Selective Thromboxane Synthetase Inhibitors. 2. 3-(1*H*-Imidazol-1-ylmethyl)-2-methyl-1*H*-indole-1-propanoic Acid and Analogues

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The preparation of a series of 3-(1*H*-imidazol-1-ylmethyl)-1*H*-indole-1-alkanoic acids is described. Several compounds were found to be more potent thromboxane synthetase inhibitors than the corresponding analogues lacking an acidic substituent. In the cases examined, compounds had no significant activity against PGI_2 synthetase or cyclooxygenase, and introduction of the carboxylic acid substituent led to a reduction in activity against adrenal steroid 11β-hydroxylase. Compound **21** strongly inhibited thromboxane formation after iv administration to anesthetized rabbits and oral administration to conscious dogs. The compound had a long duration of action, and marked inhibition of thromboxane production was observed 15 h after oral administration of 1 mg/kg to conscious dogs.

Selective inhibition of thromboxane (TxA_2) synthetase, thereby preventing formation of the vasoconstrictor and platelet aggregating agent TxA_2, is an attractive possible approach to the treatment of cardiovascular diseases where vasospasm or thrombosis may be important.[1-4] Such an approach has the additional potential advantage that unused prostaglandin H_2, the precursor to TxA_2, may be utilized for increased production of the vasodilator and antiaggregatory prostaglandin I_2.[4,5]

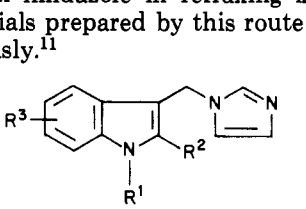
There is evidence that TxA_2 synthetase is a cytochrome P-450 enzyme[6] and it is strongly inhibited by 1-substituted imidazoles[7-11] which presumably act by coordination of the basic nitrogen at a vacant axial ligand site of a heme unit. 1-Substituted imidazoles are also known to inhibit cytochrome P-450 from a variety of other sources.[12-17]

We have reported previously that 3-(1*H*-imidazol-1-ylmethyl)-1*H*-indoles are potent inhibitors of TxA_2 synthetase, and two compounds in particular, **1** and **2**, show a high degree of selectivity with respect to other enzymes in the arachidonic acid pathway, namely PGI_2 synthetase and cyclooxygenase.[11] Further progression of **2** (UK-34,787) was not pursued since it also inhibits other cytochrome P-450 enzymes which could lead to undesirable effects in vivo. Thus, it markedly inhibited adrenal steroid 11β-hydroxylase and prolonged pentobarbitone sleeping time in rats, indicating liver microsomal enzyme inhibition.[18]

In the previous paper in this series[19] it was reported that 1-(2-phenoxyethyl)-1*H*-imidazole was a moderately potent inhibitor of TxA_2 synthetase but, like **1** and **2**, also inhibited steroid 11β-hydroxylase. However, it was found that introduction of a carboxylic acid group at a suitable distance from the imidazole ring can increase potency against TxA_2 synthetase with the additional advantage that activity against adrenal steroid 11β-hydroxylase is reduced. The most potent and selective compound was found to be dazoxiben (**31**), which has undergone extensive clinical evaluation.[20]

In view of our findings in the dazoxiben series we were interested in seeing if introduction of an acidic side chain on the indole nitrogen of **1**, **2**, and related compounds would also have a favorable effect on potency and selectivity.

Chemistry. The general route used for the preparation of compounds consisted of N-alkylation of a substituted 3-(1*H*-imidazol-1-ylmethyl)-1*H*-indole to produce an ester or nitrile derivative, followed by basic hydrolysis. Two novel starting materials **4** and **5** were prepared by treatment of the corresponding 3-[(dimethylamino)methyl]-1*H*-indole with imidazole in refluxing xylene. Other starting materials prepared by this route have been reported previously.[11]



1, $R^1=R^2=R^3=H$
2, $R^1=R^3=H$; $R^2=CH(CH_3)_2$
3, $R^1=R^3=H$; $R^2=CH_3$
4, $R^1=R^2=H$; $R^3=5\text{-}Cl$
5, $R^1=R^2=H$; $R^3=6\text{-}CF_3$
6, $R^1=C_2H_5$; $R^2=R^3=H$
7, $R^1=CH_2CO_2C_2H_5$; $R^2=R^3=H$
8, $R^1=CH_2CO_2H$; $R^2=R^3=H$

Alkylation of **1** using NaH followed by diethyl sulfate or ethyl bromoacetate in DMF gave the ethyl derivative

