Eur J Med Chem (1992) 27, 207–217
© Elsevier, Paris

Inotropic 2-arylimidazol[1,2-*a*]pyrimidines

P Barraclough[1]*, JW Black**, D Cambridge[2], E Capon[1], MR Cox[1], D Firmin[3]
VP Gerskowitch[2]**, H Giles[2], RC Glen[3], AP Hill[3], RAD Hull[2]**,
R Iyer[1], D Kettle[1], WR King[1], MS Nobbs[1], P Randall [2]**, P Skone[1],
S Smith[1], SJ Vine[1], CJ Wharton[1], MV Whiting [2]

[1]*Department of Medicinal Chemistry;*
[2]*Department of Pharmacology;*
[3]*Department of Physical Sciences, Wellcome Research Laboratories, Langley Court, Beckenham, Kent, BR3 3BS, UK*

(Received 24 June 1991; accepted 3 October 1991)

Summary — A series of 2-arylimidazo[1,2-*a*]pyrimidines has been prepared and evaluated for inotropic activity. Three of these heterocycles, ether **19**, sulphide **21** and mesylate **24** displayed more potent inotropic effects *in vitro* than isomazole. The *in vivo* inotropic potencies of 4'-mesylate **24** and 4'-carboxamido analogue **23** were similar to those of isomazole and sulmazole respectively. The effects of some 'A' and 'C' ring substituents on the inotropic activities of the imidazo[1,2-*a*]pyrimidines were different from those on the imidazopyridines. Nevertheless the inotropic potencies of several imidazo[1,2-*a*]pyrimidines were closer to those of their 1*H*-imidazo[4,5-*b*]pyridine isomers than to those of the corresponding isomazole analogues. Structure–activity relationships are discussed in detail.

cardiotonics / inotropes / imidazopyrimidine / sulmazole / isomazole

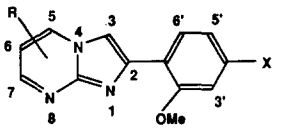
Introduction

There is currently a medical need for drugs which improve the mortality and quality of life of patients suffering from heart failure but which lack the problems associated with digoxin. Attempts to meet this need have led to the development of several new inotropic agents [1] such as sulmazole **1** [2] and isomazole **10** [3]. The potent inotropic activities displayed by sulmazole and isomazole stimulated us to investigate the structure–activity relationships of these agents. Previous studies have shown that the imidazopyridines **2**, **4**, **11** [4, 5], **13–15** [6], and **16**, **17** [7] all display potent *in vitro* inotropic properties (pA_{50} 4.50 ± 0.6; table III). Thus, although replacement of the 4'-methylsulphinyl group of sulmazole or isomazole by methoxy, methylsulphonyl, cyano, carboxamido, mesylamino or mesyloxy substituents results in only modest changes of inotropic activity *in vitro*, more pronounced changes (some desirable) of *in vivo* inotropic effects are observed. In addition, an investigation [8] of 'A' ring substituted sulmazole analogues demonstrated that analogue **5** is more potent as an inotrope *in vivo* than sulmazole whereas amine **6** displays inotropic effects *in vitro* approximately equipotent to those of sulmazole. Compounds **8** and **9**, however, proved to be much weaker inotropic agents than sulmazole.

The effects of replacing the imidazopyridine ring of sulmazole by other (6,5)-fused imidazoles have also been investigated [4, 9]. Heterocycles, which are unprotonated at physiological pH and possess an electron-rich imidazo 'B' ring nitrogen atom, are commonly found to display potent inotropic effects [9]. For a subset of active analogues a correlation between *in vitro* inotropism and the electron-density of the 'B' ring imidazo nitrogen was also observed. In view of these results we speculated that an imidazo[1,2-*a*]pyrimidine moiety would be a good bioisostere for the 1*H*-imidazo[4,5-*b*]pyridine and 1*H*-imidazo[4,5-*c*]pyridine ring systems of sulmazole and isomazole. These 3 heterocyclic systems are unprotonated [10, 11] at physiological pH and, on the basis of CNDO/2 calculations [9], should possess electron-rich

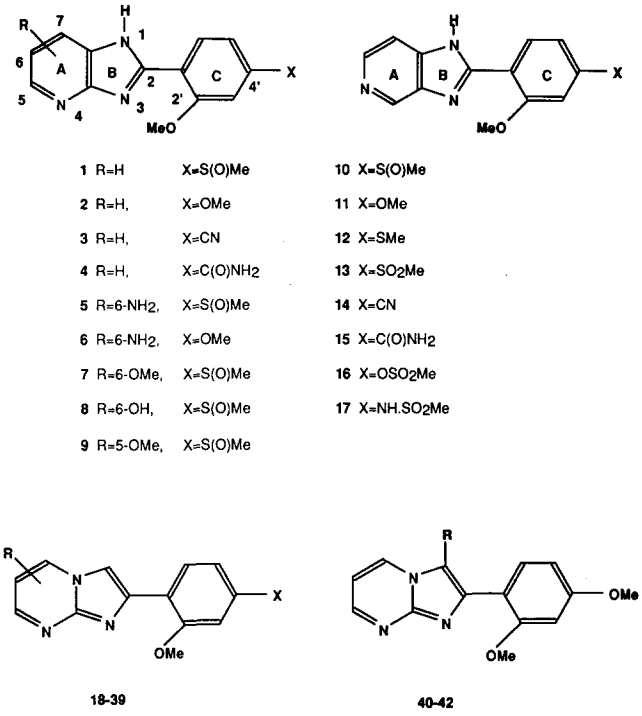
*Correspondence and reprints
**_Present address:_ The James Black Foundation, King's College School of Medicine and Dentistry, 68 Half Moon Lane, Dulwich, London, SE24 9 JE, UK

Table I. Preparation and properties of 2-arylimidazo[1,2-*a*]pyrimidines.



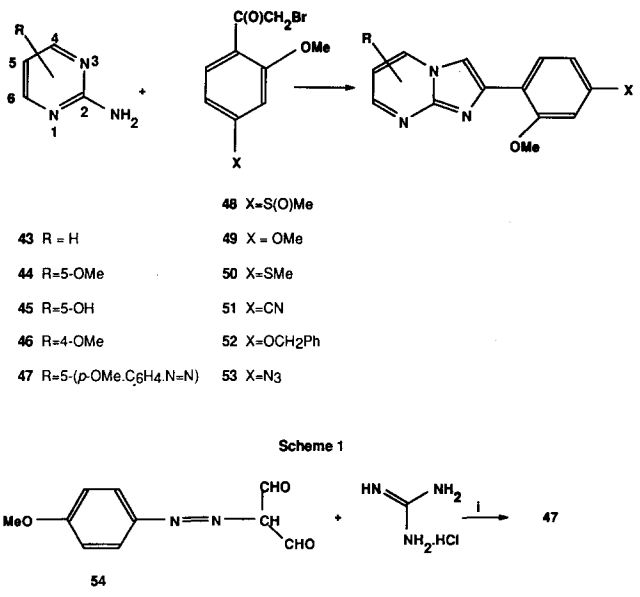
No	*R*	*X*	*Method* [a] *intermediates*	*Yield (%)*	*Formula*	*mp °C*	*Anal*
18	H	S(O)Me	A; **43**, **48**	36	$C_{14}H_{13}N_3O_2S$	235–243 dec	C, H, N, S
19	H	OMe	A; **43**, **49**	52	$C_{14}H_{13}N_3O_2$·HCl·1.25H_2O	263–265 dec	C, H, Cl, N
20	H	SO_2Me	I; **21**	15	$C_{14}H_{13}N_3O_3S$·HCl·0.75H_2O	252–255 dec	C, H, Cl, N, S
21	H	SMe	A; **43**, **50**	65	$C_{14}H_{13}N_3OS$·HCl·0.6H_2O	225–230 dec	C, H, Cl, N
22	H	CN	A; **43**, **51**	35	$C_{14}H_{10}N_4O$·HCl·1.25H_2O	264–266 dec	C, H, Cl, N
23	H	$C(O)NH_2$	J; **22**	40	$C_{14}H_{12}N_4O_2$·0.9HCl·0.75H_2O	255–257	C, H, Cl, N
24	H	OSO_2Me	E; **31**	38[c]	$C_{14}H_{13}N_3O_4S$·HCl	244–246 dec	C, H, N
25	H	$NH{\cdot}SO_2Me$	G; **33**	46	$C_{14}H_{14}N_4O_3S$·HCl	260–263	C, H, N
26[f]	6-OMe	S(O)Me	C; **35**	70	$C_{15}H_{15}N_3O_3S$	219–220	C, H, N
27	6-OH	S(O)Me	A; **45**, **48**	8	$C_{14}H_{13}N_3O_3S$·HCl·0.6H_2O	222–226 dec	C, H, Cl, S, N
28	7-OMe	S(O)Me	C; **36**	64[c]	$C_{15}H_{15}N_3O_3S$·HCl·0.75H_2O	234–235	C, H, N
29	6-NH_2	OMe	H; **37**	24	$C_{14}H_{14}N_4O_2$·HCl·1.25H_2O	275–278 dec	C, H, Cl, N
30	6-NH_2	S(O)Me	H; **38**	26[e]	$C_{14}H_{14}N_4O_2S$	219–221 dec	C, H, N
31[b]	H	OH	D; **32**	88	$C_{13}H_{11}N_3O_2$		
32[d]	H	OCH_2Ph	A; **43**, **52**	30	$C_{20}H_{17}N_3O_2$·HBr	235–237 dec	C, H, N
33	H	NH_2	F; **34**	67	$C_{13}H_{12}N_4O$	224 dec	C, H, N
34[d,f]	H	N_3	A; **43**, **53**	36	$C_{13}H_{10}N_6O$·HBr	181 dec	C, H, N
35	6-OMe	SMe	A. **44**, **50**	40	$C_{15}H_{15}N_3O_2S$	217–218 dec	C, H, N
36[b]	7-OMe	SMe	A; **46**, **50**	44	$C_{15}H_{15}N_3O_2S$		
37	6-(*p*-OMe·$C_6H_4N_2$)	OMe	B; **47**, **49**	26	$C_{21}H_{19}N_5O_3$	233–235	C, H, N
38[f]	6-(*p*-OMe·$C_6H_4N_2$)	S(O)Me	C; **39**	82	$C_{21}H_{19}N_5O_3S$	232–234	C, H, N
39	6-(*p*-OMe·$C_6H_4N_2$)	SMe	B; **47**, **50**	35	$C_{21}H_{19}N_5O_2S$·0.5H_2O	206–209	C, H, N

