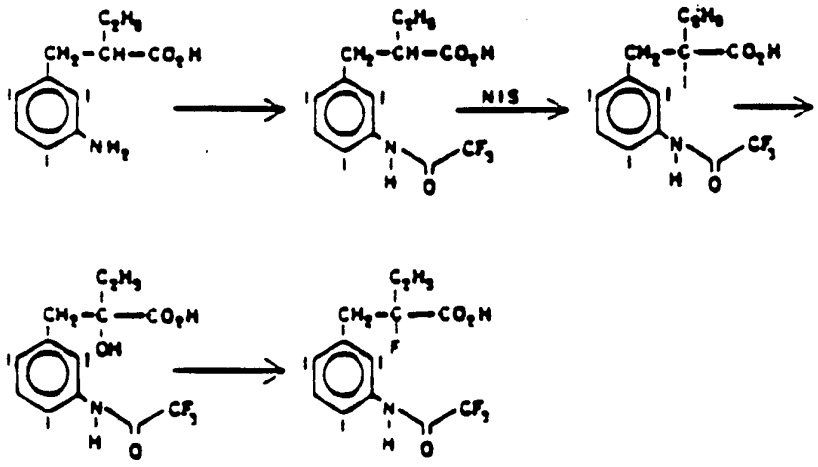
IOP was reacted with trifluoroacetic anhydride at 0°C in tetrahydrofuran. After the reaction was complete, the organic solvents were removed. The residue was dissolved in ethyl acetate and washed twice with water. The organic layer was dried over magnesium sulphate and the solvent was removed to obtain the final product. The product, N-trifluoroacetyl iopanoic acid, had a melting point of 193°C and an extension coefficient of approximately 37,000 at 232 nm. The assigned structure was verified using high resolution proton and fluorine NMR spectroscopy, elemental analysis and mass spectrum analysis. The isolated yield of the product was 97.5%.

The following summarizes the reaction.



2. Synthesis of Alpha-fluoro-N-trifluoroacetyl-Iopanoic Acid

Functional groups were placed on the carbon atom alpha to the carboxyl group of the organic contrast agent, iopanoic acid. A fluorine atom was placed on the carbon atom alpha to the carboxyl group of N-trifluoroacetyl-iopanoic acid to significantly effect its pKa and thus, effect its biodistribution and metabolism. The following summarizes the synthesis of the alpha-fluoro-N-trifluoroacetyl-iopanoic acid.



Results of elemental analysis of TFA-IOP provided by Galbraith Laboratories, Inc., Knoxville, TN are as follows:

	Galbraith	Theoretical	Error
C	24.33%	24.03%	+0.30%
H	1.93%	2.15%	-0.22%
N	2.04%	2.00%	+0.04%
F	8.50%	8.15%	-0.35%
I	55.24%	54.51%	+0.73%
O		9.16%	
		100.00%	

The calculations are based on the inclusion of a molecule of methanol with each molecule of TFA-IOP.

High resolution NMR proton spectrums (Figs. 1 and 2), high-resolution NMR fluorine spectrum (Figure 3) and mass spectrum analyses (Figures 4 and 5) were performed on TFA-IOP. The results of each confirm the expected chemical structure of the new compound. Mass spectral analysis was performed.

3. Comparative Data of Biliary Excretion of IOP and Trifluoroacetyl IOP

Experiments were conducted to compare the biodistribution and excretion of TFA-IOP to that of the parent compound IOP. TFA-IOP and IOP were each administered intravenously to rats (100 umol/kg) in order to compare the biodistribution and excretion of the compound made in accordance with the present invention and the parent compound. Tissues examined included liver, spleen, upper GI, lower GI, kidney, lung and heart. The length of each study was 90

minutes, during which time bile, urine and plasam samples were taken to monitor uptake and excretion. NMR relaxation rates for liver and plasma were also examined to note whether uptake of either compound might possible alter these parameters.

4. Results

In general, liver concentrations 90 minutes post injection were 512 uM and 202 uM after IOP and TFA-IOP injection, respectively, while kidney concentrations were 105 uM and 5 uM. Lesser concentrations were found in the other tissues. Excretion of the two compounds were found only in bile with no compound detected in urine. In bile, TFA-IOP reached a maximum concentration of .5 uM with the recovery of 40% of the injection dose during a 90 minute time period (see Figure 6). For IOP, the biliary concentration reached 10 mM with 18% of the injected does recovered during the 90 minute collection period as shown in Figure 6. Plasma disappearance curves were similar in form, as shown in Figure 7. Thin layer chromatography of bile indicated that a vast majority of the injected TFA-IOP was metabolized to a single metabolite. No nonmetabolized compound was found.

These results indicate that TFA and IOP are similar to their biodisposition except the rate of biliary excretion of TFA-IOP appears to be approximately twice that of IOP, as shown in Figure 8.

Tables 1 through 5 summarizes the results of each experiment conducted. Table 6 shows a more detailed analysis of the tissue concentration results with values such as total micromoles in tissue, percent of dose/gm, etc.

Tables 7 and 8 contain analysis of the bile excretion results.

TABLE 1

TISSUES

	-IOP CONCENTRATION (uM) 90 MIN POST INJECTION			
	I-e (IOP)	% OF DOSE	I-8 (TFA-IOP)	% OF DOSE
LIVER	511.90	14.53	281.73	6.84
KIDNEY	185.40	0.69	57.84	0.34
*UPPER GI	387.91	1.31	148.23	0.41
*LOWER GI	135.23	0.59	178.69	0.63
*SPLEEN	255.54	0.45	164.86	0.24
*LUNG	324.91	1.21	277.64	0.23
*HEART	259.38	0.72	242.95	0.72

No standard curves were compiled for these tissues. The values given represent concentrations generated using the LIVER analysis routine and standard curve. Because this routine utilizes a control LIVER spectra for background modeling, erroneous Iodine concentration values for these tissues may result due to inappropriate background removal.

