Inotropic Polyazapentalene Sulmazole Analogues

Paul Barraclough[a)*], James W. Black[b,d)], David Cambridge[b)], David Firmin[c)], V. Paul Gerskowitch[b,d)], R.C. Glen[c)], Heather Giles[b)], Janet M. Gillam[c)], Robert A.D. Hull[b,d)], Ramachandran Iyer[a)*], Peter Randall[b,d)], Gita P. Shah[a)], Steven Smith[a)], and Mark V. Whiting[b)]

Departments of Medicinal Chemistry[a)], Pharmacology[b)], and Physical Sciences[c)], Wellcome Research Laboratories, Langley Court, Beckenham, Kent BR3 3BS, U.K.

Received March 12, 1991

Aryl substituted 1*H*-imidazo[1,2-*a*]imidazole **8**, imidazo[2,1-*b*]thiazole **9**, 1,4-dihydroimidazo[4,5-*d*]imidazole **11**, and 1(2),4-dihydroimidazo[4,5-*c*]pyrazoles **12-17** have been prepared. An X-ray crystallographic study confirmed the structure of **8** and showed this analogue to exist as the 1*H*-tautomer. These heterocycles were evaluated as inotropic agents and analogues **12**, **15**, and **17** found to display inotropic properties which were less potent *in vitro*, but more potent *in vivo*, than those of sulmazole. Structure-activity relationships are discussed.

Inotrop wirksame polyazapentalen-artige Sulmazolanaloge

Die arylsubstituierten Verbindungen 1*H*-Imidazo[1,2-*a*]imidazol **8**, Imidazo[2,1-*b*]thiazol **9**, 1,4-Dihydroimidazo[4,5-*d*]imidazol **11** und die 1(2),4-Dihydroimidazo[4,5-*c*]pyrazole **12-17** wurden hergestellt. Eine Kristallstrukturanalyse von **8** bestätigte ihre Struktur und zeigte, daß diese Verbindung als 1*H*-Tautomer vorliegt. Diese Heterocyclen wurden auf inotrope Aktivität untersucht, und es wurde festgestellt, daß im Vergleich zu Sulmazol die Verbindungen **12**, **15** und **17** schwächer *in vitro*, aber stärker *in vivo* inotrop wirken. Struktur-Aktivität-Beziehungen werden diskutiert.

The search for potent inotropic agents which lack the undesirable toxicological effects associated with digoxin[1)] or sulmazole **1**[1,2)] has led to several investigations of the structure-activity relationships (SAR's) of sulmazole analogues. These studies have shown that the achiral carboxamide **2**[3)] and the imidazo[1,2-*a*]pyrimidine **3**[4,5)] display potent inotropic effects *in vitro*. In addition the 1*H*-imidazo[4,5-*b*]pyrazine **4** and the 1*H*-imidazo[4,5-*c*]pyridazine **5** were found[6)] to have *in vitro* inotropic potencies lower than that of sulmazole although analogue **5** displayed more potent inotropic effects *in vivo* than did sulmazole. A further finding of this latter investigation[6)] was that there were two common molecular properties of inotropic heterocyclic sulmazole analogues. Thus inotropic heterocycles (e.g. **5**) were essentially unprotonated at physiological pH and also possessed an electron rich imidazo 'B' ring nitrogen atom. The azaindole **6**, which lacks these properties, is devoid of inotropic activity (Scheme 1).

The N-methyl derivatives of many of the above analogues have slightly lower inotropic potencies *in vitro* than those of the unmethylated heterocycles[6,7)]. In some cases, however, larger reductions in activity are observed on methylation. The N-4-methyl derivative of sulmazole, analogue **7**[7)], for example, is a much weaker inotrope than sulmazole.

Polyazapentalenes[8)] which have a suitable disposition of N-atoms have the same number of π-electrons as several aza-analogues of the indene anion and the pentalene dianion. This fact led us to speculate that certain sulmazole analogues, possessing 10π polyazapentalene ring systems, may have similar electronic interactions to those of **1** at a common inotropic receptor site. If this hypothesis is correct these 10π polyazapentalene ring systems might also be good bio-isosteres for the imidazopyridine nucleus of sulmazole. From a consideration of the SAR's described above we further hypothesized that analogues **8**, **9**, **11**, **12**, **15**, and **17** would display inotropic effects *in vitro*. The syntheses of heterocycles **8-17** were therefore undertaken to aid the testing of this hypothesis.

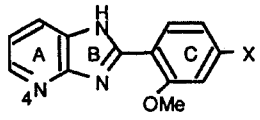
Chemistry

The 1*H*-imidazo[1,2-*a*]imidazole **8** was prepared by condensation of 2-aminoimidazole **18**[9)] with 2-bromo-2',4'-dimethoxyacetophenone (**19**) (Scheme 2). This reaction gave **8** as a minor product, and a major product, tentatively assigned structure **20**, which was converted into **8** by treatment with zinc and acetic acid. Since there are few reports[10,11)] describing the conversion of mono- (or un-) substituted 2-aminoimidazoles into 1*H*-imidazo[1,2-*a*]imidazoles we wished to confirm the structure of **8** especially since this compound is formed in low yield. An X-ray crystallographic study of the minor product from the above reaction did indeed show that it had structure **8** as shown in Figure 1. The major product was inferred to be the 1,6-disubstituted derivative **20**, rather than the 1,2-disubstituted-isomer **21**, by n.O.e. experiments. Thus, in the ^{1}H-n.m.r. spectrum of this compound an enhancement of the H-2 signal was observed on irradiation of the NCH_2 protons and *vice versa*.

Synthesis of the imidazo[2,1-*b*]thiazole **9** was achieved as described[12)]. The 1,4-dihydroimidazo[4,5-*d*]imidazole **11** was prepared by hydrolysis of nitrile **10**, this intermediate being obtained by condensation of 4,5-diamino-1-methylimidazole (**22**)[13)] with acid **23**[14)] (Scheme 3). In a similar manner the 1(2),4-dihydroimidazo[4,5-*c*]pyrazole derivatives **12**, **15**, and **17** were obtained from the precursors **13**, **14**, and **16** respectively (Scheme 4). Sulphide **13** was synthesized by reaction of 3,4-diaminopyrazole (**24**)[15)] with acid **25**[6)]. Oxidation of sulphide **13** with *m*-chloroperbenzoic acid gave sulphoxide **12**. Nitriles **14** and **16** were prepared by condensation of acid **23**[14)] with diamine **24** and

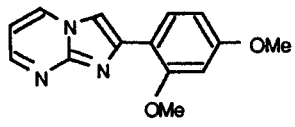
[d)] Present address: James Black Foundation, 68 Half Moon Lane, Dulwich, London, SE24 9JE, U.K.

 ©VCH Verlagsgesellschaft mbH, D-6940 Weinheim, 1992 0365-6233/92/0404-0225 $ 3.50 + .25/0