[a]Method A, R $C_4H_2N_2(NH_2)$, $X(OMe)C_6H_3{\cdot}CO{\cdot}CH_2Br$, EtOH, 80°C; method B, R $C_4H_2N_2(NH_2)$, $X(OMe)C_6H_3{\cdot}CO{\cdot}CH_2Br$, DMF, 80°C, N_2; method C, oxidation of sulphide to sulphoxide with MCPBA; method D, debenzylation with thioanisole–TFA; method E, mesylation of substituted phenol with mesyl chloride–pyridine; method F, reduction with H_2, Pd-C, NEt_3; method G, mesylation of amine with mesyl chloride–pyridine; method H, hydrogenolysis with H_2, Pd-C, NH_3–EtOH; method I, oxidation of sulphide to sulphone with > 2 equiv MCPBA at 25°C overnight; method J, nitrile hydrolysis with conc H_2SO_4. [b]This intermediate was used *in situ* without purification, estimated yield given. [c]Precursor not purified; estimated yield given. [d]This compound crystallised out from the reaction mixture, so no workup was required. [e]Hydrogenolysis carried out under 10 atm pressure of hydrogen overnight. [f]^{1}H NMR data **26** (90 MHz, $CDCl_3$) δ = 2.78 (3H, s, SMe), 3.88 (3H, s, OMe), 4.08 (3H, s, OMe), 7.16 (1H, dd, *J* = 1.5, 8 Hz, H5'), 7.46 (1H, d, *J* = 1.5 Hz, H3'), 7.92 (1H, d, *J* = 3 Hz, H7), 8.14 (1H, s, H3), 8.39 (1H, d, *J* = 3 Hz, H5), 8.64 (1H, d, *J* = 8 Hz, H6'). **34** [90 MHz, $(CD_3)_2SO$] δ = 4.04 (3H, s, OMe) 6.95–7.05 (2H, m, H3', H5'), 7.53 (1H, dd, *J* = 6.7, 4.5 Hz, H6), 8.10 (1H, d, *J* = 8.8 Hz, H6'), 8.63 (1H, s, H3), 8.90 (1H, dd, *J* = 4.5, 1.9 Hz, H7), 9.24 (1H, dd, *J* = 6.7, 1.9 Hz, H5). **38** ^{1}H NMR [90 MHz, $(CD_3)_2SO$] δ = 2.83 (3H, s, SMe), 3.88 (3H, s, OMe), 4.10 (3H, s, OMe), 7.16 (2H, d, *J* = 9 Hz, 1/2 of AB system, aromatics), 7.35–7.45 (2H, m, H3', H5'), 7.91 (2H, d, *J* = 9 Hz 1/2 of AB system, aromatics), 8.49 (1H, d, *J* = 8 Hz, H6'), 8.58 (1H, s, H3), 9.07 (1H, d, *J* = 3 Hz, H7), 9.59 (1H, d, *J* = 3 Hz, H5).

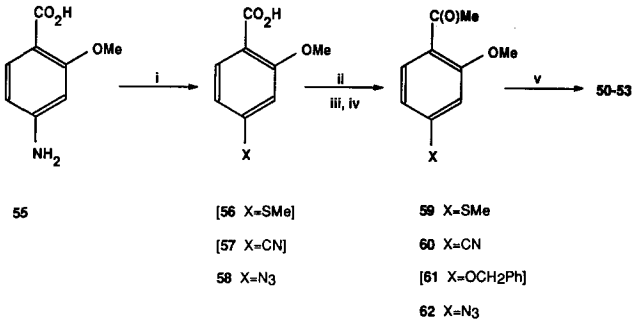


Scheme 1.

imidazo nitrogen atoms. We reasoned therefore that if the above correlation also applied to imidazo[1,2-*a*]pyrimidine sulmazole analogues these heterocycles



Scheme 2. Reagents: (i) NaOEt, EtOH, 80°C



Reagents: (i) $NaNO_2$, 0°, NaN_3 or MeSH (ii) $SOCl_2$ (iii) $CH_2(CO_2SiMe_3)_2$, BuLi (iv) H+, Δ (v) pyrrolidone hydrotribromide or $CuBr_2$

Scheme 3.

may also be potent inotropic agents *in vitro*. In particular, analogues **18–30** were selected for evaluation so that we could test this hypothesis and also determine whether 'A' and 'C' ring substituent effects would be similar to those for the imidazopyridines. Heterocycles **40** and **41** were also chosen for study to enable the effects of 2 electron-releasing 'B' ring substituents to be elucidated.

Results and discussion

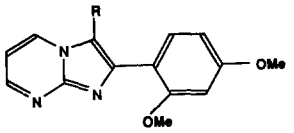
Chemistry

The 2-arylimidazo[1,2-*a*]pyrimidines required **18–39** (table I) were prepared *via* condensation of the appropriate 2-aminopyrimidines with the requisite 2-bromoacetophenones (scheme 1). The aminopyrimidines **44** [12] and **46** [13, 14] were obtained by known methods. Demethylation of the ether **44** with boron tribromide gave 2-amino-5-hydroxypyrimidine **45**, and the protected amine **47** was prepared by condensation of the malondialdehyde **54** [15, 16] with guanidine (scheme 2). Of the 2-bromoacetophenones required, bromides **50–53** were synthesized by the route shown in scheme 3. The intermediate acids **55** [17, 18], **56** [9], **57** [19], and the ketone **61** [20] were prepared as previously described.

The condensation of **46** and **50** was found to be regioselective, the sole product **36** being that derived from quaternisation of **46** at N-1. The structure of sulphide **36** was inferred from the NMR spectrum of the corresponding sulphoxide, which was found to be the 7-methoxy compound **28** rather than the 5-methoxy isomer. The assignment to **28** was confirmed by 2-D NOE experiments (enhancement between H-3 and H-5).

The syntheses of the 6-amino analogues **29** and **30** proved to be problematical. After several unsuccessful attempts to prepare these amines, involving putative

Table II. Preparation and properties of 3-substituted-2-aryl imidazo[1,2-*a*]pyrimidines.



No	*R*	*Method*[a] *intermediates*	*Yield (%)*	*Formula*	*mp (°C)*	*Anal*
40	OH	K; **49** AMPO	4	$C_{14}H_{13}N_3O_3$·HCl·0.2H_2O	225–228 dec	C, H, Cl, N
41	NH_2	L; **42**	24	$C_{14}H_{14}N_4O_2$·HCl	> 200 dec	C, H, Cl, N
42	NO	M. **19**	82	$C_{14}H_{12}N_4O_3$	203–205	C, H, N

[a]Method K, condensation of 2-aminopyrimidine-1-oxide (AMPO) and **49** in DMF at 80°C under N_2; method L, reduction of **42** with H_2, Pd–C, MeOH. Method M, nitrosation with $NaNO_2$, HOAc, 2°C.