TABLE 2

PLASMA	-IOP CONCENTRATION (uM)	
SAMPLING TIME (min)	I-6 (IOP)	I-8 (TFA-IOP)
0	****	0.00
10	****	863.19
20	****	683.93
30	556.68	573.38
40	****	518.22
50	587.76	469.19
60	462.87	414.69
70	462.46	373.79
80	483.95	483.05
90	372.89	359.94

**** Indicates that no samples were obtained for these time periods.

TABLE 3

BILE:	-IOP CONCENTRATION (uM)	
SAMPLING TIME (min)	I-6 (IOP)	I-8 (TFA-IOP)
0	****	635.0
5	1685.8	3818.0
15	3659.4	5777.6
25	18504.9	6436.1
35	9854.3	7882.9
45	9667.6	7641.1
55	7316.4	8461.4
65	7529.1	5372.5
75	7758.8	5385.7
85	9564.6	4663.1

**** Inidcates that no sample was obtained for this time period.

TABLE 4

URINE:	-IOP CONCENTRATION (uM)	
SAMPLING TIME (min)	I-6 (IOP)	I-8 (TFA-IOP)
0-20	0	0
20-40	0	0
40-60	0	***
60-80	0	***
80-90	0	***

***Indicates that no samples were obtained for these time periods.

TABLE 5

NMR DATA:

T1 VALUES (msec)

TISSUE	CONTROL VALUE	I-6 (IOP)	I-8 (TFA-IOP)
Liver	214.96	228.26	243.87
Plasma	1332.65	1486.19	1455.34

T2 VALUES (msec)

TISSUE	CONTROL VALUE	I-6 (IOP)	I-8 (TFA-IOP)
Liver	38.27	28.65	28.94
Plasma	232.18	257.87	221.56

- As expected, the values obtained do not significantly differ from control values.

TABLE 6

INTRAVENOUS IDP RAT STUDY

RAT NUMBER : 6.
DOSE : 104.umoles/kg
TIME : 90.minutes
BODY WEIGHT : 406.grams

	TISSUE WEIGHT	% OF B.WT.
LIVER	11.98	2.95
SPLEEN	.75	.18
UPPER GI	1.79	.44
LOWER GI	1.83	.45
KIDNEY	2.76	.68
LUNG	1.57	.39
HEART	1.18	.29

	uMOLES IN TISS.	uMOLES PER gram	uMOLES PER kg
LIVER	6.13	.51	511.90
SPLEEN	.19	.26	255.54
UPPER GI	.55	.31	307.91
LOWER GI	.25	.14	135.23
KIDNEY	.29	.11	105.40
LUNG	.51	.32	324.91
HEART	.31	.26	259.38

	PERCENTAGE OF DOSE IN TISS.	PERCENTAGE OF DOSE PER gram	PERCENTAGE OF DOSE PER kg b.wt
LIVER	14.52	1.21	35.77
SPLEEN	.45	.61	1.12
UPPER GI	1.31	.73	3.22
LOWER GI	.59	.32	1.44
KIDNEY	.69	.25	1.70
LUNG	1.21	.77	2.98
HEART	.72	.61	1.79

TABLE 6 (continued)

INTRAVENOUS TFA-IOP RAT STUDY

RAT NUMBER : 8.
DOSE : 100.umoles/kg
TIME : 90.minutes
BODY WEIGHT : 435.grams

	TISSUE WEIGHT	% OF B.WT.
LIVER	13.82	2.99
SPLEEN	.63	.14
UPPER GI	1.27	.29
LOWER GI	1.54	.35
KIDNEY	2.56	.59
LUNG	1.38	.30
HEART	1.29	.30

	uMOLES IN TISS.	uMOLES PER gram	uMOLES PER kg
LIVER	2.63	.20	201.73
SPLEEN	.10	.16	164.06
UPPER GI	.18	.14	140.23
LOWER GI	.27	.18	178.09
KIDNEY	.15	.06	57.84
LUNG	.36	.28	277.64
HEART	.31	.24	242.85

	PERCENTAGE OF DOSE IN TISS.	PERCENTAGE OF DOSE PER gram	PERCENTAGE OF DOSE PER kg b.wt
LIVER	6.84	.46	13.88
SPLEEN	.24	.38	.55
UPPER GI	.41	.32	.94
LOWER GI	.63	.41	1.45
KIDNEY	.34	.13	.78
LUNG	.83	.64	1.91
HEART	.72	.56	1.66

TABLE 7

09/25/86

INTRAVENOUS TFA-IOP RAT STUDY

RAT I.D. :	I-8
COMPOUND :	TFA-IOP
DOSE :	100. umoles/kg
BODY WEIGHT :	435. grams
UMOLES INJECTED :	43.50 umoles
LIVER WEIGHT :	13.02 grams
EXP. LENGTH :	90 minutes

SAMPLE PERIOD (min)	BILE FLOW ml/min	ml/min PER kg b.w.	ml/min PER kg l.w.
0 - 0	.02093	.04811	1.60753
0 - 10	.04071	.09359	3.12673
10 - 20	.03675	.08448	2.82258
20 - 30	.04050	.09310	3.11060
30 - 40	.02992	.06878	2.29800
40 - 50	.03047	.07005	2.34025
50 - 60	.02817	.06476	2.16359
60 - 70	.02721	.06255	2.08986
70 - 80	.02653	.06099	2.03763
80 - 90	.02586	.05945	1.98618

TABLE 7 (continue

SAMPLE PERIOD (min)	COMPOUND CONC. (umolar)	EXCRETION umoles/min	umoles/min PER kg b.w.	kg l.w.
		umoles / min		
10 - 0	635.0	.013	.031	1.021
0 - 10	3010.0	.123	.282	9.411
10 - 20	5777.6	.212	.488	16.308
20 - 30	6436.1	.261	.599	20.020
30 - 40	7802.9	.233	.537	17.931
40 - 50	7641.1	.233	.535	17.882
50 - 60	8461.4	.238	.548	18.307
60 - 70	5372.5	.146	.336	11.228
70 - 80	5305.7	.141	.324	10.811
80 - 90	4663.1	.121	.277	9.262