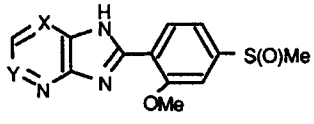


1 X = S(O)Me

2 X = $C(O)NH_2$

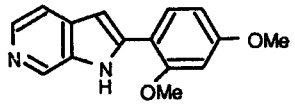


3

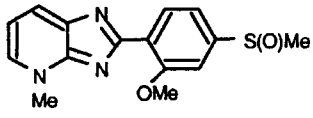


4 X = N, Y = CH

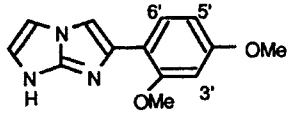
5 X = CH, Y = N



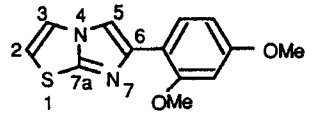
6



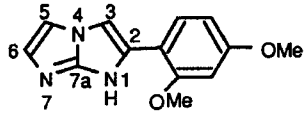
7



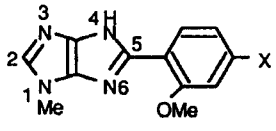
7H - 8



9

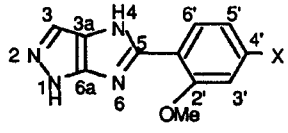


1H - 8



10 X = CN

11 X = $C(O)NH_2$

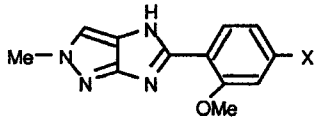


12 X = S(O)Me

13 X = SMe

14 X = CN

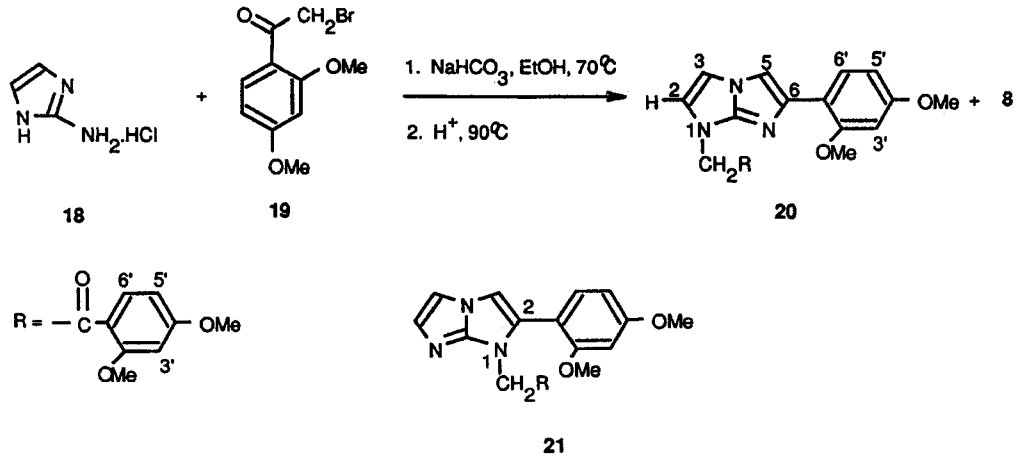
15 X = $C(O)NH_2$



16 X = CN

17 X = $C(O)NH_2$

Scheme 1



18 19 20

21

Scheme 2

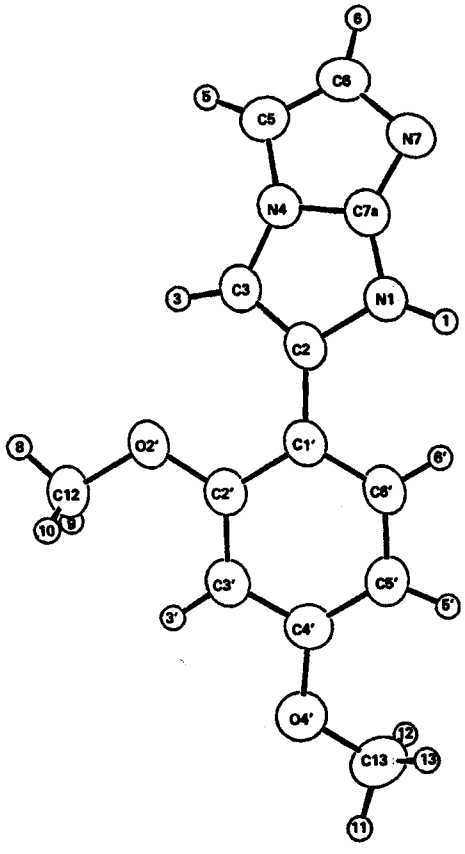


Fig. 1 Structure and crystallographic numbering of 8

16. Diamine **26** was prepared from 3(5)-acetamidopyrazole (**27**)[15] by the reaction sequence shown in Scheme 5.

Structure-activity relationships

The inotropic activities and pK_a's of the sulmazole analogues are given in Table 1. All the polyazapentalenes, with the sole exception of heterocycle **8**, displayed inotropic effects *in vitro*. However, only analogues **12**, **15**, and **17** demonstrated inotropic actions when evaluated *in vivo*.

The pK_a values indicate that at physiological pH most of these heterocycles are not substantially protonated or deprotonated. Thus, the imidazo[1,2-*a*]imidazole **8** (pK_a, BH^+ 6.80) should exist predominantly as the non-ionized species under the conditions of the *in vitro* assay system. The finding that analogue **8** is devoid of inotropic activity, therefore, cannot be so readily explained in terms of inactive protonated species as is the case for the inactive azaindole **6** (pK_a, BH^+ 8.27). Indeed, several 1*H*-imidazo[4,5-*c*]pyridine sulmazole analogues, which have pK_a's of 6.0-6.5, are potent inotropic agents[6]. Nevertheless, the proportion of protonated species present at pH 7.4 is greater for analogue **8** (20%) than for the 1*H*-imidazo[4,5-*c*]pyridines (4-11%) and this difference may be related to the changes in inotropic effects observed.

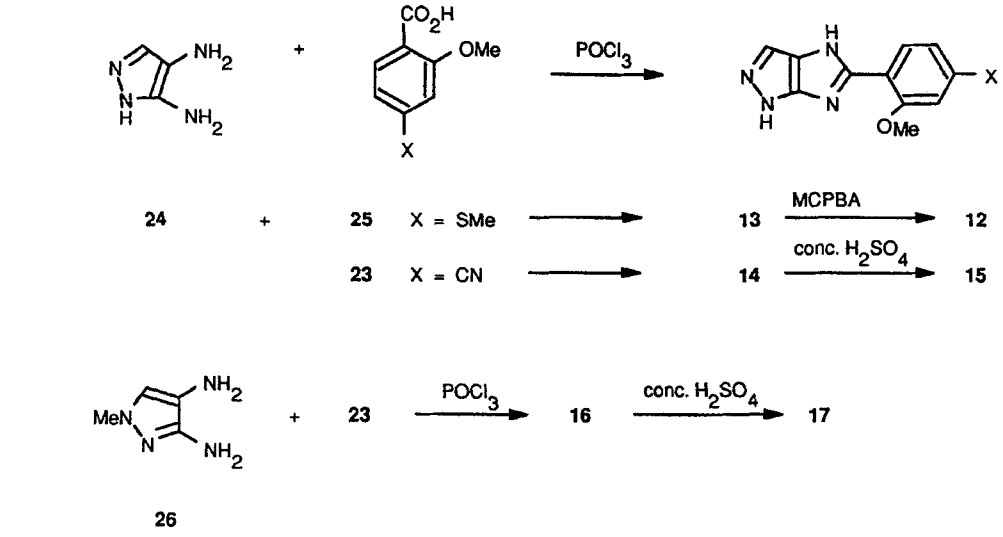
Contrary to a previous report[12], we found that the imidazo[2,1-*b*]thiazole **9** displayed modest inotropic effects *in vitro*. In an attempt to explain why analogue **9** possesses

22 23

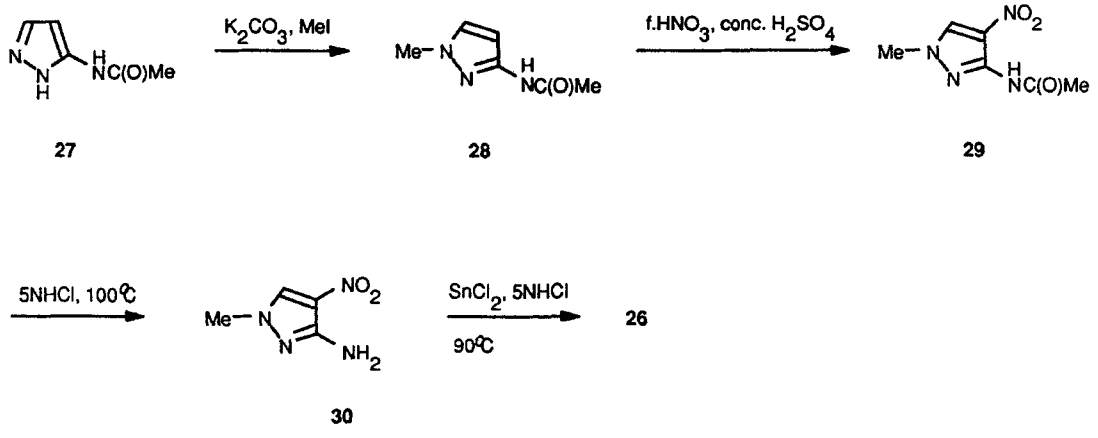
Scheme 3

3,4-diamino-1-methyl pyrazole (**26**), respectively. Hydrolysis of **14** gave amide **15** and **17** was obtained from nitrile

inotropic properties, but compound **8** does not, we have investigated the tautomerism, conformation and geometry of