Table III. Inotropic activities of 2-arylmidazo[1,2-*a*]pyrimidines and isomazole analogues.

Compound	*Inotropism*		*Compound*	*Inotropism*	
	in vitro pA_{50}[a]	*in vivo* ED_{50}[b] *(mg kg^{-1})*		*in vitro* pA_{50}	*in vivo* ED_{50}
Sulmazole	4.70 ± 0.10(9)	0.80	**18**	4.63 ± 0.09(5)	2.4
2	5.08 ± 0.09(5)	0.91	**19**	5.10 ± 0.06(4)	
3	insoluble		**20**	4.33 ± 0.07(3)	
4	4.26 ± 0.06(3)		**21**	5.27 ± 0.07(3)	
5	4.01 ± 0.07(3)	0.50	**22**	4.30 ± 0.35(2)	0.35
6	4.80 ± 0.03(3)		**23**	4.20 ± 0.29(3)	0.65
7	3.63 ± 0.02(3)		**24**	5.0 ± 0.15(5)	0.04
8	3.75 ± 0.09(3)		**25**	4.18 ± 0.09(3)	0.4
9	3.00 ± 0.12(3)		**26**	3.24 ± 0.12(3)	
Isomazole	4.64 ± 0.15(17)	0.06	**27**	3.38 ± 0.23(3)	
11	4.01 ± 0.09(9)	0.12	**28**	3.33 ± 0.08(3)	
12	Insoluble		**29**	3.71 ± 0.08(3)	
13	4.40 ± 0.26(3)	0.029	**30**	3.80 ± 0.22(4)	
14	< 6[c]	0.014	**40**	Inactive[d,e]	
15	4.43 ± 0.08(3)	0.014	**41**	3.43 ± 0.13(3)	
16	< 5[c]	0.002			
17	4.50 ± 0.09(3)	0.01			

[a]Parameter of *in vitro* inotropic activity determined in (*n*) isolated paced guinea pig papillary muscle preparations. pA_{50} is the negative logarithm of the drug concentration required to produce a 50% increase in contractile force above the basal value. [b]*In vivo* inotropic effects were determined in anaesthetised open-chest dogs. Inotropic responses were indexed by an ED_{50} value *ie* the dose (mg kg^{-1}) of drug, given as a single bolus (iv) injection, required to produce an increase of 50% in dP/dt_{max}. (dP/dt_{max} is the maximum value of the first time derivative of left ventricular pressure (*P*). [c]Biphasic dose–response curve observed; approximate value given. [d]Classified as inactive; a 50% increase in contractile force was not achieved. [e]Displayed negative inotropic effects at concentrations > 10^{-4} M.

condensations of 5-substituted-2-aminopyrimidines with either bromide **49** or **50**, reaction of the pyrimidine **47** with either of these bromides proved to be the key step in obtaining the precursors **37** and **39**. In ethanolic ammonia hydrogenolysis of **37** proceeded rapidly to give the desired 6-amino analogue **29**. Sulphide **39**, similarly prepared, was oxidised to sulphoxide **38**. Deprotection of **38** to the amino compound **30** was very slow under the hydrogenolysis conditions employed. The preparation of some of the target compounds required the modification of 'C' ring substituents in suitable precursors. Standard reaction methods were employed and details are given in table I and in the *Experimental protocols*.

The 3-hydroxy analogue **40** (table II) was prepared by condensation of 2-aminopyrimidine-1-oxide [21, 22] with bromide **49**. Nitrosation of the imidazo[1,2-*a*]pyrimidine **19**, using sodium nitrite and acetic acid gave the 3-nitroso derivative **42** in good yield. The 3-amino derivative **41** was obtained by hydrogenation of **42**.

Pharmacology

Inotropic activity was determined *in vitro* by measuring the changes in the contractility of isolated paced guinea pig papillary muscle preparations, set up under isometric conditions, when the sulmazole analogues were added. Cumulative concentration effect curves were constructed for each test compound. The response parameter chosen was pA_{50}, the negative logarithm of the drug concentration required to give a 50% increase in basal contractile force. Those compounds which displayed significant inotropic effects *in vitro*, were routinely evaluated *in vivo* by determining the effects of giving single bolus (iv) injections to anaesthetised open-chest dogs. Inotropic responses were indexed by a ED_{50} value, *ie* the dose (mg/kg) of drug required to produce an increase of 50% in dP/dt_{max} P is the left ventricular pressure and dP/dt_{max} the maximum value of the first time derivative.

Structure–activity relationships

The inotropic activities of the imidazo[1,2-*a*]pyrimidine and imidazopyridine sulmazole analogues are given in table III. All the imidazo[1,2-*a*]pyrimidines, with the sole exception of analogue **40**, displayed inotropic properties *in vitro*. Of these heterocycles, compounds **18–25** were the most potent inotropic agents *in vitro*, and the ether **19**, the sulphide **21** and the mesylate **24** proved to be more potent than sulmazole or isomazole.

A comparison of the effects of 4'-substituents on the inotropic activities of the imidazo[1,2-*a*]pyrimidines and imidazopyridines revealed some interesting similarities and differences. For the imidazo[1,2-*a*]pyrimidines the ranking order of *in vitro* potencies was found to be 4'-OMe, OMes > S(O)Me > SO_2Me, CN ≥ $C(O)NH_2$, NHMes. This ranking order is similar to that for the 1*H*-imidazo[4,5-*b*]pyridines, 4'-OMe > S(O)Me > $C(O)NH_2$. In addition, the *in vitro* inotropic potencies of each pair of sulphoxides **18** and **1**, ethers **19** and **2**, and carboxamides **23** and **4**, are almost identical. The order of potencies of the 1*H*-imidazo[4,5-*c*]pyridines was different to those above, *ie* 4'-OMes > S(O)Me > NHMes, SO_2Me, $C(O)NH_2$ > OMe. For the 7 pairs of heterocycles, **18** and **10**; **19** and **11**; **20** and **13**; **21** and **12**; **22** and **14**; and **23** and **15**, ethers **19** and **11** show the largest difference in *in vitro* inotropic potencies.

The 'A' ring substituted analogues **26–30** all display lower *in vitro* activities than the unsubstituted compounds **18** and **19**. Comparison of the activities of analogues **19** and **29** shows that introduction of a 6-amino substituent onto the imidazo[1,2-*a*]pyrimidine ring leads to a pronounced fall (Δ pA_{50}–1.4) in *in vitro* inotropic potency. This result differs from observations with the imidazopyridines where introduction of a 6-amino group has little detrimental effect (ΔpA_{50}–0.3) on *in vitro* inotropism, *cf* **2** *vs* **6**. It is also notable that sulphoxide **30** and the 4'-methoxy analogue **29** are approximately equipotent. Again this finding contrasts with the results for the imidazopyridines where the 4'-methoxy analogue **6** is more potent (Δ pA_{50}+0.8) than sulphoxide **5**. For analogues bearing a 4'-sulphoxide moiety, however, introduction of a 6-amino substituent onto the heterocyclic ring gives rise to similar reductions in *in vitro* activity, *eg* Δ pA_{50}–0.7 for **5** *vs* **1**, Δ pA_{50}–0.8 for **30** *vs* **18**. Similarly introduction of a 6- or 7-methoxy substituent produces comparable reductions in potency for both the imidazo[1,2-*a*]-pyrimidine and imidazopyridine series, *eg* ΔpA_{50}–1.1 for **7** *vs* **1**, Δ pA_{50}–1.4 for **26** *vs* **18**, Δ pA_{50}–1.7 for **9** *vs* **1**, Δ pA_{50}–1.3 for **28** *vs* **18**. Overall, 'A' ring substituent effects and inotropic potencies were most similar for the imidazo[1,2-*a*]pyrimidine and 1*H*-imidazo[4,5-*b*]pyridine 4'-sulphoxide analogues. The most potent 'A' ring substituted imidazo[1,2-*a*]-pyrimidine proved to be the 6-amino analogue **30**, this compound being only a little less active than its imidazopyridine isomer **5**.

The 3-hydroxy analogue **40** was found to be inactive, while the 3-amino heterocycle **41** displayed only weak inotropic effects *in vitro*. In the imidazopyridine series methylation at N-1 or N-3 leads to a small reduction in inotropic potencies [9]. Thus for several inotropic sulmazole analogues 'B' ring substituents do not appear to be well tolerated.

Sulmazole, isomazole and sulphoxide **18** are approximately equipotent as inotropic agents *in vitro*.

Table IV. Physicochemical properties of selected analogues.