SAMPLE PERIOD (min)	SAMPLE WEIGHT (grams)	UMOLES IN SAMPLE	RUNNING TOTAL
10 - 0	.20930	.13	.13
0 - 10	.40710	1.23	1.36
10 - 20	.36750	2.12	3.48
20 - 30	.40500	2.61	6.09
30 - 40	.29920	2.33	8.42
40 - 50	.30470	2.33	10.75
50 - 60	.28170	2.38	13.13
60 - 70	.27210	1.46	14.60
70 - 80	.26530	1.41	16.00
80 - 90	.25860	1.21	17.21

TABLE 7 (continued)

SAMPLE PERIOD (min)	PERCENTAGE OF DOSE IN SAMPLE	RUNNING TOTAL	PER gm. SAMPLE	PER kg. BODY WT.
10 - 0	.31	.31	1.46	.70
0 - 10	2.82	3.12	6.92	6.48
10 - 20	4.88	8.00	13.28	11.22
20 - 30	5.99	14.00	14.80	13.78
30 - 40	5.37	19.36	17.94	12.34
40 - 50	5.35	24.71	17.57	12.30
50 - 60	5.48	30.19	19.45	12.60
60 - 70	3.36	33.56	12.35	7.73
70 - 80	3.24	36.79	12.20	7.44
80 - 90	2.77	39.56	10.72	6.37

TABLE 8

INTRAVENOUS IOP RAT STUDY

RAT I.D. : I-6
COMPOUND : IOP
DOSE : 104. umoles/kg
BODY WEIGHT : 406. grams
UMOLES INJECTED : 42.22 umoles
LIVER WEIGHT : 11.98 grams
EXP. LENGTH : 90 minutes

SAMPLE PERIOD (min)	BILE FLOW ml/min	ml/min PER kg b.w.	ml/min PER kg l.w.
-10 - 0 *	---	---	---
0 - 10	.01375	.03386	1.14750
10 - 20	.00867	.02136	.72404
20 - 30	.01077	.02652	.89866
30 - 40	.00977	.02406	.81528
40 - 50	.01161	.02861	.96953
50 - 60	.00904	.02225	.75417
60 - 70	.01072	.02640	.89457
70 - 80	.01018	.02506	.84942
80 - 90	.00977	.02407	.81586

*No sample weight, thus cannot calculate these values

TABLE 8 (continued)

SAMPLE PERIOD (min)	COMPOUND CONC. (umolar)	EXCRETION umoles/min	umoles/min PER kg b.w.	kg l.w.
-10 - 0*	---	---	---	---
0 - 10	1685.8	.022	.054	1.843
10 - 20	8659.4	.075	.185	6.270
20 - 30	10504.9	.113	.279	9.440
30 - 40	9854.3	.096	.237	8.034
40 - 50	9667.6	.112	.277	9.373
50 - 60	7316.4	.066	.163	5.518
60 - 70	7529.1	.081	.199	6.735
70 - 80	7758.9	.079	.194	6.590
80 - 90	9564.6	.093	.230	7.803

*No sample concentrate, thus cannot calculate these values

SAMPLE PERIOD (min)	SAMPLE WEIGHT (grams)	UMOLES IN SAMPLE	UMOLES RUNNING TOTAL
-10 - 0*	---	---	---
0 - 10	.13747	.22	.22
10 - 20	.08674	.75	.97
20 - 30	.10766	1.13	2.10
30 - 40	.09767	.96	3.07
40 - 50	.11615	1.12	4.19
50 - 60	.09035	.66	4.85
60 - 70	.10717	.81	5.66
70 - 80	.10176	.79	6.45
80 - 90	.09774	.93	7.38

*No sample concentration, thus cannot calculate these values

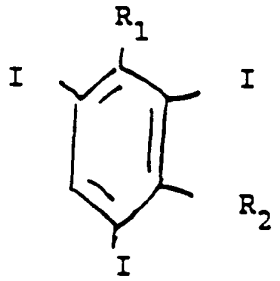
TABLE 8 (continued)

SAMPLE PERIOD (min)	PERCENTAGE OF DOSE IN SAMPLE	RUNNING TOTAL	PER gm. SAMPLE	PER kg. BODY WT.
-10 - 0*	---	---	---	---
0 - 10	.52	.52	3.80	1.29
10 - 20	1.78	2.30	20.51	4.38
20 - 30	2.68	4.98	24.80	6.60
30 - 40	2.28	7.26	23.34	5.61
40 - 50	2.66	9.92	22.90	6.55
50 - 60	1.57	11.48	17.33	3.86
60 - 70	1.91	13.40	17.83	4.71
70 - 80	1.87	15.27	18.38	4.61
80 - 90	2.21	17.48	22.65	5.45

*No sample concentration, thuse cannot calculate these values

What is claimed is:

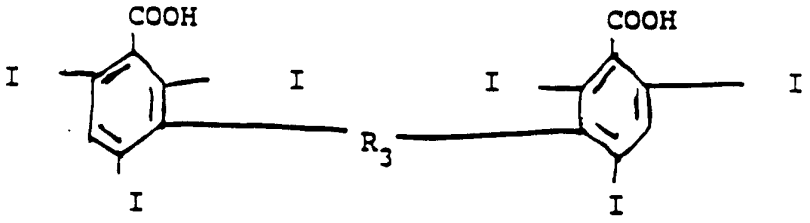
1. A modified organic contrast agent analog, said agent being an oral media having formula I:



and R_1 and R_2 are

	R_1	R_2
Iopanoic acid	$-CH_2CH(CH_2CH_3)COOH$	$-NH_2$
Ipodatic acid	$-CH_2CH_2COOH$	$-N{=}CHN(CH_3)_2$
Tyropanoic acid	$-CH_2CH(CH_2CH_3)COOH$	$-NHCOCH_2CH_2CH_3$
Iocetamic acid	$-NCH_2CH(COCH_3)CH_2COOH$	$-NH_2$
Iopronic acid	$-OCH_2CH_2OCH_2CH(CH_2CH_3)COOH$	$-NHCOCH_3$
Iosumetic acid	$-N(CH_2CH_3)COCH_2CH_2COOH$	$-NHCH_3$

or wherein said analog is an intravenous media having formula II;