Scheme 4



Scheme 5

1*H*-**8**, 7*H*-**8**, and **9** by X-ray crystallography and ^{13}C-n.m.r. studies. Furthermore, charge densities and dipole moments have been calculated by CNDO/2[16] and geometries, bond orders and heats of formation by AM1[17] methods utilising the semi-emperical molecular orbital ((M.O.) program MOPAC[18-20]). *Bird* aromaticity indices[21] and bond orders (n) of 1*H*-**8** and **9** have also been estimated from their X-ray derived bond lengths (R) by employing the *Gordy* equation $n = aR^{-2} + b$ where a and b are constants (Table 2, Figure 2). The CNDO/2 imidazo nitrogen charge densities of sulmazole, 7*H*-**8** and **9** were calculated to be -0.266, -0.300, and -0.226, respectively. In addition, the results of AM-1 calculations[17] performed on each tautomer of **8** indicate that the 1*H*-tautomer of **8** is of lower energy than 7*H*-**8**. The electron-rich imidazo nitrogen atoms of the 7*H*-tautomer of **8** and analogue **9** both reside in the 'B' ring, whereas the 1*H*-tautomer of **8** has such an imidazo nitrogen atom in the 'A' ring. Thus, 7*H*-**8** and **9** have the two molecular properties commonly associated with inotropic sulmazole analogues. However, 1*H*-**8** and the inactive azaindole **6** possess 'B' ring pyrrolic nitrogen atoms and hence one might expect 1*H*-**8** to be inactive. If 1*H*-**8** were the major tautomer present at the inotropic receptor site(s) for **9** the above reasoning would explain the inactivity of analogue **8**.

The X-ray crystallographic study of heterocycle **8** only detected the 1*H*-tautomer in the conformation shown in Figure 1. From the bond lengths and angles determined for 1*H*-**8**, and those reported[22] for 6-phenylimidazo[2,1-*b*]thiazole a comparison could be made between the geometries derived from M.O. calculations and those from the X-ray data (Figures 2 and 3). Thus, the calculated and observed values of the bond lengths and angles are in reasonable agreement for several, but not all, bonds and indicate a delocalised, almost symmetrical N1-C7a(N4)-N7 moiety for 1*H*-**8**. In addition the 2,3 and 5,6 bonds of 1*H*-**8** and **9** have bond lengths typical of almost pure double bonds (ethylene 1.34 Å) and in general the divergence from the calculated bond lengths and angles is greater for **9** than for 1*H*-**8**. These differences may be due to crystal packing forces not accounted for in the quantum mechanical calculations on the isolated molecules and also to the larger number of approximations[20] involved in the M.O. calculations of the sulphur containing heterocycle **9**.

Table 1: Inotropic Activities of Sulmazole Analogues

Compound	pA_{50}% [a]	n	ED_{50} [b]	pK_A [c]	
				BH^+	B^-
1	4.70±0.10	9	0.8	3.91	
2	4.26±0.06	3			
3	5.10±0.06	3	>3.0	4.34 [d]	
4	4.03±0.05	3	>10	<1	9.00
5	3.45±0.33	3	0.49	3.65	8.73
6	Inactive	2		8.27	
7	3.10±0.07	3	>3.0		
8	Inactive	2		6.80	
9	3.6±0	3		4.68	
11	3.24±0.07	3	>3.0	3.80	11.7
12	3.64±0.09	3	0.63	3.80	12.1
15	3.75±0.10	3	0.28		
17	3.88±0.05	3	0.22	3.99	12.4

a Parameter of in vitro inotropic potency; negative logarithm of drug concentration required to give a 50% increase in basal contractile force for n experiments. Paced guinea pig papillary muscle preparations were employed. Inactive; 50% increase not achieved.

b Parameter of *in vivo* inotropic potency: ED_{50} is the effective dose (mg/kg i.v.) of drug required to produce a maximum increase of 50% in dP/dt in anaesthetized open-chest dogs, where P is left ventricular pressure:

c refers to equilibrium between non-ionized hetercycle and monocation (BH^+) or monoanion (B^-). Values were determined spectrophotometrically [30] at 25°C in water and their accurancy varied as a result of stability and solubility differences but a typical error was ± 0.08. For the BH^+ measurements the ionic strengh (I) < 0.07, but for B^- determinations I > 0.07.

d determined in DMSO-H_2O (1:9)

Tab. 2:

Compound	ΔH_f	μ	q
9(NH)	37.3	2.8	-0.226
9(NO)	40.5	1.8	-0.219
1*H*-8(NO)	58.8	5.6	-0.274
1*H*-8(NH)	60.4	5.1	-0.293
7*H*-8(NH)	61.7	2.3	-0.301
7*H*-8(NO)	63.5	2.6	-0.301

ΔH_f = Heat of Formation Kcal $mole^{-1}$

μ = dipole moment (D)

q = atom-centred charge density of Imidazo N.

Bond orders (n) have been calculated for 1*H*-**8** and **9** by the method of *Bird* [21] utilising the *Gordy* equation $n = aR^{-2} + b$ and also from molecular orbital calculations using MOPAC. It is interesting to note that the bond orders estimated by the *Gordy* equation are always higher (by 0.02-0.53) than those derived from M.O. calculations. Furthermore there are several discrepancies between the relative bond orders obtained by the two methods. Nevertheless the calculated bond orders for **9** and 1*H*-**8** are in broad agreement with those calculated for the corresponding parent heterocycles[8,23] by CNDO/2 and n.m.r. methods. Interestingly, the *Bird* aromaticity indices[21] for 1*H*-**8** obtained from the two sets of bond orders are almost identical ($I_{5,5}$ 51 and 52) whereas for **9** the indicies are different ($I_{5,5}$ 48 by *Gordy* equation and 39 by M.O. calculations). This latter difference may reflect the greater errors in M.O. calculations for the sulphur containing heterocycle **9**. Whether these emperical $I_{5,5}$ values indicate any real difference in aromatic character between the two heterocycles is not certain[24,25]. The lower heat of formation of **9**, relative to **8**, may be due to reduction of angle strain and to sulphur d-orbital participation.

^{13}C-n.m.r. studies[26] have shown that while 1*H*-**8** is the major tautomer observed in $CDCl_3$ solution its conformation has the NH and 2'-OMe groups in close proximity, in contrast to the conformation adopted in the crystal where the NH and H-6' protons are adjacent. These studies[26] also indicate, that **8** exists predominantly as the 7*H*-tautomer in $(CD_3)_2SO$, CD_3OD, or D_2O-CD_3OD solutions. The changes in tautomer and conformation found between the solid state and various solvents are not surprising in view of the small energy difference between the tautomers of **8** i.e. the heat of formation of 1*H*-**8** is calculated to be 1.3-4.8 kcal (depending on conformation) lower than that of 7*H*-**8**. An explanation for the existence of the 1*H*-tautomer in the crystal lattice may be that the calculated dipole moment of the 1*H*-form (5.07 D) is much greater than that of the 7*H*-form (2.3