Compound	*pKa*[a] *BH+*	*log P*[b]	*Charge*[c] *imidazo N*	pA_{50}[d]
Sulmazole	3.91	1.22	–0.266	4.7
Isomazole	6.17	1.23	–0.256	4.6
2	4.63	2.56	–0.282	5.1
5	3.90	0.33	–0.263	4.0
6	–	1.62	–0.276	4.8
11	6.52	2.56	–0.259	4.0
15	–	1.18	–	4.4
18	3.70	0.63	–0.309	4.6
19	4.34	1.94	–0.315	5.1
21	–	2.44	–0.310	5.3
23	–	0.70	–0.323	4.2
24	3.95	1.05	–0.310	5.0
25	4.17	0.72	–0.320	4.2
29	–	1.68	–0.308	3.7
30	–	0.37	–0.303	3.8

[a]Relates to equilibrium between non-ionised heterocycle and monocation, BH^+. p*K*a values (± 0.01–0.04) were determined in aqueous solution at 25°C. Further details are given in [11]. [b]*P* = Octanol–aqueous phosphate buffer partition coefficient at 25°C and pH 7.4. Experimental values are reproducible within ± 0.02, by shake-flask and filter chamber techniques [26]. [c]Calculated by CNDO/2. [d]Approximate pA_{50} value for *in vitro* inotropic effects.

Carboxamides **4**, **15** and **23** also display similar *in vitro* inotropic effects. The 4'-methoxy analogue **11**, however, has a lower inotropic potency *in vitro* than its isomers **2** and **19**. The imidazo[1,2-*a*]pyrimidine ring is thus a good bioisostere for the 1*H*-imidazo[4,5-*b*]pyridine nucleus with regard to *in vitro* inotropism. Where differences exist in the effects of substituents on *in vitro* inotropism for the imidazopyridines and imidazo[1,2-*a*]pyrimidines the reasons for these divergent effects are at present not clear. A previous study has demonstrated that the *in vitro* inotropic activities of heterocyclic sulmazole analogues are sensitive to changes in lipophilicity [5, 6] and electron density [8, 9] at the imidazo nitrogen atom. Several of the imidazo[1,2-*a*]pyrimidines described in the present work were found to be more water-soluble and less lipophilic than their imidazopyridine isomers (*eg* log P's of **1** and **18** are 1.22 and 0.63 respectively; table IV). Sulphide **21** and nitrile **22**, for example, unlike imidazopyridines **12** and **3**, were sufficiently soluble to enable a precise determination of their potent *in vitro* inotropic properties. Hence in these cases the differences in inotropic properties primarily reflect differences in water solubility.

It seems unlikely, however, that the differences in 'A' ring substituent effects for the imidazopyridines and imidazo[1,2-*a*]pyrimidines can be explained solely in terms of changes of water solubility or lipophilicity. Thus although analogues **2**, **19**, **21** and **24** have similar *in vitro* inotropic potencies, pA_{50}'s 5.0–5.3, their lipophilicities range from log P 1.1–2.6 (see table IV).

'A' and 'C' ring substituent effects also proved difficult to reconcile with the electronic properties of the heterocycles. No correlation was observed between the *in vitro* inotropic potencies of the imidazo[1,2-*a*]pyrimidines and their calculated [9] imidazo nitrogen charge densities (table IV). This finding contrasts with the correlation between these 2 parameters found for the imidazopyridines [8, 9]. Nevertheless, several of the more potent inotropic imidazo[1,2-*a*]pyrimidines did all have a higher charge density at the imidazo nitrogen atom relative to other members of the series and to the imidazopyridines *eg* CNDO/2 charge densities, q = –0.315 and –0.282 for **19** and **2** respectively. These differences in electronic and physicochemical parameters may be associated with changes in the pharmacological and biochemical mechanisms (*eg* phosphodiesterase inhibition, calcium sensitization) contributing to the overall inotropic effect. These mechanisms are at present poorly understood [9], but large changes in phosphodiesterase III inhibition have been observed between several inotropic imidazopyridines and their isomeric imidazo[1,2*a*]pyrazine derivatives (Barraclough *et al*, unpublished observations).

Conclusions

Cardiovascular profiles after *iv* administration to anaesthetised dogs were determined for selected analogues and compared to those of sulmazole, isomazole and mesylate **16** (see table V). Sulphoxide **18** displayed the weakest inotropic effects and was not studied further. The major effects of compounds **22–25** were a dose-dependent inotropic effect (increase in dP/dt_{max}), a rise in heart rate and a fall in diastolic blood pressure. The mesylate **24** was approximately equipotent as an inotrope with isomazole but the blood pressure-

lowering effects of mesylate **24** were much less pronounced than those of isomazole. However, analogue **24** did not display an increased separation between its inotropism and its effects on heart rate, relative to isomazole. The duration of the inotropic effects of the imidazo[1,2-*a*]pyrimidines were similar (30 ± 15 min) to those of sulmazole. Thus when carboxamide **23**, mesylate **24** and sulmazole were administered to dogs as a single bolus at the E_{50} dose, their inotropic actions persisted for 45, 20 and 30 min respectively. Overall, carboxamide **23** and mesylate **24** were found to display the most interesting cardiovascular profiles *in vivo* of all the new inotropes investigated.

A key finding of the present SAR study is that the imidazo[1,2-*a*]pyrimidine ring is a good bioisostere for the 1*H*-imidazo[4,5-*b*]pyridine moiety of sulmazole with regard to both *in vitro* and *in vivo* inotropism. This conclusion was also reached independently by Spitzer *et al* [23] based apparently on the inotropic activities of 2 compounds, the ethers **2** and **19**. Our investigation has shown that several isomers from these 2 series of heterocycles have similar inotropic potencies but in general the imidazo[1,2-*a*]pyrimidine analogues are less potent as inotropes *in vivo* than the corresponding 1*H*-imidazo[4,5-*c*]pyridine isomers.

A second important conclusion is that both 'A' and 'C' ring substituent effects on inotropic activity were sometimes markedly different for the imidazo[1,2-*a*]pyrimidines and imidazopyridines. These differences may possibly reflect changes in water solubility/lipophilicity, electronic properties or pharmacological mechanisms but further investigations are required before any conclusions may be drawn. Unlike some 'A' ring substituted 1*H* imidazo[4,5-*b*]pyridines the isomeric imidazo[1,2-*a*]pyrimidines show poorer inotropic properties than the unsubstituted analogues. The potent inotropic properties of the imidazo[1,2-*a*]pyrimidines **18–25** led us to investigate other diazaindolizine bioisosteres for the imidazopyridines and associated substituent effects. These studies will be reported elsewhere.

Experimental protocols

Chemistry

Melting points are uncorrected. ^{1}H NMR spectra were obtained on Bruker HFX90, AM-200 or WM-360 spectrometers. EI mass spectra were obtained on an AEI MS 902 spectrometer, interfaced to a VG Multispec data system at 70 eV. TLC separations were effected on Merck silica gel $60F_{254}$, gravity column chromatography on Merck silica gel (60–120 mesh) and flash chromatography on Merck silica gel (230–400 mesh). All products were shown to be homogeneous by TLC. Analyses indicated by the symbols of the elements were within ± 0.4 of the theoretical percentage values.

Preparation of aminopyrimidines

*2-Amino-5-hydroxypyrimidine **45***

To a stirred solution of 2-amino-5-methoxypyrimidine **44** [12] (7.50 g, 0.06 mol) in dry benzene (150 ml) boron tribromide (11.5 ml, 0.12 mol) was added dropwise. The mixture was heated at reflux for 6 h, then allowed to stand at room temperature overnight before being evaporated to dryness. The residue was added to ice-water (200 ml) and the resulting solution passed through a column of Amberlyst A21 resin, eluting with more water. Evaporation of the eluates and further purification of the residue by chromatographing on silica, eluting with chloroform–methanol–water (55:45:10), gave 5.60 g (84%) of **45**, mp 205–210°C (dec). ^{1}H NMR [90 MHz, $(CD_3)_2SO$] δ = 5.90(2H, brs, NH_2, exchangeable), 7.85 (2H, s, H4, H6), 8.90 (1H, brs, OH, exchangeable). Anal $C_4H_5N_3O$ (C,H,N).

Table V. *In vivo* cardiovascular effects[a] of sulmazole and analogues. Maximum percentage change in d*P*/dt, diastolic blood pressure and heart rate, produced by selected analogues and the effective dose mg kg^{-1} *iv*) of these compounds to produce an increase of 50% in dP/dt_{max} (ED_{50} d*P*/dt), 30% decrease in diastolic blood pressure (ED_{30} DBP) and 10% increase in heart rate (ED_{10} HR) as compared to those of isomazole and sulmazole in anaesthetised open chest dogs.

