NEWCASTLE UNIVERSITY

SEMESTER 1 2022/23

MSc Drug Chemistry –Pharmacokinetics, Metabolism and Toxicology

Time allowed – 2 hours

Instructions to Candidates:

(a) Answer BOTH QUESTIONS. Each QUESTION carries equal weight.

(b) Answer each section in a separate answer book, and make sure that any separate answer sheets, including graphs, are secured to the appropriate answer book.

(c) Where questions are subdivided, percentages are given as a guide to the weighting of marks for each section. For questions where this percentage is not given, equal apportioning of marks may be assumed.

(d) In answers to problems and calculations, intermediate steps should be given and, wherever possible, chemical formulae and equations should also be given.

(e) Chemistry Data cards and graph paper are provided. Approved calculators and foreign language dictionaries may be used.

(f) Please do not use red or green pens.

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SECTION A

Pharmacokinetics and Metabolism

Answer this section in a separate book

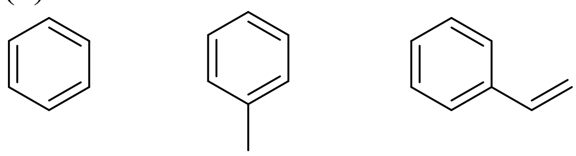
A1. Answer ***BOTH*** parts (a) and (b).

(a) Draw idealised plots of plasma concentration versus time for a drug dosed intravenously and orally.
(b) Define the parameters of clearance, volume of distribution and bioavailability and describe how they are defined from the plots you have drawn.

[30%]

A2. Answer BOTH parts (a) and (b).

(a) Suggest likely products arising from cytochrome P450 (CYP) mediated oxidation of the compounds containing benzene rings such as **1**, benzylic methyl groups as in **2** and alkenes such as in **3**.
(b) Give mechanisms for each of these transformations.



1 **2** **3**

[30%]

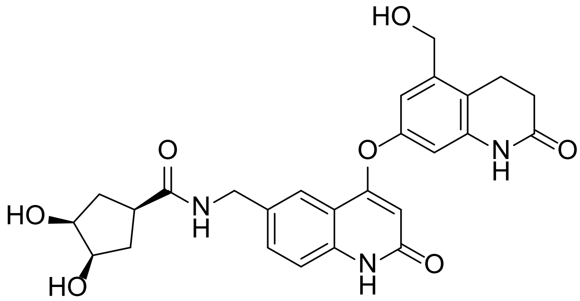
A3. After being dosed orally to a rat, no blood levels of compound **4** were detected.

(a) Describe the reasons why this might be the case.

(b) Identify which of these reasons are most likely (you can choose more than one)?

(c) For each reason you gave, suggest a further experiment or test that could be done to help decide whether that was the cause of the problem.

(d) Can you suggest two structural modifications of compound **4** that would address the problems you have highlighted giving reasons for your decisions.



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[40%]

[continued...

Section B

Toxicology

Answer this section in a separate book

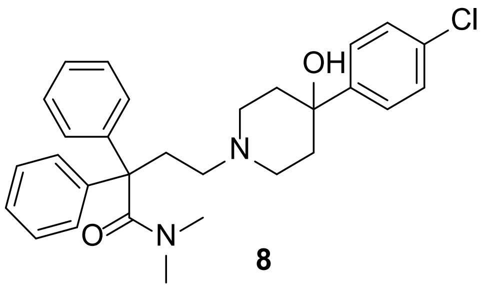
B5. Answer ***ALL*** parts (a), (b) and (c).

(a) Define the terms acute and chronic toxicity and explain the differences between the two.
(b) Define the terms LD_{50} and ED_{50}. Explain how these terms are used to define the therapeutic index and what it means.
(c) Draw a dose / response curve for a compound with an LD50 of 50 mg/kg and a therapeutic index of 5.

[30%]

B6. Describe the structural and physicochemical features of drug molecules that give rise to hERG binding. With reference to your answer, describe why loperamide **8** is a hERG channel blocker.
Suggest two changes to the structure that might reduce its hERG activity, giving reasons for your choices.

[30%]



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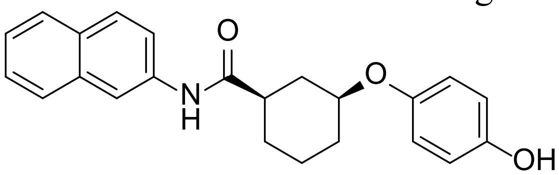
B7 Suggest two reasons why compound **9** might be toxic. For each one, suggest a modification to the structure that might reduce the toxicity.