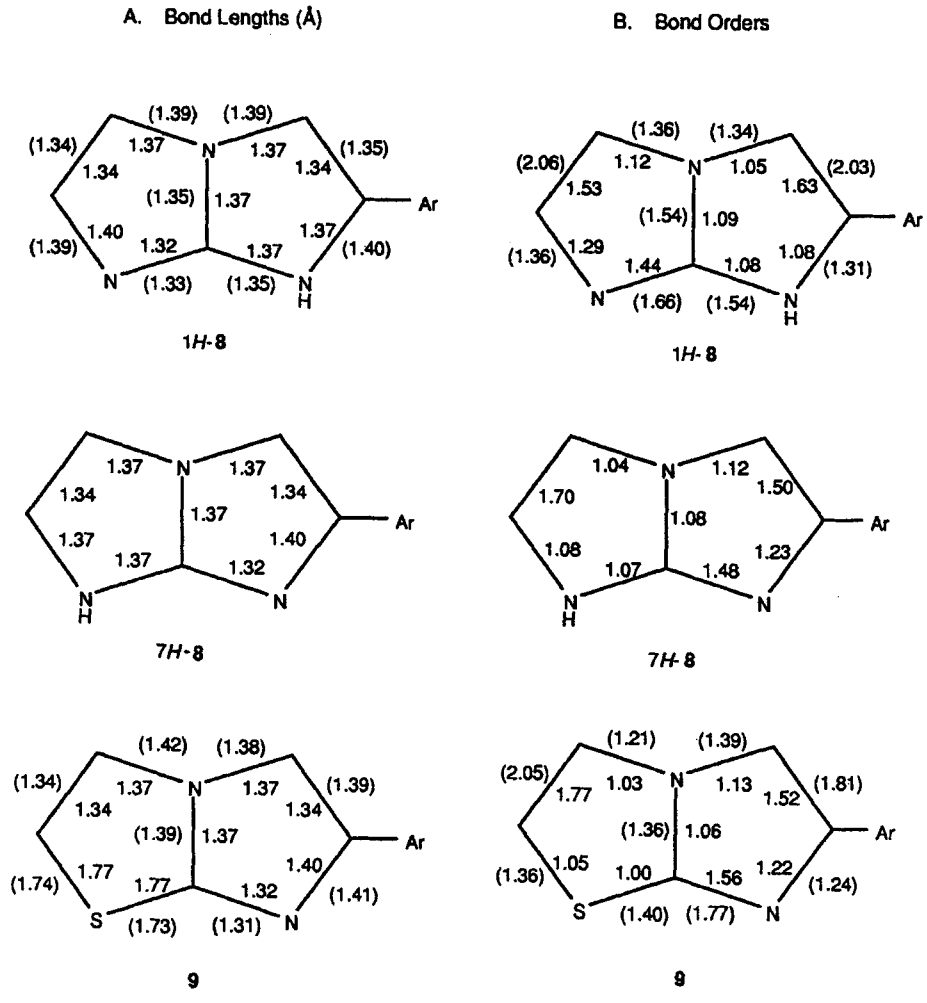


Fig. 2:

A. Bond lengths (Å) derived from M.O. calculations and (in parentheses) those from those X-ray crystallographic studies on 1H-**8** and 6-phenylimidazo[2,1-*b*]thiazole.

B. Bond orders derived from M.O. calculations and (in parentheses) those from the *Gordy* equation

D) and the stabilization energy for interaction of two 1*H*-forms is greater than that for two 7*H*-forms. In solution hydrogen bonding could be the most important solute-solvent interaction determining the relative stabilities of the tautomers. Thus, in $CDCl_3$, 1*H*-**8** may be stabilized by an intramolecular hydrogen bond between the NH and 2'-OMe groups. Intermolecular hydrogen bonding between the NH group of 7*H*-**8** and the oxygen atom of $(CD_3)_2SO$ or CD_3OD might be the dominant interaction stabilizing the 7*H*-form in these solvents. It is difficult to predict the tautomeric ratio of **8** in the environment of the inotropic receptor. If 7*H*-**8** is the major species present we are unable to explain the relationship between its physicochemical properties and lack of inotropic activity.

The 1,4-dihydroimidazo[4,5-*d*]imidazole **11** had a lower *in vitro* inotropic potency than analogue **4** and this finding may reflect primarily the presence of the methyl group in **11** rather than changes in 'A' ring electronic properties. Both **11** and **4** possess a common structural unit [(N)NC-CN(N)] in their heterocyclic rings. Interestingly both heterocycles display only very weak inotropic effects *in vivo* although analogue **11** has a higher pK_a value than that of **4**. These observations are consistent with one requirement for *in vivo* inotropism being the presence of a basic ($1 < pK_a < 7$) or electron-rich 'A' ring nitrogen atom in the heterocyclic sulmazole analogue. However, analogues **11**, **7**, and **3** (but not **4**), which possess such a 'A' ring nitrogen atom, are poor inotropes *in vivo*. Thus, several molecular properties may be associated with *in vivo* activity, and for heterocycles **11** and **7** the presence of the methyl groups appear to have detrimental effects on both *in vitro* and *in vivo* activity.

Heterocycles **12**, **15**, and **17** have similar inotropic potencies *in vitro* to that of the 1*H*-imidazo[4,5-*c*]pyridazine **5**. *In vivo*, however, carboxamide **15** displayed more potent inotropic effects than sulphoxides **12** and **5**. Replacement of a 4'-S(O)Me group by a 4'-$C(O)NH_2$ substituent led to similar changes in the inotropic activities of the imidazopyridines[3].

Carboxamides **15** and **17** are inotropic agents of approximately equal potency, both *in vitro* and *in vivo*. Thus, N-2

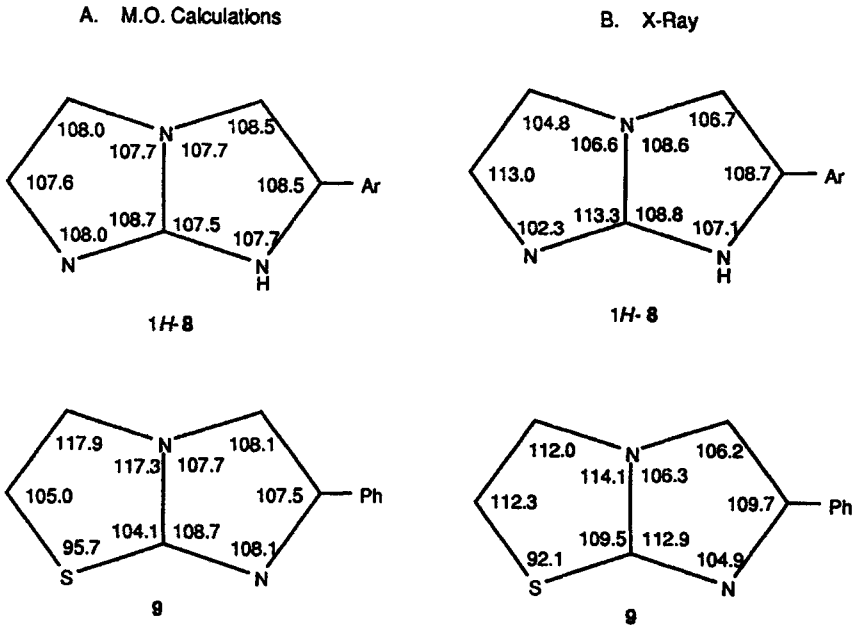


Fig. 3: Bond angles derived from (A) M.O. Calculations and (B) from X-ray crystallographic studies on 1*H*-**8** and 6-phenylimidazo[2,1-*b*]thiazole

Tab. 3: Atomic Co-ordinates of **8**

Atom	x	y	z
O2'	0.2297(2)	-0.0629(2)	-0.0392(1)
O4'	0.0363(2)	-0.0330(2)	0.2760(1)
N1	0.4226(3)	0.3262(2)	-0.0103(2)
N4	0.5141(3)	0.2315(2)	-0.1400(2)
N7	0.5903(3)	0.4486(2)	-0.1195(2)
C2	0.3731(3)	0.1906(3)	-0.0178(2)
C3	0.4292(3)	0.1319(3)	-0.0972(2)
C5	0.6054(3)	0.2583(3)	-0.2157(2)
C6	0.6496(4)	0.3882(3)	-0.2007(2)
C7a	0.5093(3)	0.3477(3)	-0.0859(2)
C1'	0.2819(3)	0.1347(3)	0.0579(2)
C2'	0.2106(3)	0.0069(3)	0.0470(2)
C3'	0.1296(3)	-0.0440(3)	0.1208(2)
C4'	0.1181(3)	0.0303(3)	0.2077(2)
C5'	0.1845(3)	0.1556(3)	0.2213(2)
C6'	0.2642(4)	0.2067(3)	0.1456(2)
C12	0.1665(4)	-0.1958(3)	-0.0504(2)
C13	0.0330(4)	0.0284(4)	0.3709(2)
H1	0.408(3)	0.392(3)	0.041(2)
H3	0.412(3)	0.040(3)	-0.125(2)
H5	0.630(3)	0.188(2)	-0.265(2)
H6	0.710(3)	0.443(3)	-0.240(2)
H3'	0.076(3)	-0.131(2)	0.112(2)
H5'	0.180(3)	0.218(3)	0.279(2)
H6'	0.313(3)	0.295(3)	0.156(2)
H8	0.189(3)	-0.229(3)	-0.118(2)
H9	0.213(3)	-0.262(3)	0.002(2)
H10	0.053(3)	-0.193(3)	-0.058(2)
H11	-0.037(3)	-0.033(3)	0.411(2)
H12	0.138(3)	0.037(3)	0.407(2)
H13	-0.016(3)	0.129(3)	0.361(2)

methylation of heterocycle **15** appears to have little, if any, effect on its inotropic properties. This result contrasts with the reduction in inotropism usually observed[6,7] when other sulmazole analogues are methylated. In view of this finding it will be of interest to determine the inotropic activities of the N-methyl derivatives corresponding to the four possible tautomers of heterocycle **15** and also to investigate the tautomerism of **15** and **17**.