Compound	*ED_{50} dP/dt*	*% Max increase (dose, mg kg^{-1})*	*ED_{30} DBP*	*% Max decrease (dose, mg kg^{-1})*	*Ratio (ED_{50} dP/dt: ED_{30} DBP)*	*ED_{10} HR*	*% Max increase (dose mg kg^{-1})*
Sulmazole (n = 4)	0.80	73 (3.0)	1.0	36 (3.0)	0.80	0.50	20 (3)
Isomazole (n = 9)	0.06	88 (0.3)	0.16	43 (1)	0.32	0.056	15 (0.3)
Mesylate **16** (n = 3)	0.002	113 (0.3)	0.003	63 (0.3)	0.67	0.002	21 (0.01)
Nitrile **22** (n = 2)	0.35	88 (3.0)	> 3.0	28 (3.0)	< 0.12	0.37	16 (1.0)
Amide **23** (n = 3)	0.65	92 (3.0)	2.8	32 (3.0)	0.23	0.29	23 (3.0)
Mesylate **24** (n = 3)	0.04	150 (1.0)	> 1.0	29 (1.0)	< 0.04	0.034	30 (1.0)

2-Amino-5-(4-methoxyphenylazo)pyrimidine ***47***
A freshly prepared solution of sodium ethoxide (from sodium (0.78 g, 34 mmol) and ethanol (15 ml)) was added to a stirred mixture of 2-(4-methoxyphenylazo)malondialdehyde **54** [15, 16] (2.50 g, 12.1 mmol), guanidine hydrochloride (2.2 g, 23 mmol) and ethanol (45 ml). The resulting mixture was heated at reflux for 1.5 h and then allowed to stand at room temperature for 2 days. A solid precipitated over this period; it was removed by filtration and washed successively with water, aqueous sodium hydrogen carbonate and water. After drying the solid was washed with methanol and then recrystallised from acetic acid to give 1.98 g (71%) of **47**, mp 248–250°C *m/z* 229(M^+) Anal $C_{11}H_{11}N_5O$ (C,H,N).

Preparation of acetophenones

4-Azido-2-methoxybenzoic acid ***58***
A stirred solution of 4-amino-2-methoxybenzoic acid **55** [17, 18] (16.7 g, 0.10 mol) in aqueous sulphuric acid (200 ml of 11% w/v, 0.22 mol) was cooled to 0°C and treated dropwise over 15 min with a cold solution of sodium nitrite (47.7 g, 0.69 mol) in water (100 ml). The reaction mixture was stirred for 45 min at 0–5°C and then a solution of sodium azide (73.0 g, 1.12 mol) in water (300 ml) was added over 15 min, the temperature being maintained below 10°C by vigorous stirring and external cooling. After re-cooling to 0°C and stirring at this temperature for 45 min the suspension was filtered, yielding a straw-coloured solid. This material was washed with water and recrystallised from ethanol to give 7.9 g (41%) of **58**, mp 151–152°C. ^{1}H NMR [90 MHz, $(CD_3)_2SO$] δ = 3.83(3H, s, OMe), 6.76 (2H, m, H3, H5), 7.74 (1H, d, J = 8 Hz, H6). Anal $C_8H_7N_3O_3$ (C, H, N).

4'-Azido-2'-methoxyacetophenone ***62***
The acid **58** (6.2 g, 0.032 mol) and thionyl chloride (50 ml) were stirred and heated at reflux under dry nitrogen for 1 h. Removal of the excess reagent under reduced pressure and then by azeotroping with benzene gave 4-azido-2-methoxybenzoyl chloride as a pale yellow crystalline solid. Bis-(trimethylsilyl)malonate (16.3 g, 0.066 mol) was added to dry ether (100 ml) and the solution stirred under nitrogen and cooled to –60°C. *n*-Butyllithium (42 ml of 1.55 M solution in hexane, 0.065 mol) was added dropwise for 20 min to the above solution, resulting in the formation of a white precipitate of lithiobis(trimethylsilyl)malonate. This mixture was allowed to warm to 0°C and then a solution of 4-azido-2-methoxybenzoyl chloride (6.90 g, 0.032 mol) in dry tetrahydrofuran (70 ml) was added over 5 min. Stirring was continued at 0–5°C for 1 h and then at room temperature for 2 h. The reaction mixture was shaken with saturated aqueous sodium hydrogen carbonate solution, the organic phase dried over Na_2SO_4 and evaporated. The aqueous phase was acidified to pH 2 with 2 N sulphuric acid and extracted twice with ethyl acetate. These extracts were also dried (Na_2SO_4) and evaporated. The 2 residues were combined, dissolved in dioxan (100 ml), and the resulting solution heated to reflux for 30 min (to decarboxylate the intermediate β-ketoacid). Evaporation of the solvent gave an oil which was dissolved in ethyl acetate, the resulting solution washed with saturated aqueous sodium hydrogen carbonate, and dried over Na_2SO_4. Removal of the solvent and crystallisation of the residue from ethyl acetate–hexane gave 4.1 g (66%) of **62**, mp 51–54°C. ^{1}H NMR (90 MHz, $CDCl_3$) δ = 2.59(3H, s, CMe), 3.91 (3H, s, OMe), 6.54 (1H, d, J = 1.8 Hz, H3'), 6.73 (1H, dd, J = 8.2, 1.8 Hz, H5'), 7.81(1H, d, J = 8.2 Hz, H6'). *m/z* 191 (M^+). Anal $C_9H_9N_3O_2$ (C, H, N).

In a similar manner, 2-methoxy-4-methylthiobenzoic acid **56** [9] was converted in 86% yield to 2'-methoxy-4'-methylthioacetophenone **59** mp 57–59°C. ^{1}H NMR (90 MHz, $CDCl_3$) δ = 2.50(3H, s, Me), 2.57(3H, s, Me), 3.88 (3H, s, OMe), 6.70–6.90 (2H, m, H3', H5'), 7.68(1H, d, J = 8 Hz, H6'). υ_{max} (Nujol) 1652 cm^{-1}. Anal $C_{10}H_{12}O_2S$ (C, H, S).

4-Cyano-2-methoxybenzoic acid **57** [19] was also converted in 72% yield to 4'-cyano-2'-methoxyacetophenone **60**, mp 111–113°C. ^{1}H NMR (200 MHz, $CDCl_3$) 2.63 (3H, s, CMe), 4.00 (3H, s, OMe), 7.54 (2H, m, H3', H5'), 7.67 (1H, d, J = 8.2 Hz, H6') *m/z* 175(M^+). Anal $C_{10}H_9NO_2$ (C, H, N).

Preparation of 2-bromoacetophenones

2-Bromo-4'-benzyloxy-2'-methoxyacetophenone 52
2-Pyrrolidone hydrotribromide (59.0 g, 0.12 mol) was added in portions over 20 min to a stirred solution of 2-pyrrolidone (10.2 g, 0.12 mol) and 4'-benzyloxy-2'-methoxyacetophenone **61** [20] (30.7 g, 0.12 mol) in dry tetrahydrofuran (400 ml) at 50°C. The reaction mixture was heated at reflux for 20 min, cooled in ice, and then filtered. Evaporation of the filtrate gave a syrup which was triturated with aqueous sodium hydrogen carbonate. The resulting waxy solid was collected by filtration, washed with water and dried. This material was chromatographed on silica, eluting with dichloromethane–hexane (1:1) to give 21.4 g (53%) of **52**, mp 94–96°C. *m/z* 334, 336 (M^+). Anal $C_{16}H_{15}BrO_3$ (C, H, Br).

Bromination of ketone **62** in a similar manner gave 71% 2-bromo-4'-azido-2'-methoxyacetophenone, **53** mp 104–106°C (EtOAc–hexane). ^{1}H NMR (90 MHz, $CDCl_3$) δ = 3.95(3H, s, OMe), 4.57 (2H, s, CH_2Br), 6.57 (1H, d, J = 2 Hz, H3'), 6.76 (1H, dd, J = 8, 2 Hz, H5'), 7.92 (1H, d, J = 8 Hz, H6'). Anal $C_9H_8BrN_3O_2$ (C, H, N).