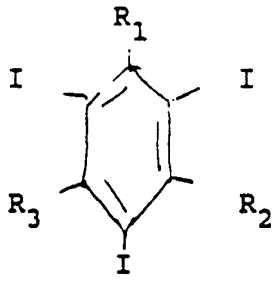


and R_3 is

	R_5
Iodipamide	$-NHCO(CH_2)_4CONH-$
Iogiycamide	$-NHCOCH_2-O-CH_2CONH-$
Iodoxamate	$-NHCO(CH_2CH_2O)_4CH_2CH_2CONH-$
Iotroxamide	$-NHCO(CH_2OCH_2)_2CONH-$
Iosulamide*	$-NHCOCH_2CH_2SO_2CH_2CH_2CONH-$

* $-N(COCH_3)(CH_2CH_3)$ at position 5

or wherein said analog is an urographic media having formula III;



wherein said analog includes a flourine substitution or addition.

2. An analog as set forth in claim 1 wherein said flourine moiety added or substitute is at least one $-CF_3$ moiety.

3. An analog as set forth in claim 2 wherein said agent is N-Triflouroacetyl-iopanoic acid.

4. An analog as set forth in claim 2 wherein said agent is alpha-fluoro-N-trifluoroacetyl-iopanoic acid.

5. A method of making an organic contrast agent analog, said method including the steps of: forming a organic contrast agent analog having the general formulas I, II, or III, and increasing the

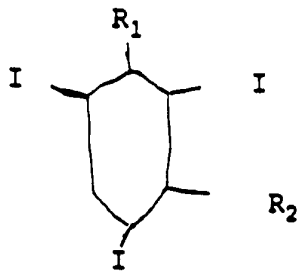
acidity of the agent while increasing the choleretic activity of the agent to render the agent less toxic by adding or substituting fluorine on the agent.

6. A method as set forth in claim 5 wherein said adding or substituting flourine step is further defined as adding or substituting at least one $-CF_3$ on the organic contrast agent analog.

7. A method as set forth in claim 6 wherein the flourinated analog is N-triflouroacetyl-iopanoic acid.

8. A method as set forth in claim 6 wherein the flourinated analog is alpha-flouro-N-triflouracetyl-iopanoic acid.

9. A modified organic contrast agent analog, said agent being an oral media having formula I:



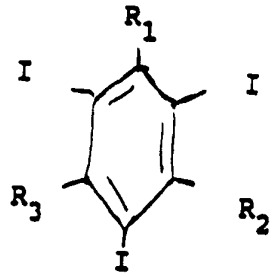
and R_1 and R_2 are

	R_1	R_2
Iopanoic acid	$-CH_2CH(CH_2CH_3)COOH$	$-NH_2$
Ipodatic acid	$-CH_2CH_2COOH$	$-N{=}CHN(CH_3)_2$
Tyropanoic acid	$-CH_2CH(CH_2CH_3)COOH$	$-NHCOCH_2CH_2CH_3$
Iocetamic acid	$-NCH_2CH(COCH_3)CH_2COOH$	$-NH_2$
Iopronic acid	$-OCH_2CH_2OCH_2CH(CH_2CH_3)COOH$	$-NHCOCH_3$
Iosumetic acid	$-N(CH_2CH_3)COCH_2CH_2COOH$	$-NHCH_3$

wherein said analog includes a fluorine substitution of or addition to a carbon or nitrogen moiety on R_1 or R_2.

AMENDED CLAIMS

[received by the International Bureau on 6 April 1993 (06.04.93); original claim 9 cancelled; original claims 2-8 amended; new claims 9- 16 added; other claims unchanged (3 pages)]



wherein said analog includes a fluorine substitution or addition.

2. The analog as set out in claim 1 wherein said fluorine moiety added or substituted is at least one $-COCF_3$ moiety.

3. An analog as set forth in claim 1 wherein said agent is N-trifluoroacetyl-iopanoic acid.

4. An analog as set forth in claim 1 wherein said agent is alpha-fluoro-N-trifluoroacetyl-iopanoic acid.

5. A method of making an organic contrast agent analog, said method including the steps of: forming a organic contrast agent analog having the general formulas I, II, or III, and increasing the acidity of the agent while increasing the choleretic activity of the agent to render the agent less toxic by adding or substituting one or more fluorine containing moieties to R_1, R_2 or R_3 of said general formulas.

6. A method as set forth in claim 5 wherein said adding fluorine step is further defined as adding at least one $-COCF_3$ to R_1, R_2 or R_3 of said general formulas.

7. A method as set forth in claim 5 wherein said organic contrast agent is N-trifluoroacetyl-iopanoic acid.

8. A method as set forth in claim 5 wherein said organic contrast agent is alpha-fluoro-N-trifluoroacetyl-iopanoic acid.

9. A nuclear magnetic resonance or magnetic resonance imaging agent comprising a compound being modified to include one or more $-COCF_3$ moieties producing a single intense resonance resulting in a maximum signal to noise ratio, whereby the resulting compound contains $-COCF_3$ as the only fluorine magnetic resonance producing moiety with the proviso that the modified substituent is not an aromatic ring.

10. A compound as set forth in claim 9 wherein said compound is a bifunctional compound including iodine compounds rendering said compound usable as an x-ray contrast agent as well as a nuclear magnetic imaging agent.