The principal effects of analogues **12**, **15**, and **17** *in vivo* were a dose-dependent inotropic effect (increase in dP/dt), a rise in heart rate (HR), and a fall in diastolic blood pressure (BP). A preliminary evaluation of these analogues showed that compound **12** and sulmazole had similar potencies for eliciting these effects. Heterocycles **15** and **17**, however, appeared to be a little more selective as inotropes than sulmazole (**15**, $ED_{30}BP$ 1.2, $ED_{10}HR > 3.0$; **17**, $ED_{30}BP > 3.0$, $ED_{10}HR$ 0.5, n = 2; sulmazole, $ED_{30}BP$ 1.25, $ED_{10}HR$ 0.5 mg kg^{-1}), and the duration of the inotropic effects of **15** also appeared greater than that for sulmazole (60 *vs* 30 min, bolus *iv*). Further comparative experiments (n > 3) will be required, however, to determine whether these apparent small selectivity differences are significant.

In summary, our SAR hypotheses, with the exception of the prediction for analogue **8**, appeared to be correct. The 1,4-dihydroimidazo[4,5-*c*]pyrazole ring system proved to be the best bio-isostere for the imidazopyridine moiety of sulmazole. Further studies of analogues **15** and **17**, and their methyl derivatives may prove to be of value in understanding the SAR's of sulmazole analogues.

We wish to thank the staff of Molecular Structure Corporation, 3304 Longmire Drive, College Station, Texas 77840, U.S.A. for the X-ray crystallographic study and Mr. *C.J. Wharton* for valuable discussions.

Experimental Part

Melting points: Kofler hot-stage instrument, uncorrected.- ^{1}H-NMR spectra: Bruker HFX90 (90 MHz), Bruker AM-200 (200 MHz), or WM 360 (360 MHz), TMS as internal standard.- Mass spectra: Kratos MS-25 70 eV.- Org. extracts were dried over $MgSO_4$.

2-(2,4-Dimethoxyphenyl)-1H-imidazo[1,2-a]imidazole (**8**) *and 1-(2,4-Dimethoxybenzoylmethyl)-6-(2,4-dimethoxyphenyl)-1H-imidazo [1,2-a]imidazole* (**20**)

2-Aminoimidazole hydrochloride (**18**)[9] (478 mg, 4.0 mmol) was stirred in ethanol (10 ml) at 70°C as 2-bromo-2',4'-dimethoxyacetophenone (**19**) (1.04 g, 4.0 mmol) was added, followed by $NaHCO_3$ (672 mg, 8.0 mmol). After 20 min a white solid precipitated. Heating was continued for 3 h, and the mixture allowed to stand overnight. Conc. HCl (1 ml) was added and the mixture refluxed for 5 h. Ethanol was then evaporated, the mixture neutralized with $NaHCO_3$ and extracted with $CHCl_3$. The extracts were dried and the solvent removed *in vacuo*. T.l.c. (silica, $CHCl_3$-MeOH 10:1) showed two components, R_f 0.34 and 0.59 which were separated by column chromatography (silica, $CHCl_3$-MeOH 19:1). The lower R_f compound was **8** (170 mg, 17%) m.p. 170°C.- $C_{13}H_{13}N_3O_2 \cdot 0.1\ H_2O$ (245.1) Calcd. C 63.7 H 5.43 N 17.2 Found C 63.5 H 5.39 N 17.0.- ^{1}H-NMR (200 MHz, $CDCl_3$): δ (ppm) = 3.81 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 6.45 (2H, m, H-3', H-5'), 6.99 (2H, s, H-5, H-6), 7.42 (1H, s, H-3), 7.73 (1H, d, J = 8.5 Hz, H-6'), 8.47 (1H, s, exch., NH).- m/z 243 (M^+).- The higher R_f compound was assigned structure **20** (360 mg, 43%), m.p. 161-167°C.- $C_{23}H_{23}N_3O_5$ (421.5) Calcd. C 65.5 H 5.50 N 9.98 Found C 65.3 H 5.56 N 9.75.- ^{1}H-NMR (200 MHz, dmso-d_6): δ (ppm) = 3.78 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 4.04 (3H, s, OCH_3), 5.34 (2H, s, NCH_2), 6.53 (1H, dd, J = 1; 8 Hz, H-5'), 6.61 (1H, d, J = 1 Hz, H-3'), 6.70 (1H, dd, J = 1; 8 Hz, H-5'), 6.78 (1H, d, J = 1 Hz, H-3'), 7.05 (1H, d, J = 2.5 Hz, H-2), 7.25 (1H, d, J = 2.5 Hz, H-3), 7.57 (1H, s, H-5), 7.85 (1H, d, J = 8 Hz, H-6'), 7.88 (1H, d, J = 8 Hz, H-6'). n.O.e. experiments: Irradiation of the δ = 5.34 signal (NCH_2) gave a strong enhancement of the δ = 7.05 signal (H-2); irradiation of the δ = 7.57 signal (H-5) gave an enhancement of the δ = 7.25 signal (H-3).

Ketone **20** (0.30 g, 0.71 mmol) was dissolved in 80% aqueous acetic acid (12 ml) and zinc powder (0.90 g, 13.8 mmol, acid-washed) was added in portions with vigorous stirring over 10 min. The mixture was stirred at room temp. for 5 h, the excess zinc removed by filtration and the filtrate evaporated. 2 N HCl (25 ml) was added to the residue, the resulting solution washed twice with ethyl acetate, and then basified with 6% aqueous $NaHCO_3$ solution. The mixture was extracted twice with chloroform, the extracts dried and evaporated to yield a gum. This material was stirred with ethylenediaminetetracetic acid disodium salt (0.50 g) and water (10 ml) for 1 h and then warmed until solution occurred. After cooling, the mixture was basified with 6% aqueous $NaHCO_3$ solution and extracted twice with chloroform. The extracts were dried and evaporated giving a crystalline solid. Recrystallisation from ethyl acetate yielded 0.12 g (70%) of **8**, m.p. 171-173°C. Admixture with the sample isolated by chromatography, as described above, did not depress the m.p. Treatment with methanolic HCl gave **8** · HCl, m.p. 232-235°C (dec.) (ethanol-ether).- $C_{13}H_{13}N_3O_2 \cdot HCl$ (279.7) Calcd. C 55.8 H 5.04 N 15.0 Cl 12.7 Found C 56.0 H 5.17 N 15.0 Cl 13.0.

6-(2,4-Dimethoxyphenyl)imidazo[2,1-b]thiazole (**9**)

was prepared by reaction of 2-aminothiazole with bromide **19** according to *Andreani* et al.[12]. **9** · HCl, m.p. 231-233°C.- $C_{13}H_{12}N_2O_2S \cdot HCl \cdot 0.5\ H_2O$ (305.8) Calcd. C 51.1 H 4.61 Cl 11.6 N 9.16 S 10.5 Found C 51.3 H 4.38 Cl 11.4 N 8.87 S 10.8.

5-(4-Cyano-2-methoxyphenyl)-1,4-dihydro-1-methylimidazo [4,5-d]imidazole (**10**)

1-Methyl-4,5-diaminoimidazole (**22**) hydrochloride[13] (1.48 g, 0.01 mol) and 2-methoxy-4-cyanobenzoic acid (**23**)[14] (1.77 g, 0.01 mol) were pulverized together and added portionwise to $POCl_3$ (50 ml). The mixture was heated at reflux for 3 h, cooled to room temp. and the resulting precipitate collected by filtration. This material was stirred in water and the mixture neutralized with 2 N NaOH solution. The resulting solid was filtered off and recrystallized from EtOH-H_2O to give 0.95 g (38%) of **10**, m.p. 293-295°C (dec.).- $C_{13}H_{11}N_5O$ (253.3) Calcd. C 61.7 H 4.38 N 27.7 Found C 61.5 H 4.51 N 27.5.- ^{1}H-NMR (200 MHz, dmso-d_6): δ (ppm) = 3.80 (3H, s, NMe), 4.04 (3H, s, OMe), 7.47 (1H, dd, J = 8; 1 Hz, H-5'), 7.61 (1H, d, J = 1Hz, H-3'), 7.65 (1H, s, H-2), 8.31 (1H, d, J = 8 Hz, H-6').- m/z = 253 (M^+).