2-Bromo-2'-methoxy-4'-methylthioacetophenone ***50***
The acetophenone **59** (30.5 g, 0.156 mol) in chloroform (300 ml) was added during 20 min to a stirred suspension of cupric bromide (69.0 g, 0.31 mol) in ethyl acetate (300 ml). The mixture was stirred and heated at reflux for 3 h, then cooled and filtered through Celite and the solvent evaporated. The residue was recrystallised from ethyl acetate–hexane to give 27.8 g (65%) of **50**, mp 113–114°C. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 2.52(3H, s, SMe), 3.93 (3H, s, OMe), 4.54 (2H, s, CH_2Br), 6.75 (1 H, d, J = 2Hz, H3'), 6.85 (1H, dd, J = 9, 2 Hz, H5'), 7.82 (1H, d, J = 9 Hz, H6'). υ_{max} (Nujol) 1663 cm^{-1}. Anal $C_{10}H_{11}BrO_2S$ (C, H, Br, S).

In a similar manner 4'-cyano-2'-methoxyacetophenone **60** was converted in 66% yield to 2-bromo-4'-cyano-2'-methoxyacetophenone **51**, mp 135–136°C ^{1}H NMR (200 MHz, $CDCl_3$) δ = 4.00 (3H, s, OMe), 4.53 (2H, s, CH_2Br), 7.26 (1H, d, J = 1.3 Hz, H3'), 7.34 (1H, dd, J = 8.0, 1.3 Hz, H5'), 7.85 (1H, d, J = 8.0 Hz, H6'), Anal $C_{10}H_8BrNO_2$ (C, H, Br, N).

2-Bromo-2'-methoxy-4'-methylsulphinylacetophenone ***48***
m-Chloroperbenzoic acid (2.4 g, 85%, 0.012 mol) in chloroform (40 ml) was added, dropwise for 30 min, to a stirred solution of sulphide **50** (3.0 g, 0.011 mol) in chloroform (40 ml) cooled in ice. Stirring at 0°C was continued for 3 h. The solution was then washed with aqueous sodium hydrogen carbonate, dried over Na_2SO_4, and evaporated. The residue was flash-chromatographed on silica, eluting with chloroform-methanol (97:3) to give 1.9 g (60%) of 48, mp 74–75°C (ethyl acetate–hexane) ^{1}H NMR (200 MHz, $CDCl_3$) δ = 2.76 (3H, s, SMe), 4.04 (3H, s, OMe), 4.58 (2H, s, CH_2Br), 7.09 (1H, dd, J = 8, 2 Hz, H5'), 7.48 (1H, d, J = 2 Hz, H3'), 7.91 (1H, d, J = 8 Hz, H6'). Anal $C_{10}H_{11}BrO_3S$ (C, H, Br, S).

Preparation of imidazo[1,2-a]pyrimidines

Method A: 6-hydroxy-2-(2-methoxy-4-methylsulphinylphenyl)imidazo[1,2a]pyrimidine 27 hydrochloride
The bromide **48** (2.0 g, 6.9 mmol), 2-amino-5-hydroxypyrimidine **45** (0.77 g, 6.9 mmol) and ethanol (50 ml) were stirred and heated at 80°C for 2 h. More of the bromide **48** (0.20 g) was then added and the reaction mixture heated for a further 3 h at 80°C. The solvent was then evaporated and the residue partitioned between chloroform and aqueous sodium hydrogen carbonate. Separation and neutralisation of the aqueous phase with 1 N HCl resulted in precipitation. The solid deposited was filtered off, dissolved in hot methanol and the resulting solution treated with decolourising charcoal. After filtration 2 M ethereal hydrogen chloride solution was added to the filtrate and volatile material removed *in vacuo*. The residue was recrystallised from methanol–ether to give 200 mg (8%) of **27** hydrochloride, mp 222–226°C (decomp). Anal $C_{14}H_{13}N_3O_3S{\cdot}HCl{\cdot}0.6H_2O$ (C, H, Cl, S, N).

In a similar manner were obtained 2-(2-methoxy-4-methylsulphinylphenyl) imidazo[1,2-*a*]pyrimidine **18**, 2-(2,4-dimethoxyphenyl)imidazo[1,2-*a*]pyrimidine **19** hydrochloride, 2-(2-methoxy-4-methylthiophenyl)imidazo[1,2-*a*]pyrimidine **21** hydrochloride, 2-(4-cyano-2-methoxyphenyl)imidazo[1,2-*a*]pyrimidine **22** hydrochloride, 2-(4-benzyloxy-2-methoxyphenyl)-imidazo[1,2-*a*]pyrimidine **32** hydrobromide, 2-(4-azido-2-methoxyphenyl) imidazo[1,2-*a*]pyrimidine hydrobromide **34**, 6-methoxy-2-(2-methoxy-4-methylthiophenyl)imidazo[1,2-*a*]pyrimidine **35**, 7-methoxy-2-(2-methoxy-4-methylthiophenyl)imidazo[1,2-*a*]pyrimidine **36**. Details are given in table I.

Method B: 2-(2,4-Dimethoxyphenyl)-6-(4-methoxyphenylazo)-imidazo[1,2-a]pyrimidine 37
The pyrimidine **47** (1.83 g, 8.0 mmol), 2-bromo-2',4'-dimethoxyacetophenone **49** (2.07 g, 8.0 mmol) and dry dimethylformamide (30 ml) were stirred under nitrogen at 80°C for 2 h. More **47** (0.30 g, 1.3 mmol) was then added and the reaction mixture heated for a further 2 h. Chloroform was then added and the resulting solution washed with aqueous sodium hydrogen carbonate and then 4 times with water. After drying over Na_2SO_4 the solvent was removed *in vacuo* and the residue chromatographed on silica. Elution with chloroform–methanol (20:1) and subsequent crystallisation of the major fraction from methanol–chloroform–hexane gave 0.81 g (26%) of **37**, mp 233–235°C. ^{1}H NMR [200 MHz, $(CD_3)_2SO$] δ = 3.85 (3H, s, OMe), 3.90 (3H, s, OMe), 4.00 (3H, s, OMe), 6.65–6.75 (2H, m, H3', H5'), 7.13 (2H, d, *J* = 8 Hz, 1/2 of AB system, aromatics), 7.89 (2H, d, *J* = 8 Hz, 1/2 of AB system, aromatics), 8.22 (1H, d, *J* = 8 Hz, H6'), 8.36 (1 H, s, H3), 9.00 (1 H, d, *J* = 2 Hz, H7), 9.48 (1H, d, *J* = 2 Hz, H5). Anal $C_{21}H_{19}N_5O_3$ (C, H, N).

In a similar manner 2-(2-methoxy-4-methylthiophenyl)-6-(4-methoxyphenylazo)imidazo[1,2-*a*]pyrimidine **39** was obtained; details are given in table I.

Method C: 7-methoxy-2-(2-methoxy-4-methylsulphinylphenyl) imidazo[1,2a]pyrimidine 28
To a solution of sulphide **36** (0.57 g, 1.9 mmol) in chloroform (25 ml) at 0°C was added dropwise a solution of *m*-chloroperbenzoic acid (370 mg, 80%,1.7 mmol) in chloroform (10 ml). The reaction solution was stirred at 0°C for a further 1 h, then washed with 5% aqueous sodium hydrogen carbonate (2 x 10 ml and dried over $MgSO_4$. Removal of the solvent *in vacuo* and chromatography of the residue on silica, eluting with chloroform–methanol (98:2), gave 405 mg (*ca* 64%) of **28** as an off-white solid, mp 234–235°C (EtOAc). ^{1}H NMR (D_2O + DCl) δ = 2.65 (3H, s, SMe), 3.70 (3H, s, OMe), 3.82 (3H, s, OMe), 6.62 (1H, d, *J* = 7 Hz, H6), 6.80–6.92 (2H, m, H3', H5'), 7.16 (1H, d, *J* = 8 Hz, H6'), 7.81 (1H, s, H3), 8.33 (1H, d, *J* = 7 Hz, H5). NOE experiments: irradiation of the δ 6.9 signal (H3') gave an enhancement at the δ 3.70 signal (2'-OMe); irradiation of the δ 6.62 signal (H6) gave enhancement at the δ 3.82 (7-OMe) and δ 8.33 (H5) signals and *vice versa*; irradiation of the δ 7.81 signal (H3) gave enhancement at δ 8.33 (H5); irradiation of the δ 7.16 signal (H6') gave enhancement at δ 6.8 (H5'). Anal $C_{15}H_{15}N_3O_3S{\cdot}0.75H_2O$ (C, H, N).

In a similar manner was obtained 6-methoxy-2-(2-methoxy-4-methylsulphinylphenyl) imidazo [1,2-*a*]pyrimidine **26** and 2-(2-methoxy-4-methylsulphinylphenyl)-6-(4-methoxyphenylazo)imidazo[1,2-*a*]pyrimidine **38**; details are given in table I.