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[40%

NEWCASTLE UNIVERSITY
School of Chemistry
Data Card

SI UNITS

BASIC		
mass	kilogram	kg
length	metre	m
time	second	s
temperature	kelvin	K
electric current	ampere	A
amount of substance	mole	mol
luminous intensity	candela	cd

DERIVED			
energy	joule	J	$kg\ m^2\ s^{-2} = N\ m = C\ V$
force	newton	N	$kg\ m\ s^{-2} = J\ m^{-1}$
pressure	pascal	Pa	$N\ m^{-2} = J\ m^{-3}$
power	watt	W	$J\ s^{-1} = A\ V$
frequency	hertz	Hz	s^{-1}
magnetic flux density	tesla	T	$kg\ s^{-2}\ A^{-1} = N\ m^{-1}\ A^{-1}$
electric charge	coulomb	C	A s
electric potential	volt	V	$J\ C^{-1} = J\ A^{-1}\ s^{-1}$
electric capacitance	farad	F	$A\ V^{-1}\ s = C^2\ J^{-1}$
electric resistance	ohm	Ω	$V\ A^{-1}$
electric conductance	siemens	S	$\Omega^{-1} = A\ V^{-1}$

FRACTIONS and MULTIPLES

10^{18}	exa	E
10^{15}	peta	P
10^{12}	tera	T
10^{9}	giga	G
10^{6}	mega	M
10^{3}	kilo	K
10^{-1}	deci	d
10^{-2}	centi	c
10^{-3}	milli	m
10^{-6}	micro	μ
10^{-9}	nano	n
10^{-12}	pico	p
10^{-15}	femto	f
10^{-18}	atto	a

CONVERSION FACTORS

1 Å (Ångström)	$= 10^{-10}$ m = 100 pm
1 μ (micron)	= 1 μm = 10^{-6} m
1 litre	= 1 $dm^3 = 10^{-3}\ m^3$
1 calorie	= 4.184 J
1 erg	$= 10^{-7}$ J
1 eV	$= 9.6485 \times 10^4\ J\ mol^{-1}$
1 dyne	$= 10^{-5}$ N
1 atm	= 101325 Pa = 101.325 kN m^{-2} = 760 mmHg
1 bar	$= 10^5\ Pa = 10^5\ N\ m^{-2}$
1 torr	= 1 mmHg = 133.322 Pa
1 debye (D)	$= 3.336 \times 10^{-30}$ C m
1 centipoise (cP)	$= 10^{-3}$ Pa s

PHYSICAL CONSTANTS

charge of proton	e	1.6022×10^{-19} C
rest mass of electron	m_e	9.1094×10^{-31} kg
rest mass of proton	m_p	1.6726×10^{-27} kg
unified atomic mass constant	m_u	1.6605×10^{-27} kg
speed of light in vacuum	c	$2.9979 \times 10^{8}\ m\ s^{-1}$
Planck constant	h	6.6261×10^{-34} J s
$\hbar$	$h/2\pi$	1.0546×10^{-34} J s
Boltzmann constant	k	$1.3807 \times 10^{-23}\ J\ K^{-1}$
Avogadro constant	L or N_A	$6.0221 \times 10^{23}\ mol^{-1}$
gas constant	R	$8.3145\ J\ K^{-1}\ mol^{-1}$
ice-point temperature	T_{ice}	273.15 K
Faraday constant	F	$9.6485 \times 10^{4}\ C\ mol^{-1}$
standard gravitational acceleration	g	$9.80665\ m\ s^{-2}$
permeability of vacuum	μ_0	$4\pi \times 10^{-7}\ kg\ m\ s^{-2}\ A^{-2}$ (or $N\ A^{-2}$)
permittivity of vacuum	ε_0	$\mu_o^{-1}c^{-2} = 8.8542 \times 10^{-12}\ F\ m^{-1}$
Bohr radius	a_0	$\varepsilon_0 h^2/\pi m_e e^2 = 52.9$ pm
Bohr magneton	μ_B	$eh/4\pi m_e = 9.2740 \times 10^{-24}\ A\ m^{-2}$ (or $J\ T^{-1}$)
Rydberg constant	R_∞	$\mu_o^2 m_e e^4 c^3/8h^3 = 1.097373 \times 10^5\ cm^{-1}$
Hartree energy	E_H	$2R_\infty hc = 4.3598 \times 10^{-18}$ J

ENERGY CONVERSION FACTORS

	energy E J	energy E eV	molar energy E_m kJ mol^{-1}	frequency ν Hz	wave number cm^{-1}
J	1	6.2415×10^{18}	6.0221×10^{20}	1.5092×10^{33}	5.0341×10^{22}
eV	1.6022×10^{-19}	1	96.485	2.4180×10^{14}	8.0655×10^{3}
kJ mol^{-1}	1.6605×10^{-21}	1.0364×10^{-2}	1	2.5061×10^{12}	83.594
Hz	6.6261×10^{-34}	4.1357×10^{-15}	3.9903×10^{-13}	1	3.3356×10^{-11}
cm^{-1}	1.9864×10^{-23}	1.2398×10^{-4}	1.1963×10^{-2}	2.9979×10^{10}	1

Revised October 2011//KJI

Periodic Table (incorporating 1991 atomic-weights) scaled to the Relative Atomic Mass $^{12}C = 12$.