5-(4-Carbamoyl-2-methoxyphenyl)-1,4-dihydro-1-methylimidazo [4,5-d]imidazole (**11**)

Nitrile **10** (0.70 g) and conc. H_2SO_4 (15 ml) were stirred together at 0°C for 2 h. The resulting solution was allowed to stand at room temp. for 48 h, then poured onto ice, and the mixture neutralized with 10 N NaOH at 10°C. The insoluble solid was filtered off, dried, and then dissolved in 2 N HCl solution. The solution was evaporated to dryness and the residue recrystallized from EtOH to give 0.32 g (35%) of **11** hydrochloride hydrate, m.p. 281-283°C (dec.).- $C_{13}H_{13}N_5O_2 \cdot 1.1\ HCl \cdot 1.1\ H_2O$ (331.2) Calcd. C 47.1 H 4.96 N 21.2 Cl 11.8 Found C 47.3 H 5.10 N 20.8 Cl 11.8.- ^{1}H-NMR (200 MHz, dmso-d_6): δ (ppm) = 3.98 (3H, s, NMe), 4.06 (3H, s, OMe), 3.6-4.4 (2H, v.br. peak, NH_2, exchang.), 7.46 (1H, br. s, NH, exchang.), 7.61 (1H, dd, J = 8; 1 Hz, H-5'), 7.68 (1H, d, J = 1 Hz, H-3'), 8.10 (1H, br. s, NH, exchang.), 8.17 (1H, d, J = 8 Hz, H-6'), 8.58 (1H, br. s, H-2).- m/z = 271 (M^+).

1,4-Dihydro-5-(2-methoxy-4-methylthiophenyl)imidazo[4,5-c]pyrazole (**13**)

3,4-diaminopyrazole **24** dihydrochloride[15] (3.42 g, 0.02 mol) and 2-methoxy-4-methylthiobenzoic acid (**25**)[6] (3.96 g, 0.02 mol) were pulverized to a fine powder and added in portions to $POCl_3$ (100 ml) with stirring. The reaction mixture was then heated at reflux for 3 h. Volatiles were removed *in vacuo* and the residue triturated with ice-water. The resulting yellow solid was collected by filtration, then stirred in water and the pH of the suspension adjusted to 9.0 with 0.880 NH_3. After standing for 1 h, the solid was collected by filtration, recrystallized from EtOH-H_2O, and dried at room temp. to give 4.0 g (72%) of **13**, m.p. 250-251°C.- $C_{12}H_{12}N_4OS \cdot H_2O$ (278.3) Calcd. C 51.8 H 5.06 N 20.1 Found C 52.0 H 5.00 N 19.9.- ^{1}H-NMR (200 MHz, dmso-d_6): δ (ppm) = 2.54 (3H, s, SMe), 4.02 (3H, s, OMe), 6.88-7.05 (2H, m, H-3', H-5'), 7.40 (1H, br. s, H-3), 8.12 (1H, d, J = 8 Hz, H-6').

1,4-Dihydro-5-(2-methoxy-4-methylsulphinylphenyl)imidazo [4,5-c]pyrazole (**12**)

Sulphide **13** (3.90 g, 0.014 mol) was suspended in dry $CHCl_3$ (180 ml) and cooled to -15°C. A solution of *m*-chloroperbenzoic acid (3.0 g, 85%, 0.015 mol) in dry $CHCl_3$ (35 ml) was added dropwise to the above suspension at such a rate that the temp. was maintained below -10°C. The reaction mixture was stirred at -10°C for 2 h and then filtered to remove unreacted **13**. The filtrate was washed with 5% aqueous $NaHCO_3$ solution (3 x 100 ml), the aqueous layers were saturated with NaCl, and then extracted with $CHCl_3$ (3 x 100 ml). The combined $CHCl_3$ extracts were dried and evaporated *in vacuo* to give a tan foam. This material was purified by flash chromatography (R_f 0.3, SiO_2, CH_2Cl_2 - MeOH, 94:6), then dissolved in N HCl and evaporated to dryness. The residue was crystallized from MeOH-ether to give 1.3 g (28%) of **12** hydrochloride, m.p. 185-188°C.- $C_{12}H_{12}N_4O_2S \cdot HCl \cdot 1.2\ H_2O$ (334.4) Calcd. C 43.1 H 4.64 N 16.8 Cl 10.6 Found C 43.0 H 4.55 N 16.7 Cl 10.8.- ^{1}H-NMR (200 MHz, dmso-d_6): δ (ppm) = 2.88 (3H, s, SMe), 4.11 (3H, s, OMe), 7.52 (1H, dd, J = 8; 1 Hz, H-5'), 7.61 (1H, d, J = 1 Hz, H-3'), 8.10 (1H, s, H-3), 8.36 (1H, d, J = 8 Hz, H-6').- m/z = 276 (M^+).

5-(4-Cyano-2-methoxyphenyl)-1,4-dihydroimidazo[4,5-c]pyrazole (**14**)

3,4-Diaminopyrazole (**24**)[15] dihydrochloride (3.45 g, 0.02 mol), 4-cyano-2-methoxybenzoic acid (**23**)[14] (3.66 g, 0.02 mol) and $POCl_3$ (100 ml) were reacted as for the preparation of **10**. The mixture was worked up as before and the crude product was chromatographed on silica, eluting

with CH_2Cl_2 - MeOH (9:1), to give 0.62 g (12%) of **14**, m.p. 256-258°C.- $C_{12}H_9N_5O$ (239.2) Calcd. C 60.2 H 3.79 N 29.3 Found C 60.5 H 4.01 N 29.1.- ^{1}H-NMR (200 MHz, dmso-d_6): δ (ppm) = 4.06 (3H, s, OMe), 7.48 (1H, br. s, H-3), 7.51 (1H, dd, J = 1; 8 Hz, H-5'), 7.68 (1H, d, J = 1 Hz, H-3'), 8.35 (1H, d, J = 8 Hz, H-6'), 11.8 (br. peak, NH, exchang.), 12.7 (br. peak, NH, exchang.).- m/z = 239 (M^+).

5-(4-Carbamoyl-2-methoxyphenyl)-1,4-dihydroimidazo[4,5-c]pyrazole(**15**)

Nitrile **14** (0.50 g) and conc. H_2SO_4 (10 ml) gave, by the method used to prepare **11**, a 46% yield (0.30 g) of **15** hydrochloride, m.p. 225-226°C (dec.).- $C_{12}H_{11}N_5O_2 \cdot HCl \cdot H_2O$ (311.7) Calcd. C 46.2 H 4.53 N 22.5 Cl 11.4 Found C 46.0 H 4.49 N 22.8 Cl 11.6.- ^{1}H-NMR (200 MHz, dmso-d_6) δ (ppm) = 3.0-5.0 (3H, v. br. peak, NH's, exchang.), 4.08 (3H, s, OMe), 7.62 (1H, br. s, NH, exchang.), 7.68 (1H, dd, J = 8; 1Hz, H-5'), 7.77 (1H, d, J = 1 Hz, H-3'), 8.08 (1H, br. s, H-3), 8.26 (2H, br. d, J = 8 Hz, H-6', NH, 1H exchang.).- m/z = 257 (M^+).