11. An agent as set forth in claim 9 wherein said agent consists essentially of fluorinated iopanoic acid.

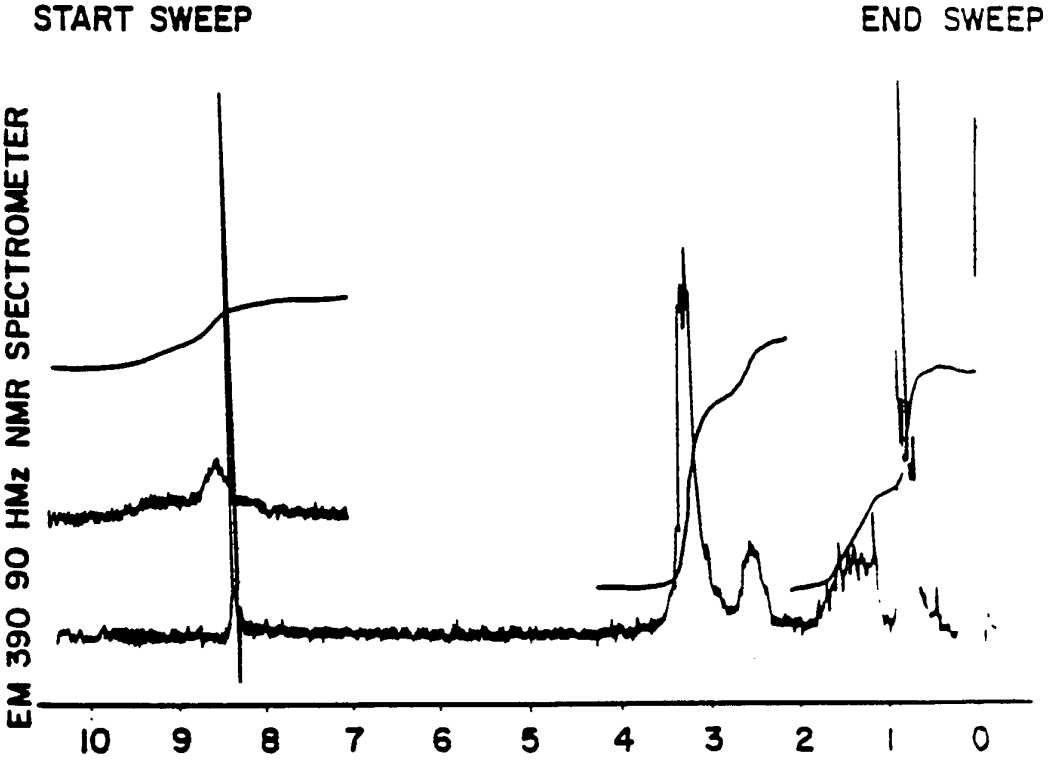
12. An agent as set forth in claim 9 wherein said agent is N-trifluoroacetyl-iopanoic acid.

13. A method of modifying a compound which contains no 19-fluorine to render the compound active as a nuclear magnetic resonance or magnetic resonance imaging agent by adding or substituting one or more $-COCF_3$ moieties to said compound producing a single intense resonance resulting in a maximum signal to noise ratio with the proviso that the modified substituent is not an aromatic ring.

14. A method of imaging an organ in a biological system, said method including the steps of administering the compound of claim 10, concentrating the agent in the organ or system, and radiographically imaging the agent.

15. A method of magnetic resonance imaging comprising: administering the compound of claim 9, and carrying out an MRI examination.

16. A nuclear magnetic resonance or magnetic resonance imaging compound comprising a compound having a sufficient number of iodine atoms to allow the use of said compound in x-ray and at least one $-CF_3$ moiety added or substituted to said compound producing a single intense resonance resulting in a maximum signal to noise ratio.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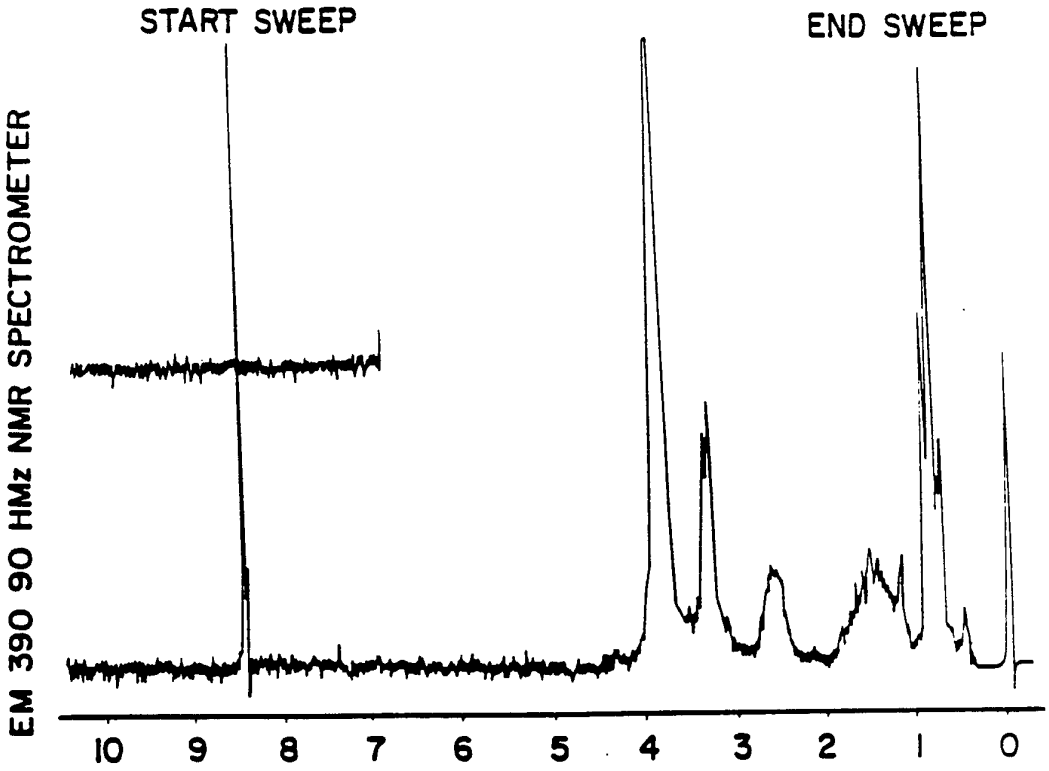
EM 390 90 HMz NMR SPECTROMETER
10
9
8
7
6
5
4
3
2
1
0