1 H 1.008 *b,d*																	2 He 4.003 *b,c*
3 Li 6.941 *c,d,e,g*	4 Be 9.012 *a*											5 B 10.81 *c,d,e*	6 C 12.01 *b,d*	7 N 14.01 *b,c*	8 O 16.00 *b,c,d*	9 F 19.00 *a*	10 Ne 20.18 *c,e*
11 Na 22.99 *a*	12 Mg 24.31 *c,g*											13 Al 26.98 *a*	14 Si 28.09 *d*	15 P 30.97 *a*	16 S 32.07 *d*	17 Cl 35.45 *c*	18 Ar 39.95 *b,c,d,g*
19 K 39.10	20 Ca 40.08 *g*	21 Sc 44.96 *a*	22 Ti 47.88	23 V 50.94 *b,c*	24 Cr 52.00 *c*	25 Mn 54.94 *a*	26 Fe 55.85	27 Co 58.93 *a*	28 Ni 58.69	29 Cu 63 55 *c,d*	30 Zn 65.39	31 Ga 69.72	32 Ge 72.61	33 As 74.92 *a*	34 Se 78.96	35 Br 79.90 *c*	36 Kr 83.80 *e*
37 Rb 85.47 *c*	38 Sr 87.62 *g*	39 Y 88.91 *a*	40 Zr 91.22	41 Nb 92.91 *a*	42 Mo 95 94	43 Tc 98.91 *f*	44 Ru 101.1	45 Rh 102.9 *a*	46 Pd 106.4	47 Ag 107.9 *c*	48 Cd 112.4	49 In 114.8	50 Sn 118.7	51 Sb 121.8	52 Te 127.6	53 I 126.9 *a*	54 Xe 131.3 *e*
55 Cs 132.9 *a*	56 Ba 137.3	57 La 138.9 *b*	72 Hf 178.5	73 Ta 180.9 *b*	74 W 183.8	75 Re 186 2 *c*	76 Os 190.2 *g*	77 Ir 192.2	78 Pt 195 1	79 Au 197.0 *a*	80 Hg 200.6	81 Tl 204 4	82 Pb 207.2 *d,g*	83 Bi 209.0 *a*	84 Po 210.0	85 At 210.0	86 Rn 222.0
87 Fr 223.0	88 Ra 226.0 *a,f,g*	89 Ac 227.0															
				58 Ce 140.1	59 Pr 140.9 *a*	60 Nd 144 2	61 Pm 144.9	62 Sm 150.4	63 Eu 152.0	64 Gd 157.3	65 Tb 158.9 *a*	66 Dy 162.5	67 Ho 164.9 *a*	68 Er 167.3	69 Tm 168.9 *a*	70 Yb 173.0	71 Lu 175.0
				90 Th 232.0 *a,f,g*	91 Pa 231.0 *a,f*	92 U 238 0 *b,c,e,g*	93 Np 237.0 *b,f*	94 Pu 239.1	95 Am 243.1	96 Cm 247.1	97 Bk 247.1	98 Cf 252.1	99 Es 252.1	100 Fm 257.1	101 Md 256.1	102 No 259.1	103 Lr 260.1

Footnotes:

a Mononuclidic element.
b Element with one predominant isotope (about 99-100 per cent abundance).
c Element for which the atomic weight is based on calibrated measurements.
d Element for which variation in isotopic abundance in terrestrial samples limits the precision of the atomic weight given.
e Element for which users are cautioned against the possibility of large variations in atomic weight due to inadvertent or undisclosed artificial isotopic separation in commercially available materials.
f Most commonly available long-lived isotope.
g In some geological specimens this element has a highly anomolous isotopic composition corresponding to an atomic weight significantly different from that given.

TABLE OF NATURAL ABUNDANCES AND NUCLEAR SPIN QUANTUM NUMBERS FOR SELECTED ISOTOPES.