5-(4-Cyano-2-methoxyphenyl)-2,4-dihydro-2-methylimidazo[4,5-c]pyrazole (**16**)

3,4-Diamino-1-methylpyrazole (**26**) dihydrochloride (1.10 g, 6.0 mmol), acid **23**[14] (1.06 g, 6.0 mmol) and $POCl_3$ (30 ml) gave, by a procedure analogous to that used for the preparation of **10**, a 53% yield (0.80 g) of **16**, m.p. 235-237°C.- $C_{13}H_{11}N_5O$ (253.3) Calcd. C 61.7 H 4.37 N 27.7 Found C 61.5 H 4.45 N 27.4.- ^{1}H-NMR (200 MHz, dmso-d_6): δ (ppm) = 3.98 (3H, s, NMe), 4.04 (3H, s, OMe), 7.52 (1H, dd, J = 8; 1 Hz, H-5'), 7.61 (1H, s, H-3), 7.69 (1H, d, J = 1 Hz, H-3'), 8.37 (1H, d, J = 8 Hz, H-6'), 11.5 (1H, br. s, NH, exchang.).- m/z = 253 (M^+).

5-(4-Carbamoyl-2-methoxyphenyl)-2,4-dihydro-2-methylimidazo [4,5-c]pyrazole (**17**)

Nitrile **16** (0.7 g) and conc. H_2SO_4 (15 ml) gave by the method used to prepare **11** 0.50 g (54%) of **17** hydrochloride, m.p. 218-222°C (dec.).- $C_{13}H_{13}N_5O_2 \cdot 1.1\ HCl \cdot 1.25\ H_2O$ (333.7) Calcd. C 46.8 H 5.01 N 21.0 Cl 11.7 Found C 46.8 H 4.89 N 20.9 Cl 11.8.- ^{1}H-NMR (200 MHz, dmso-d_6): δ (ppm) = 3.6-4.4 (2H, v. br. peak, NH_2, exchang.), 4.08 (6H, s, NMe, OMe), 7.62 (1H, br. s, NH, exchang.), 7.68 (1H, dd, J = 8; 1 Hz, H-5'), 7.77 (1H, d, J = 1 Hz, H-3'), 8.12 (1H, s, H-3), 8.27 (2H, br. d, J = 8 Hz, H-6', NH, 1H exchang.).- m/z = 271 (M^+).

3-Acetamido-1-methylpyrazole (**28**)

3(5)-Acetamidopyrazole (**27**)[15] (15.0 g, 0.12 mol), acetonitrile (150 ml), K_2CO_3 (50.0 g, 0.36 mol) and iodomethane (75 ml, 1.2 mol) were stirred and heated at reflux for 3 h. More iodomethane (75 ml) was added and heating continued for a further 3 h. After cooling, the mixture was evaporated, the residue stirred with $CHCl_3$ (150 ml) for 15 min and then filtered. The filtrate was evaporated, the residual solid chromatographed on silica, and elution with CH_2Cl_2-MeOH (99:1) gave 7.5 g (45%) of **28**, m.p. 103-104°C.- $C_6H_9N_3O$ (139.2) Calcd. C 51.8 H 6.52 N 30.2 Found C 52.0 H 6.64 N 29.9.- ^{1}H-NMR (200 MHz, dmso-d_6): δ (ppm) = 1.97 (3H, s, C-Me), 3.71 (3H, s, N-Me), 6.40 (1H, d, J = 0.7 Hz, H-4), 7.50 (1H, d, J = 0.7 Hz, H-5), 10.3 (1H, br. s, NH, exchang.). n.O.e. experiments: Irradiation of the δ = 3.71 signal (N-Me) gave an enhancement of the δ = 7.50 signal (H-5) only. Irradiation of the δ = 10.3 signal (NH) gave an enhancement of the δ = 1.97 signal (C-Me).

3-Acetamido-1-methyl-4-nitropyrazole (**29**)

Amide **28** (7.0 g, 0.05 mol) was dissolved in conc. H_2SO_4 (28 ml at 0°C) and fuming HNO_3 (2.80 ml, d = 1.52, 0.07 mol) added over 10 min with stirring and external cooling to maintain the temp. at 0°C. The mixture was stirred at 0-5°C for 2 h, poured onto ice (150 g) with vigorous stirring, and the solid collected by filtration. This material was crystallized from water and dried under vacuum at 80°C to give 5.3 g (56%) of **29** hydrate, m.p. 154-157°C; lit.[27,28]: m.p. 181-182°C (anhyd.).- $C_6H_8N_4O_3 \cdot 0.25\ H_2O$ (188.7) Calcd. C 38.2 H 4.54 N 29.7 Found C 38.2 H 4.26 N 29.9.- ^{1}H-NMR (200 MHz, dmso-d_6): δ (ppm) = 2.04 (3H, s, C-Me), 3.84 (3H, s, N-Me), 8.75 (1H, s, H-5), 10.1 (1H, br. s, NH, exchang.). The aqueous filtrate from the above experiment was extracted with $CHCl_3$ (3x), the combined extracts were dried and evaporated to give 2.2 g of a yellow solid. This material was shown, by n.m.r., to be a 6:1 mixture of **30** and **29**.

3-Amino-1-methyl-4-nitropyrazole (**30**)

Amide **29** (5.0 g, 0.03 mol) and 5 N HCl (40 ml, 0.20 mol) were stirred and heated at reflux for 3 h. The cooled mixture was evaporated to dryness and the residue crystallized from methanol to give 3.4 g (88%) of **30**, m.p. 197-199°; lit:[28]: m.p. 200°C.- $C_4H_6N_4O_2$ (142.1) Calcd. C 33.8 H 4.25 N 39.4 Found C 33.9 H 4.35 N 39.2.- ^{1}H-NMR (200 MHz, dmso-d_6): δ (ppm) = 3.66 (3H, s, Me), 6.22 (2H, br. s, NH_2, exchang.), 8.45 (1H, s, H-5). n.O.e. experiments: Irradiation of the δ = 3.66 signal (Me) gave an enhancement of the δ = 8.45 signal (H-5) only.

3,4-Diamino-1-methylpyrazole (**26**) *dihydrochloride*

Nitroamine **30** (2.60 g, 0.02 mol) and 5 N HCl (40 ml, 0.20 mol) were stirred at 95°C and a suspension of $SnCl_2 \cdot 2\ H_2O$ (12.4 g, 0.06 mol) in water (50 ml) was added over 75 min. The mixture was stirred at 95°C for 2 h, cooled to room temp. and H_2S bubbled through the solution until precipitation ceased. Inorganic material was removed by filtration and washed with hot 2 N HCl. The combined filtrates were evaporated and the residue crystallized from ethanol-ether to give 1.9 g (56%) of **26** · dihydrochloride, m.p. 210-212°C.- $C_4H_8N_4 \cdot 2\ HCl$ (185.1) Calcd. C 26.0 H 5.45 N 30.3 Cl 38.3 found C 25.8 H 5.67 N 30.0 Cl 38.1.- ^{1}H-NMR (200 MHz, dmso-d_6): δ (ppm) = 3.72 (3H, s, NMe), 4.0-5.0 (5H, br. peak, NH, exchang.), 7.80 (1H, s, H-5).

Crystallographic data for **8**

$C_{13}H_{13}N_3O_2$, M = 243.3, m.p. 170°C, monoclinic, a = 8.960 (2) Å, b = 9.781 (3) Å, c = 13.411 (2) Å, β = 95.49 (2) Å, V = 1169.9 Å^3, z = 4, D_c = 1.38 g cm^{-3}, F (000) = 512, space group P2(1)/c. Cu-K_α Radiation. μ = 8.0 cm^{-1}, R = 0.051, Rw = 0.060 for 2415 unique reflections. The structure was solved by direct methods using a PDP-11/60 TEXRAY system and refined by weighted full-matrix least-squares techniques with anisotropic temp. factors for all non-H atoms. H-atoms were located and their positions and isotropic thermal parameters refined. No peaks greater than 0.2 eÅ^{-3} were observed in the final difference electron density maps.

Bond lengths (in Å): N1-C2 1.400 (3), N1-C7a 1.351 (3), N4-C3 1.393 (3), N4-C5 1.388 (3), N4-C7a 1.351 (3), N7-C6 1.389 (3), N7-C7a 1.329 (3), N1-H1 0.96 (3), C2-C3 1.349 (4), C1-C1' 1.468 (4), C3-H3 0.98 (3), C5-C6 1.340 (4), C5-H5 0.99 (3), C6-H6 0.96 (3), C1'-C2' 1.405 (3).