Fig. 1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END SWEEP
EM 390 90 HMz NMR SPECTROMETER
10 9 8 7 6 5 4 3 2 1 0

Fig. 2

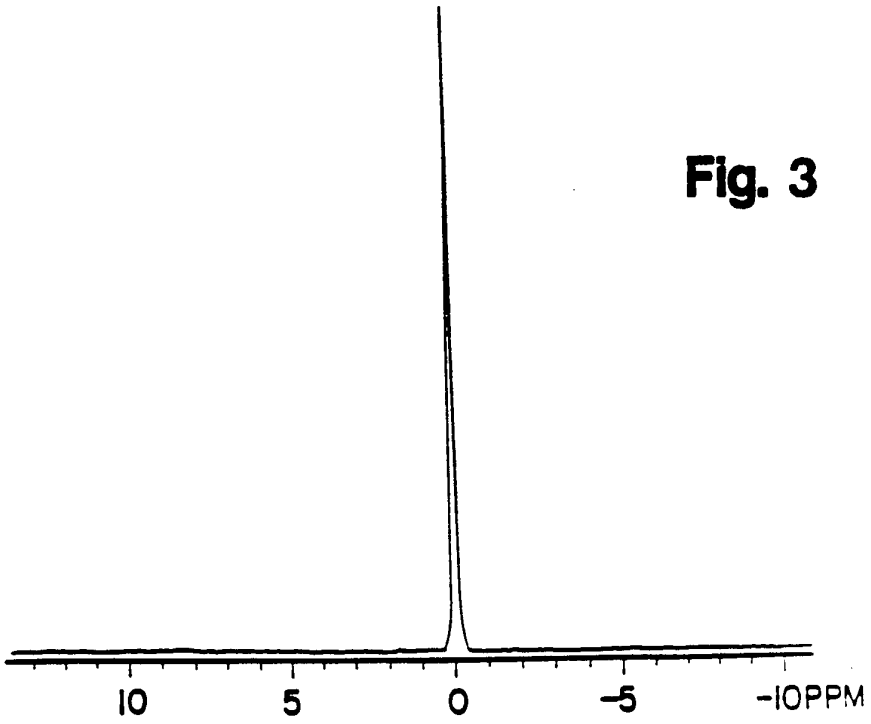
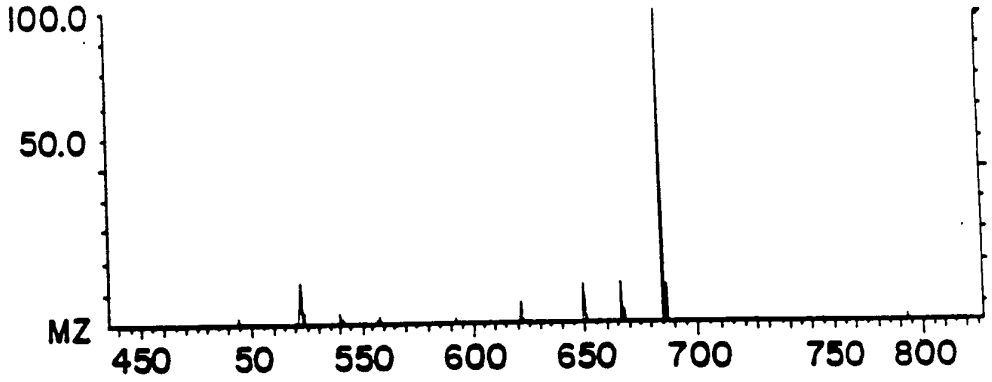

10 5 0 -5 -10PPM

Fig. 3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50.0
MZ
450
50
550
600
650
700
750
800

Fig. 4

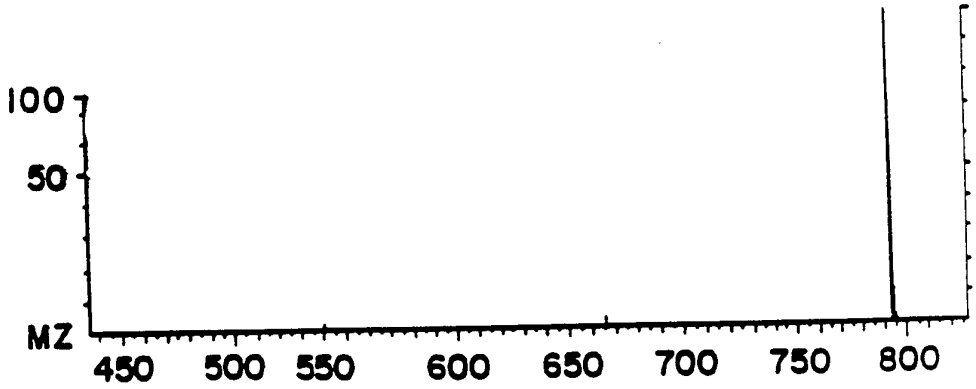
100
50
MZ
450
500
550
600
650
700
750
800