Method D: 2-(4-hydroxy-2methoxyphenyl)imidazo[1,2a]-pyrimidine 31
The hydrobromide of the benzyl ether **32** (1.75 g, 4.2 mmol), trifluoroacetic acid (6 ml) and thioanisole (0.60 g, 4.8 mmol) were stirred at room temperature for 3 h. The reaction mixture was poured onto ice-sodium hydrogen carbonate solution, triturated and the resulting solid filtered off. After washing with water and drying 0.90 g (*ca* 88%) of crude **31** was obtained as a yellow solid which was used without further purification.

Method E: 2-(2-methoxy-4-methylsulphonyloxyphenyl)-imidazo[1,2-a]pyrimidine 24 hydrochloride
The phenol **31** (0.72 g, 3.0 mmol), dry pyridine (16 ml) and methanesulphonyl chloride (1.0 ml, 13 mmol) were stirred at 50°C for 3 h. Volatile material was removed *in vacuo*, the residue treated with aqueous sodium hydrogen carbonate, and the mixture extracted twice with dichloromethane. The combined organic extracts were washed with water, dried over $MgSO_4$, and concentrated to *ca* 10 ml. Ethereal hydrogen chloride (40 ml of 2 M solution) was added, the mixture stirred for 1 h, and then evaporated to dryness. The residue was taken up in dichloromethane–methanol (19:1), filtered, and the filtrate diluted with ether to give 0.40 g (38%) of **24** hydrochloride, mp 244–246°C (decomp). ^{1}H NMR [90 MHz, $(CD_3)_2SO$] δ = 3.50 (3H, s, SMe), 4.06 (3H, s, OMe), 7.15–7.29 (2H, m, H3', H5'), 7.54 (1H, m, H6), 8.29 (1H, d, *J* = 8 Hz, H6'), 8.72 (1H, s, H3), 8.92 (1H, dd, *J* = 2, 4 Hz, H7), 9.29 (1H, dd, *J* = 2, 7 Hz, H5), *m/z* 319 (M^+-HCl). Anal $C_{14}H_{13}N_3O_4S{\cdot}HCl$ (C, H, N).

Method F: 2-(4-amino-2-methoxyphenyl)imidazol[1,2-a]-pyrimidine 33
A solution of **34** hydrobromide (1.30 g, 3.7 mmol) in ethanol (60 ml) containing triethylamine (0.76 g, 7.5 mmol) and 5% palladium on charcoal catalyst (0.13 g) was shaken under 1 atm pressure of hydrogen until TLC indicated that all the starting material had been consumed (*ca* 2 h). The catalyst was removed by filtration and the filtrate evaporated to dryness *in vacuo*. The residue was purified by column chromatography on silica gel, eluting with $CHCl_3$–MeOH (8:1) to yield 0.60 g (67%) of **33** as a yellow solid, mp 224°C (decomp). Anal $C_{13}H_{12}N_4O$ (C, H, N).

Method G: 2-(2-Methoxy-4-methylsulphonylaminophenyl)-imidazo[1,2-a]pyrimidine 25 hydrochloride
To a stirred solution of **33** (0.50 g, 2.1 mmol) in dry pyridine (45 ml) at 0°C was added, over 30 min, a solution of methanesulphonyl chloride (0.23 g, 2.0 mmol) in dry pyridine (10 ml). The reaction mixture was stirred at 0–5°C for 17 h, the pyridine removed *in vacuo*, and the residue triturated with water and chloroform. The resulting solid was filtered off and recrystallised from ethanolic hydrogen chloride to give 0.32 g (46%) of **25** hydrochloride as a yellow solid, mp 260–263°C. ^{1}H NMR

[90 MHz, $(CD_3)_2SO$] δ = 3.14 (3H, s, SMe), 3.99 (3H, s, OMe), 6.9–7.1 (2H, m, H3', H5'), 7.56 (1H, m, H6), 8.09 (1H, d, *J* = 8 Hz, H6'), 8.61 (1H, s, H3), 8.91 (1H, dd, *J* = 2, 4 Hz, H7), 9.24 (1H, dd, *J* = 2, 7 Hz, H5), 10.3 (brs, 1H, exchangeable, NH). Anal $C_{14}H_{14}N_4O_3S$·HCl (C, H, N).

*Method H: 6-amino-2-(2,4-dimethoxyphenyl)imidazo[1,2-a]-pyrimidine **29** hydrochloride*

The hydrobromide of azo-compound **37** (2.5 g, 5.3 mmol), ethanolic ammonia (120 ml of 12% w/v) and 10% palladium on charcoal (0.25 g) were stirred under hydrogen at atmospheric pressure. After uptake of 2 equivalents of hydrogen had occurred (*ca* 4 h), the catalyst was removed by filtration and the filtrate evaporated to dryness. The residue was dissolved in chloroform, washed with 5% aqueous sodium hydrogen carbonate, and dried over Na_2SO_4. Removal of the solvent *in vacuo* gave a tan solid which was chromatographed on silica. Elution with chloroform–methanol (10:1), crystallisation from ethanol-ethyl acetate and treatment with 1 equivalent of methanolic hydrogen chloride gave 0.55 g (24%) of **29** hydrochloride, mp 275–278°C (decomp) (MeOH–H_2O). ^1H NMR [90 MHz, $(CD_3)_2SO$ + NaOD] δ = 3.81 (3H, s, OMe), 3.94 (3H, s, OMe), 5.10 (2H, brs, NH_2, exchangeable), 6.60–6.75 (2H, m, H3', H5'), 8.00–8.25 (4H, m, H6', H3, H5, H7). Anal $C_{14}H_{14}N_4O_2$·HCl·1.25H_2O (C, H, Cl, N).

In a similar manner was obtained 6-amino-2-(2-methoxy-4-methylsulphinylphenyl) imidazo[1,2-*a*]pyrimidine **30**; details are given in table I.

*Method I: 2-(2-methoxy-4-methylsulphonylphenyl)imidazo[1,2-a]pyrimidine **20** hydrochloride*

To a stirred solution of 2-(2-methoxy-4-methylthiophenyl)-imidazo[1,2-*a*]pyrimidine **21** (1.0 g, 3.69 mmol) in chloroform (50 ml) was added a solution of *m*-chloroperbenzoic acid (1.50 g, 85%, 7.39 mmol) in chloroform (20 ml) over 15 min. This was followed 16 h later by a second addition of *m*-chloroperbenzoic acid (0.50 g, 85%, 2.46 mmol). After being stirred for a further 1 h, the reaction mixture was washed with saturated aqueous sodium bicarbonate. The organic phase was separated, dried and evaporated. Trituration of the residue with ethyl acetate–methanol gave a powdery solid which was then dissolved in chloroform and treated with ethereal hydrogen chloride. The solid which deposited was filtered off and recrystallised from aqueous ethanol to give 0.19 g (15%) of **20** hydrochloride, mp 252–255°C (dec). ^1H NMR (90 MHz, $(CD_3)_2SO$, NaOD) δ = 3.28 (3H, s, SMe), 4.11 (3H, s, OMe), 7.10 (1H, dd, *J* = 6, 4 Hz, H6), 7.61–7.69 (2H, m, H3', H5'), 8.50–8.59 (3H, m, H3, H6', H7), 8.96 (1 H, dd, *J* = 6, 2 Hz, H5), *m/z* 303 (M^+). Anal $C_{14}H_{13}N_3O_3S$·HCl·0.75H_2O (C, H, Cl, N, S).

*Method J: 2-(4-carbamoyl-2-methoxyphenyl)imidazol[1,2-a]pyrimidine **23** hydrochloride*

The nitrile **22** (0.50 g, 2.0 mmol) and conc sulphuric acid (15 ml) were stirred at room temperature for 48 h. The resulting solution was poured onto ice, neutralised with 10 N sodium hydroxide and then re-cooled to 0°C. The solid which deposited was filtered off, washed with water and dried. Purification of this material by flash chromatography on silica gel eluting with chloroform–methanol (19:1) gave 0.3 g of the free base, which on treatment with excess methanolic hydrogen chloride solution yielded 0.25 g (40%) of **23** hydrochloride, mp 255–257°C. ^1H NMR (200 MHz, $(CD_3)_2SO$) 4.09 (3H, s, OMe), 7.46 (1H, dd, *J* = 6, 4 Hz, H6), 7.57 (1H, brs, NH, exchangeable), 8.22 (1H, d, *J* = 8 Hz, H6'), 8.68(1H, s, H3), 8.86 (1H, dd, *J* = 4, 2 Hz, H7), 9.21 (1H, dd, *J* = 6, 2 Hz, H5). Anal $C_{14}H_{12}N_4O_2$·0.9HCl·0.75H_2O (C, H, Cl, N).