Bond Angles: C2-N1-C7a 107.1 (2), C3-N4-C7a 108.6 (2), C3-N4-C5 144.8 (2), C5-N4-C7a 106.6 (2), C6-N7-C7a 102.3 (2), C2-N1-H1 129. (2), C7a-N1-H1 124. (2), N1-C2-C3 108.7 (2), N1-C2-C1' 119.8 (2), N4-C3-C2 106.7 (2), N4-C3-H3 124. (2), C2-C3-H3 129. (2), N4-C5-C6 104.8 (3), N4-C5-H5 123. (2), C6-C5-H5 132. (2), N7-C6-C5 113.0 (3), N7-C6-H6 118. (2), C5-C6-H6 129. (2), N4-C7a-N7 113.3 (3), N4-C7a-N1 108.8 (2), N7-C7a-N1 137.8 (3), C2-C1'-C2' 122.5 (2). Atomic Co-ordinates: Tab. 3.

Further details of the crystallographic study, including a full list of bond lengths, bond angles, torsion angles, Beq values etc. are available from the authors.

Crystallographic data for 6-phenylimidazo[2,1-b]thiazole has been reported[22].

Bond lengths: S-C2 1.735 (6), S-C7a 1.725 (5), N4-C3 1.420 (6), N4-C5 1.382 (6), N4-C7a 1.389 (7), N7-C6 1.413 (6), N7-C7a 1.311 (6), C2-C3 1.344 (8), C5-C6 1.389 (7), C6-C1' 1.450 (7).

Bond angles: C2-S-C7a 92.1 (5), S-C7a-N4 109.5 (5), N4-C7a-N7 112.9 (7), C3-N4-C7a 114.1 (8), C5-N4-C7a 106.3 (7), S-C2-C3 112.3 (7), C2-C3-N4 112.0 (8), N4-C5-C6 106.2 (7), C5-C6-N7 109.7 (7), C6-N7-C7a 104.9 (7).

Calculations of Molecular Properties

The geometries, bond orders and heats of formation of the heterocycles were deduced by AM1 (Austin Method 1) calculations[17] using MOPAC[18,19] software on a Cray X-MP28 supercomputer. The semi-emperical molecular orbital program MOPAC uses the AM1, MNDO, MINDO/3, and MNDO-PM3 Hamiltonians. The AM1 method has been parameterized for the elements C, H, N, and O. For the sulphur atom MNDO parameters[20] were used. Atom-centred charge densities and dipole moments were calculated using the semi-empirical molecular orbital method CNDO/2[16,29]. Two conformers of each heterocycle were studied, namely those in which the 'B' ring N-atom and 2'-OMe group are in close proximity (conformer NO as shown in the structural formulaes) and those were the 'B' ring N-atoms and H-6' are adjacent (conformers NH as in Figure 1). The bond orders (n) obtained from the AM1 (Mulliken Population Analysis) show little variation (+ 0.01) with conformation and are given in Figure 2. Other molecular properties are given in Table 2.

Bond orders (*n*) and *Bird* aromaticity indices were also calculated from the experimentally determined bond lengths (R) using the *Gordy* relationship, $n = aR^{-2} + b$ employing the values for constants a and b utilised by Bird[21]. The magnitudes of a and b are based on standard pure bond lengths and electronegativity values.

Pharmacological Methods

Paced Guinea-pig Papillary Muscles

Single right ventricular muscle preparations, from male guinea-pigs, were employed in organ-bath experiments at 34°C. Stimulation was effected by rectangular pulses of 1 msec 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 concentration required to increase basal contractility by 50% ($pA_{50\%}$). Full details of the experimental protocol have been described[3].

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, dP/dt, were measured by the insertion of a short cannula (containing heparinized 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 heparinized 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 i.e. the dose required to produce a maximum increase of 50% above the basal value of dP/dt. 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[3].

References

1 P.W. Erhardt, J. Med. Chem. *30*, 231 (1987) and references therein.
2 D. El Allaf, V. D'Orio, and J. Carlier, Arch. Int. Physiol. Biochim. *92*, S69 (1984).
3 P. Barraclough, J.W. Black, D. Cambridge, V.P. Gerskowitch, R.A.D. Hull, R. Iyer, W.R. King, C.O. Kneen, M.S. Nobbs, G.P. Shah, S. Smith, S.J. Vine, and M.V. Whiting, Arch. Pharm. (Weinheim) *323*, 501 (1990).
4 P. Barraclough, S. Smith, R. Iyer, and M.S. Nobbs, Eur. Patent Appl. 166, 609; C.A. *104*, 224913d (1986).
5 W.A. Spitzer, F. Victor, G.D. Pollock, and J.S. Hayes, J. Med. Chem. *31*, 1590 (1988).
6 P. Barraclough, R.M. Beams, J.W. Black, D. Cambridge, D. Collard, D.A. Demaine, D. Firmin, V.P. Gerskowitch, R.C. Glen, H. Giles, A.P. Hill, R.A.D. Hull, R. Iyer, W.R. King, D.J. Livingstone, M.S. Nobbs, P. Randall, G. Shah, S.J. Vine, and M.V. Whiting, Eur. J. Med. Chem. *25*, 467 (1990) and references therein.
7 Authors unpublished results.
8 J. Elguero, R.M. Claramunt, and A.J.H. Summers, Adv. Heterocyclic Chem., ed., A.R. Katritzky and A.J. Boulton, Academic Press, Vol. 22, p. 183-320 (1978).
9 G. Heinisch and W. Reusser, Sci. Pharm. *42*, 19 (1974).
10 B.A. Priimenko and P.M. Kochergin, Khim. Issled. Farm. *53* (1970); C.A. *76*, 34170q (1972).
11 F. Compernolle and S. Toppet, J. Heterocycl. Chem. *23*, 541 (1986).
12 A. Andreani, M. Rambaldi, D. Bonazzi, G. Lelli, R. Bossa, and I. Galatulas, Eur. J. Med. Chem. *19*, 219 (1984).
13 R.P. Panzica and L.B. Townsend, J. Chem. Soc. Perkin 1, *1973*, 244.
14 P. Barraclough, R. Iyer, J.C. Lindon, and J.M. Williams, Tetrahedron Lett. *27*, 5997 (1986).
15 H. Dorn and H. Dilcher, Liebigs Ann. Chem. *707*, 141 (1967).
16 CNDO/2 (1966) CICPE91, Quantum Chemical Program Exchange, Department of Chemistry, University of Indiana, Bloomington, IN, USA.
17 M.J.S. Dewar, E.G. Zoebisch, E.F. Healy, and J.J.P. Stewart, J. Am. Chem. soc. *107*, 3902 (1985).
18 J.J.P. Stewart, J. Comp. Aid. Mol. Design *4*, 1 (1990).
19 MOPAC, Version 5.0. J.J.P. Stewart, Quantum Chemical Program Exchange, Department of Chemistry, University of Indiana, Bloomington, Indiana IN, U.S.A.
20 M.J.S. Dewar and C.H. Reynolds, J. Comp. Chem. *7*, 140 (1986).
21 C.W. Bird, Tetrahedron *41*, 1409 (1985).
22 L. Cavalca, P. Domiano, and A. Musatti, Cryst. Struct. Comm. *1*, 345 (1972).
23 L. Marchetti, L. Pentimalli, P. Lazzeretti, L. Schenetti, and F. Taddei, J.C.S. Perkin II, *1973*, 1926.
24 A.R. Katritzky, M. Karelson, and N. Malhotra, Heterocycles *32*, 127 (1991).
25 F. Fringuelli, G. Marino, A. Taticchi, and G. Grandolini, J.C.S. Perkin Trans 2, *1974*, 332.
26 P. Barraclough, R.D. Farrant, R.C. Glen, J.C. Lindon, M. Liu, and S. Smith, Magn. Reson. Chem. *29*, 1147 (1991).
27 M.E.C. Biffin, D.J. Brown, and Q.N. Porter, J. Chem. Soc. (C) *1968*, 2159.
28 M.A. Khan and B.M. Lynch, Can. J. Chem. *49*, 3566 (1971).
29 J.A. Pople and G.A. Segal, J. Chem. Phys. *44*, 3289 (1966).
30 P. Barraclough, D. Firmin, R. Iyer, W.R. King, J.C. Lindon, M.S. Nobbs, S. Smith, C.J. Wharton, and J.M. Williams, J. Chem. Soc. Perkin Trans 2, *1988*, 1839.

[Ph949]