Fig. 5

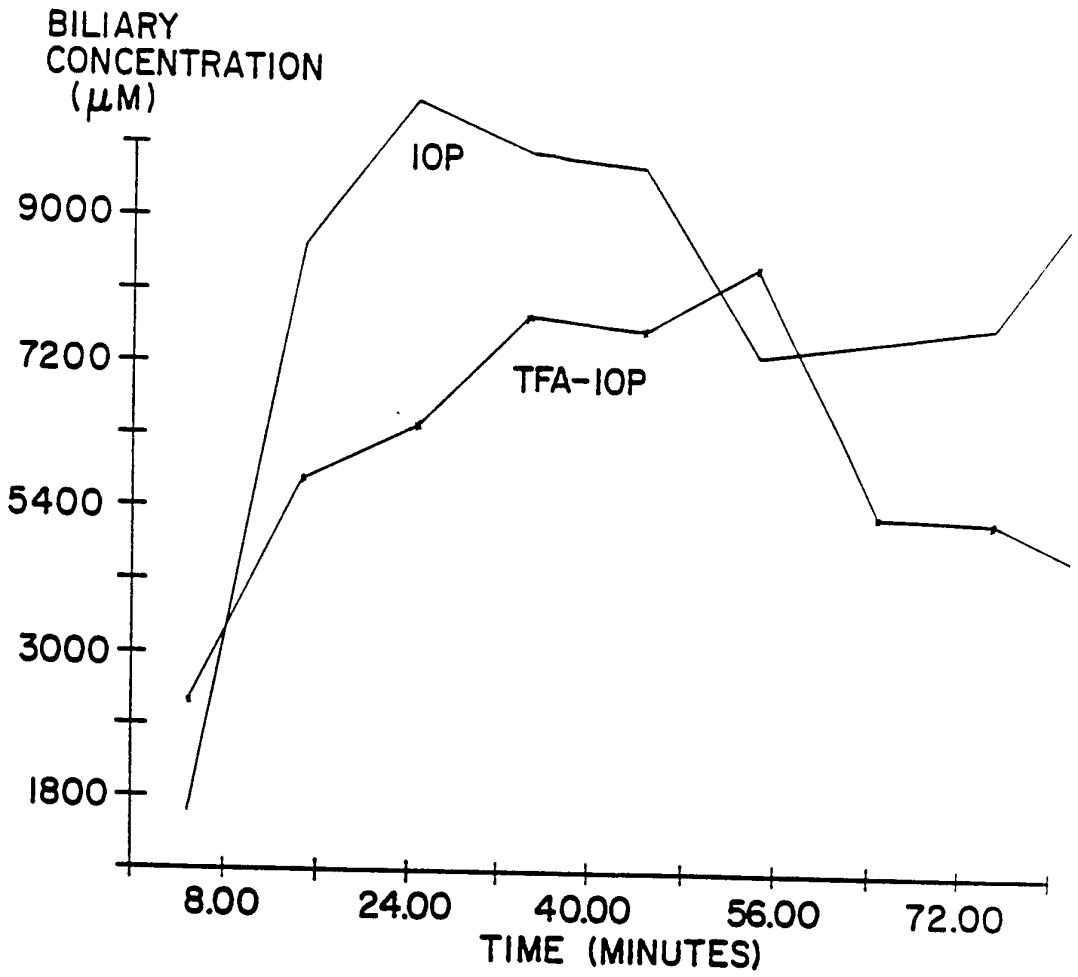
BILIARY
CONCENTRATION
(μM)
9000
7200
5400
3000
1800
IOP
TFA-IOP
8.00
24.00
40.00
56.00
72.00
TIME (MINUTES)

Fig. 6

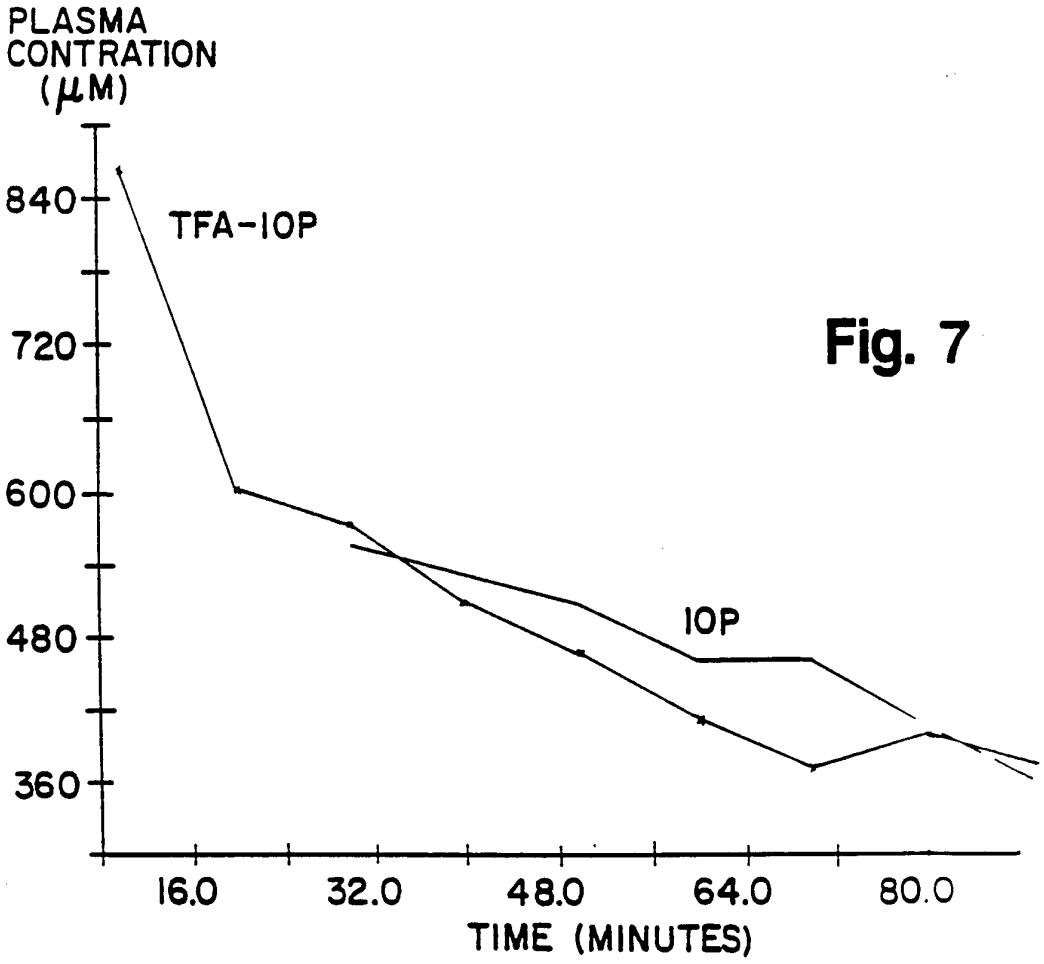
PLASMA
CONTRATION
(μM)
840
720
600
480
360
TFA-IOP
IOP
16.0
32.0
48.0
64.0
80.0
TIME (MINUTES)