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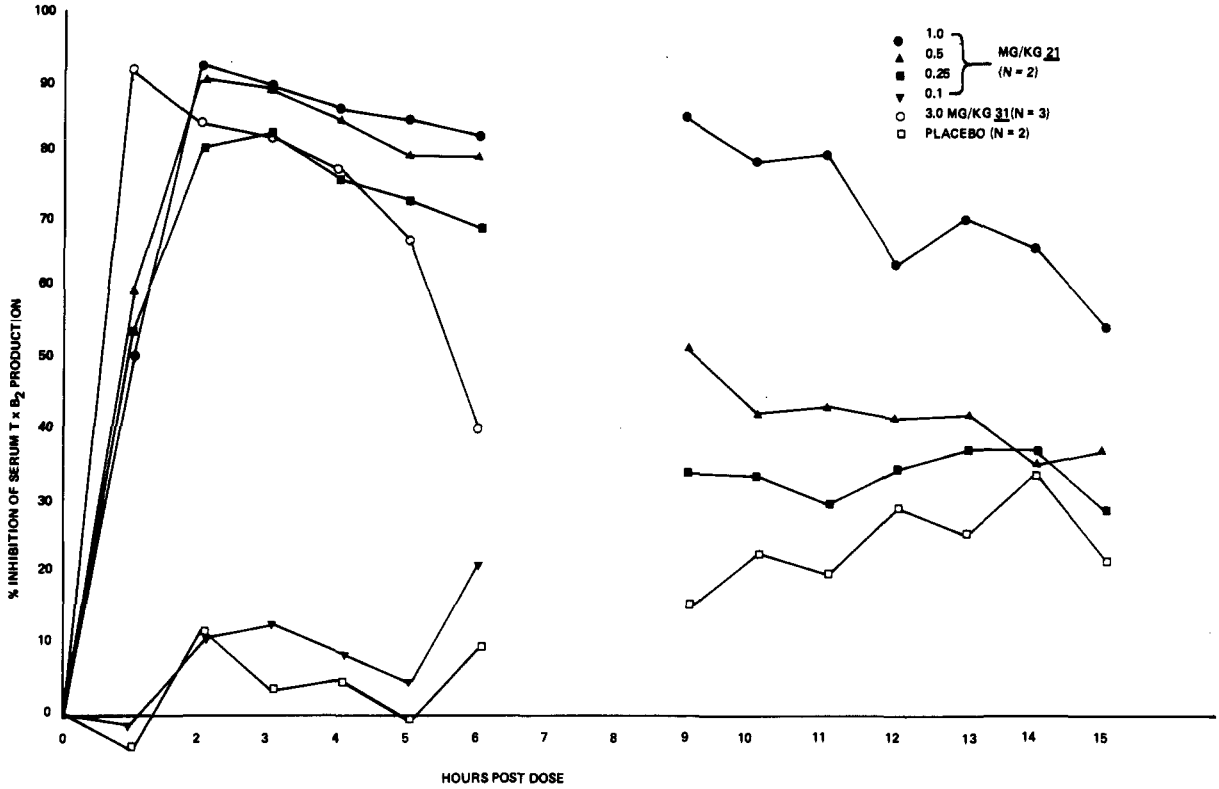
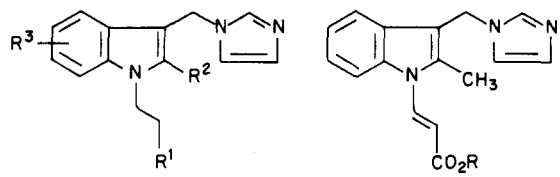


Figure 1. Inhibition of TxB_2 production in whole blood from dogs following a single oral dose of **21**.

6 and the ester **7**, respectively. Compound **6** was prepared to provide a comparison with a nonacidic N-substituent. Nitrile precursors (**8–17**) to *N*-propanoic acid derivatives were prepared by treatment of a 3-(1*H*-imidazol-1-ylmethyl)-1*H*-indole with acrylonitrile in dioxane in the presence of benzyltrimethylammonium hydroxide. Treatment of **3** with ethyl propiolate under the same conditions gave only a low yield of the propenoic ester **18** together with much tarry material. A higher yield (52%) was obtained in THF in the presence of tetrabutylammonium fluoride. The propenoic ester was assigned the *E* configuration on the basis of the olefinic proton coupling in the ^1H NMR spectrum (J = 14.3 Hz). The carboxylic acid derivatives **19–30** were prepared by base hydrolysis of the esters **7** and **18** and the nitriles **8–17**.



8–17, R^1 = CN
20–29, R^1 = CO_2H

18, R = C_2H_5
30, R = H

Results and Discussion

The results in Table II show that most of the carboxylic acid analogues have a similar level of activity against TxA_2 synthetase in vitro but that none is as potent as **31**. Comparison of the activity of individual compounds with the corresponding analogue lacking a carboxylic acid side chain shows that the effect of the acidic substituent is variable. Thus, the 5-chloro and 6-trifluoromethyl analogues **26** and **29** are more potent than the precursors **4** and **5**. The 5-methoxy and 5-bromo compounds **25** and **27** are also more potent than the corresponding analogues lacking the acidic side chain,[11] but, in the case of other compounds, there seems to be no particular potency advantage on introducing an acid side chain. In fact, the *N*-ethyl analogue **6** is slightly more potent than the acid derivatives **19** and **20**.