*Method K: 2-(2,4-dimethoxyphenyl)-3-hydroxyimidazo[1,2-a]pyrimidine **40** hydrochloride*

2-Aminopyrimidine-1-oxide (4.50 g, 0.04 mol) [21, 22], 2-bromo-2',4'-dimethoxyacetophenone **49** (10.49 g, 0.04 mol) and dimethylformamide (90 ml) were stirred at 80°C under nitrogen for 2 h. After standing at room temperature overnight the mixture was evaporated *in vacuo*. The residue was dissolved in chloroform, washed with aqueous sodium hydrogen carbonate, and dried over Na_2SO_4. Evaporation of the solvent gave a gum which was chromatographed on silica. Elution with chloroform–methanol (10:1), removal of the solvent from the appropriate fractions, and recrystallisation of the residue from ethanol–chloroform gave yellow crystals. Treatment with ethanolic hydrogen chloride yielded 0.50 g (4%) of **40** hydrochloride, mp 225–228°C (decomp) (ethanol–ethyl acetate). *m/z* 271 (M^+-HCl). Anal $C_{14}H_{13}N_3O_3$·HCl·0.2H_2O (C, H, Cl, N).

*Method L: 3-amino-2-(2,4-dimethoxyphenyl)imidazo[1,2-a]pyrimidine **41** hydrochloride*

The nitroso compound **42** (1.70 g), methanol (80 ml), and 10% palladium on charcoal (0.1 g) were stirred under hydrogen at atmospheric pressure for 1 h. Fresh catalyst (0.1 g) was then added and the mixture stirred until hydrogen uptake ceased (*ca* 2 h). The catalyst was removed by filtration, the filtrate evaporated and the residue chromatographed on silica. Elution with chloroform–methanol (20:1) gave, after removal of a less polar impurity, an oil (1.2 g). Crystallisation from methanol–ether and treatment with ethanolic hydrogen chloride gave 0.45 g (24%) of **41** hydrochloride as orange crystals, mp > 200°C (decomp). *m/z* 270 (M^+-HCl). Anal $C_{14}H_{14}N_4O_2$·HCl (C, H, Cl, N).

*Method M: 2-(2,4-dimethoxyphenyl)-3-nitrosoimidazo[1,2-a]pyrimidine **42***

The heterocycle **19** (2.30 g, 9.0 mmol) was dissolved in warm acetic acid (9 ml), water (13.5 ml) added and the mixture stirred and cooled to 2–5°C. Sodium nitrite (0.83 g,12 mmol) was added in small portions during 20 min and the reaction mixture was then stirred at 2–4°C overnight. The green solid was removed by filtration, washed with water, and slurried with hot methanol–isopropanol. On cooling, crystals deposited which were filtered off and dried to give 2.1 g (82%) of **42** mp 203–205°C. *m/z* 284 (M^+). Anal $C_{14}H_{12}N_4O_3$ (C, H, N).

Pharmacology

Paced guinea pig papillary muscles

Single right ventricular papillary muscle preparations from male guinea pigs were used in organ-bath experiments at 34°C. Stimulation was effected by rectangular pulses of 1 ms duration by a SRI stimulator and a Grass transducer was used to record isometric tension. The inotropic potency is expressed as the negative logarithm of the drug concentration required to increase basal contractility by 50% (pA_{50}). Other workers [24] have also recently used a similar parameter (pD_2 value) to describe inotropic potency. Full details of our experimental protocol have been described previously [5, 9].

In vivo experiments utilising anaesthetized dogs

Those compounds which displayed significant inotropic effects *in vitro* were routinely evaluated *in vivo* by determining the effects of giving single bolus (*iv*) injections to anaesthetized open-chest dogs. Left ventricular pressure (*P*) and its first derivative, d*P*/dt, were measured by the insertion of a short cannula (containing heparinised saline and connected to a Statham pressure transducer) into the left ventricular chamber

via the apex of the heart. Arterial blood pressure was measured by means of a catheter (containing heparinised saline and connected to a Statham pressure transducer) inserted into the right femoral artery.

Heart rate was derived by use of a tachograph triggered either by the arterial pulse or the ECG–QRS complex. *In vivo* inotropic activity was indexed by an ED_{50} value, *ie* the dose required to produce an increase of 50% in the value of dP/dt_{max}, where dP/dt_{max} is the maximum rate of rise of left ventricular pressure. Hypotensive effects were described by an ED_{30} value, the dose required to produce 30% decrease in diastolic blood pressure. The parameter used to quantify tachycardia was the ED_{10}, the dose required to produce a 10% increase in heart rate. Further details relating to the experimental methods employed have been described [6, 9, 25].

References

1 Erhardt PW (1987) *J Med Chem* 30, 231
2 Unterhalt B (1981) *Drugs Future* 6, 421
3 Robertson DW, Hayes JS (1985) *Drugs Future* 10, 295
4 Robertson DW, Beedle EE, Krushinski JH, Pollock GD, Wilson H, Wyss VL, Hayes JS (1985) *J Med Chem* 28, 717
5 Barraclough P, Black JW, Cambridge D, Gerskowitch VP, Hull RAD, Iyer R, King WR, Kneen CO, Nobbs MS, Randall P, Shah GP, Smith S, Vine SJ, Whiting MV (1990) *Arch Pharm (Weinheim)* 323, 501
6 Barraclough P, Black JW, Cambridge D, Demaine DA, Gerskowitch VP, Giles H, Hill AP, Hull RAD, Iyer R, King WR, Livingstone DJ, Nobbs MS, Randall P, Shah GP, Whiting MV (1990) *Arch Pharm (Weinheim)* 323, 507
7 Hauel N, Austel V, Heider J, Reiffen M, Diederen W (1984) *Br Pat* 2, 122, 995; *Chem Abstr* (1984) 100; 139110n
8 Barraclough P, Black JW, Cambridge D, Collard D, Firmin D, Gerskowitch VP, Glen RC, Giles H, Hill AP, Hull RAD, Iyer R, King WR, Kneen CO, Lindon JC, Nobbs MS, Randall P, Shah GP, Smith S, Vine SJ, Whiting MV, Williams JM (1990) *J Med Chem* 33, 2231
9 Barraclough P, Beams RM, Black JW, Cambridge D, Collard D, Demaine DA, Firmin D, Gerskowitch VP, Glen RC, Giles H, Hill AP, Hull RAD, Iyer R, King WR, Livingstone DJ, Nobbs MS, Randall P, Shah GP, Vine SJ, Whiting MV (1990) *Eur J Med Chem* 25, 467 and references therein
10 Barraclough P, Firmin D, Iyer R, King WR, Lindon JC, Nobbs MS, Smith S, Wharton CJ, Williams JM (1988) *J Chem Soc Perkin Trans* 2, 1839
11 Barraclough P, Firmin D, Lindon JC, Nobbs MS, Sanderson PN, Smith S, Gillam JM (1991) *Magn Reson Chem* 29, 468
12 Budesinsky Z, Kopecky J, Prikryl J (1962) *Czech Pat* 104, 969 *Chem Abstr* (1964) 60; 8043a
13 Adams RR, Whitmore FC (1945) *J Am Chem Soc* 67, 735
14 Hultquist ME, Kuh ER (1944) *Br Pat* 559, 455; *Chem Abstr* (1945) 39, 5410(9)
15 Reichardt C, Grahn W (1970) *Chem Ber* 103, 1065
16 Hensel HR (1964) *Chem Ber* 97, 96
17 Murakami M, Inukai N, Koda A, Nakano K, Katsuno K, Okabe N, Kusumoto M, Niigata K, Nakanishi T, Minobe H (1975) *Austr Pat* 326, 638; *Chem Abstr* (1976) 85, 20877z
18 Société d'Études Scientifiques et Industrielles de l'Ile-de-France (1965) *Fr Pat* 1, 407, 055; *Chem Abstr* (1965) 63, 17987d
19 Barraclough P, Iyer R, Lindon JC, Williams JM (1986) *Tetrahedron Lett* 27, 5997
20 Duffley RP, Stevenson R (1977) *J Chem Soc Perkin Trans* 1, 802
21 Deady LW (1977) *Synth Commun* 7, 509
22 Deady LW, Stanborough MS (1981) *Aust J Chem* 34, 1295
23 Spitzer WA, Victor F, Pollock GD, Hayes JS (1988) *J Med Chem* 31, 1590
24 Takeya K, Itoigawa M, Furukawa H (1989) *Eur J Pharmacol* 169, 137
25 Allan G, Cambridge D, Follenfant MJ, Stone D, Whiting MV (1988) *Br J Pharmacol* 93, 387
26 Hersey A, Hill AP, Hyde RM, Livingstone DJ (1989) *Quant Struct–Act Relat* 8, 288