Fig. 7

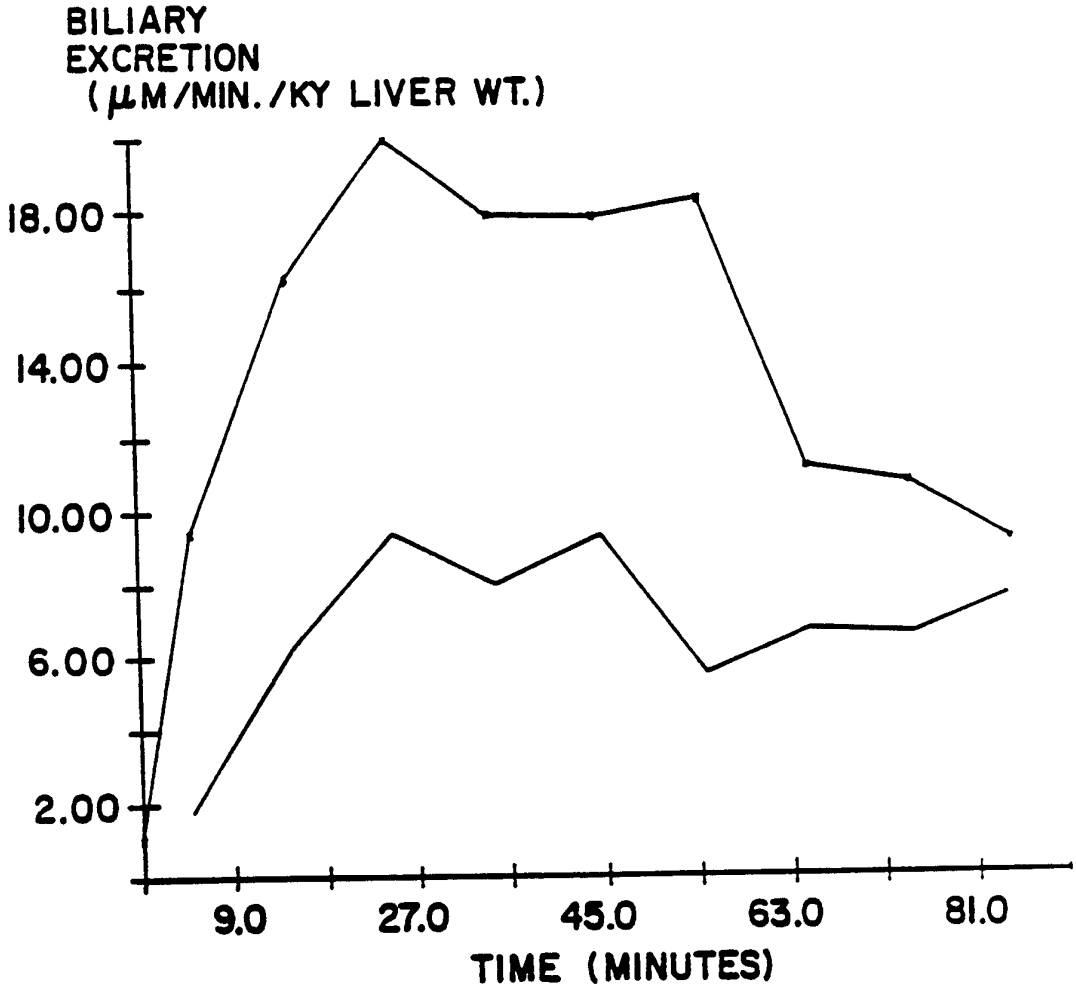
BILIARY
EXCRETION
(μM/MIN./KY LIVER WT.)
18.00
14.00
10.00
6.00
2.00
9.0
27.0
45.0
63.0
81.0
TIME (MINUTES)

Fig. 8

INTERNATIONAL SEARCH REPORT

PCT/US92/07431

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61K 49/04

US CL :424/5

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. :

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US,A, 3,883,578 (GRIES) 13 MAY 1975 See abstract	1-9
A	US,A, 4,125,709 (SMITH) 14 NOVEMBER 1978 See abstract	1-9
A	US,A, 3,446,837 (WALLINGFORD) 27 MAY 1969 See abstract	1-9
A	US,A, 3,842,124 (FELDER) 15 OCTOBER 1974 See abstract	1-9

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be part of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 16 NOVEMBER 1992	Date of mailing of the international search report 01 FEB 1993
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. NOT APPLICABLE	Authorized officer for JAMES H. REAMER Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US92/07431

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US,A, 4,474,747 (DIMO) 02 OCTOBER 1984 See abstract	1-9
A	US,A, 4,395,391 (PFEIFFER) 26 JULY 1983 See abstract	1-9
A	US,A, 4,160,015 (WIEGERT) 03 JULY 1979 See abstract	1-9
A	US,A, 4,132,731 (KLIEGER) 02 JANUARY 1979 See abstract	1-9
A	US,A, 4,094,966 (TILLY) 13 JUNE 1978 See abstract	1-9
A	US,A, 3,856,853 (ACKERMAN) 24 DECEMBER 1974 See abstract	1-9