	%	*I*		%	*I*		%	*I*		%	I		%	I
^{1}H	99.985	1/2	^{30}Si	3.10	0	^{73}Ge	7.8	9/2	^{121}Sb	57.3	5/2	^{171}Yb	14.3	1/2
^{2}H	0.015	1	^{31}P	100.	1/2	^{75}As	100.	3/2	^{123}Sb	42.7	7/2	^{173}Yb	16.12	5/2
^{4}He	100.	0	^{32}S	95.0	0	^{77}Se	7.6	1/2	^{123}Te	0.91	1/2	^{175}Lu	97.41	7/2
^{6}Li	7.50	1	^{33}S	0.75	3/2	^{79}Br	50.69	3/2	^{125}Te	7.14	1/2	^{176}Lu	2.59	7
^{7}Li	92.50	3/2	^{34}S	4.21	0	^{81}Br	49.31	3/2	^{127}I	100.	5/2	^{177}Hf	18.61	7/2
^{9}Be	100.	3/2	^{35}Cl	75.77	3/2	^{83}Kr	11.55	9/2	^{129}Xe	26.4	1/2	^{179}Hf	13.63	9/2
^{10}B	19.9	3	^{37}Cl	24.23	3/2	^{85}Rb	72.17	5/2	^{131}Xe	21.2	3/2	^{181}Ta	99.988	7/2
^{11}B	80.1	3/2	^{36}Ar	0.337	0	^{87}Rb	27.84	3/2	^{133}Cs	100.	7/2	^{183}W	14.3	1/2
^{12}C	98.90	0	^{40}Ar	99.60	0	^{87}Sr	7.00	9/2	^{135}Ba	6.59	3/2	^{185}Re	37.40	5/2
^{13}C	1.10	1/2	^{39}K	93.3	3/2	^{89}Y	100.	1/2	^{137}Ba	11.23	3/2	^{187}Re	62.60	5/2
^{14}N	99.63	1	^{41}K	6.73	3/2	^{91}Zr	11.22	5/2	^{139}La	99.91	7/2	^{187}Os	1.6	1/2
^{15}N	0.37	1/2	^{43}Ca	0.135	7/2	^{93}Nb	100.	9/2	^{141}Pr	100.	5/2	^{189}Os	16.1	3/2
^{16}O	99.762	0	^{45}Sc	100.	7/2	^{95}Mo	15.92	5/2	^{143}Nd	12.18	7/2	^{191}Ir	37.3	3/2
^{17}O	0.038	5/2	^{47}Ti	7.3	5/2	^{97}Mo	9.55	5/2	^{145}Nd	8.30	7/2	^{193}Ir	62.7	3/2
^{18}O	0.200	0	^{49}Ti	5.5	7/2	^{99}Ru	12.7	5/2	^{147}Sm	15.0	7/2	^{195}Pt	33.8	1/2
^{19}F	100.	1/2	^{51}V	99.75	7/2	^{101}Ru	17.0	5/2	^{149}Sm	13.8	7/2	^{197}Au	100.	3/2
^{20}Ne	90.48	0	^{53}Cr	9.50	3/2	^{103}Rh	100.	1/2	^{151}Eu	47.8	5/2	^{199}Hg	16.84	1/2
^{21}Ne	0.27	3/2	^{55}Mn	100.	5/2	^{105}Pd	22.33	5/2	^{153}Eu	52.2	5/2	^{201}Hg	13.22	3/2
^{22}Ne	9.25	0	^{57}Fe	2.2	1/2	^{107}Ag	51.84	1/2	^{155}Gd	14.8	3/2	^{203}Tl	29.52	1/2
^{23}Na	100.	3/2	^{59}Co	100.	7/2	^{109}Ag	48.16	1/2	^{157}Gd	15.65	3/2	^{205}Tl	70.48	1/2
^{24}Mg	78.99	0	^{61}Ni	1.13	3/2	^{111}Cd	12.80	1/2	^{159}Tb	100.	3/2	^{207}Pb	22.1	1/2
^{25}Mg	10.00	5/2	^{63}Cu	69.17	3/2	^{113}Cd	12.22	1/2	^{161}Dy	18.9	5/2	^{209}Bi	100.	9/2
^{26}Mg	11.01	0	^{65}Cu	30.83	3/2	^{113}In	4.3	9/2	^{163}Dy	24.9	5/2			
^{27}Al	100.	5/2	^{67}Zn	4.1	5/2	^{115}In	95.7	9/2	^{165}Ho	100.	7/2			
^{28}Si	92.23	0	^{69}Ga	60.1	3/2	^{117}Sn	7.68	1/2	^{167}Er	22.95	7/2			
^{29}Si	4.67	1/2	^{71}Ga	39.9	3/2	^{119}Sn	8.58	1/2	^{169}Tm	100.	1/2			