Although the acids **20–22** do not show a significant increase in potency against TxA_2 synthetase, they do show a reduction in potency against steroid 11β-hydroxylase relative to the compounds **1**, **2**, and **6**, which lack a carboxyl group. None of the compounds tested has activity against cyclooxygenase or PGI_2 synthetase at 10^{-4} M.

The efficacy of compounds in vivo was evaluated after intravenous administration to anesthetized rabbits by measurement of the reduction in serum TxB_2, the stable degradation product of TxA_2. In this way **21** (UK-38,485, dazmegrel) was identified as having a high level of activity and results for this compound are summarized in Table III.

Activity was also measured after oral administration to conscious dogs, and two sets of experiments were carried out. In the first, blood samples were taken at hourly intervals for 6 h after dosing, while in the second, samples were taken at hourly intervals between 9 and 15 h after dosing in order to determine the duration of action. The changes in serum TxB_2 levels produced by 0.1 mg/kg of **21** were not significantly different from the placebo values (Figure 1). In contrast, doses of 0.25 mg/kg and above markedly reduced TxB_2 production, and a near maximal effect was obtained 2 h after a dose of 0.5 mg/kg. Of particular note is the duration of inhibition after 1 mg/kg, which was still significantly greater than the placebo level 15 h after dosing. The reason for the higher placebo response after the longer time period is not clear. The long duration of action of 1 mg/kg of **21** contrasts with the relatively short-lived effect of a 3 mg/kg dose of **31** where inhibition of TxB_2 had declined to below 50% after 6 h.

Initial investigations in human volunteers have confirmed that **21** has greater potency and a longer duration of action than **31** after oral administration.[21]

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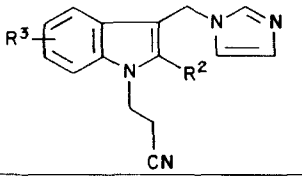
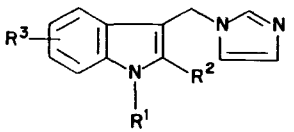
Table I. 3-(1*H*-Imidazol-1-ylmethyl)-1*H*-indole-1-propanenitriles

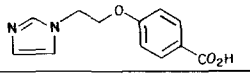


no.	R^2	R^3	mp, °C	yield, %	recrystn solvent	formula[a]
8	H	H	167–169	67	butan-2-one	$C_{15}H_{14}N_4 \cdot C_4H_4O_4$[b]
9	CH_3	H	118–119	49	$CHCl_3$/PE	$C_{16}H_{16}N_4$
10	$CH(CH_3)_5$	H	*c*	80		
11	c-C_3H_5	H	113–114	54	EtOAc/PE	$C_{18}H_{18}N_4$
12	H	5-CH_3	68–70	82	EtOAc	$C_{16}H_{16}N_4$
13	H	5-OCH_3	129–130	65.5	$CHCl_3$/PE	$C_{16}H_{16}N_4O$
14	H	5-Cl	128–130	77	EtOAc	$C_{15}H_{13}ClN_4$
15	H	5-Br	139–141	80	EtOAc/PE	$C_{15}H_{13}BrN_4$
16	H	5-$N(CH_3)_2$	98–99	54	EtOAc/PE	$C_{17}H_{19}N_5$
17	H	6-CF_3	145–146	79	EtOAc/PE	$C_{16}H_{13}F_3N_4$

[a] Compounds gave C, H, and N analyses within 0.4% of the theoretical values. [b] Fumarate salt. [c] Oil, IR 2250 (C≡N). Used without further characterization.

Table II. Chemical Data and Enzyme Inhibition Results for Substituted 3-(1*H*-Imidazol-1-ylmethyl)-1*H*-indoles



								IC$_{50}$,[a] M			
no.	R^1	R^2	R^3	mp, °C	yield, %	recrystn solvent[b]	formula[c]	TxA_2 synthetase	PGI_2 synthetase	cyclo-oxygenase	11β-hydroxylase
1	H	H	H				$C_{12}H_{11}N_3$[d]	2.5×10^{-8}[e]	6.5×10^{-4}	$>10^{-3}$	1.0×10^{-5}
2	H	$CH(CH_3)_2$	H				$C_{15}H_{17}N_3$[d]	1.5×10^{-8}	$>10^{-4}$	$>10^{-4}$	2.0×10^{-6}
4	H	H	5-Cl	195–197	84	*i*-PrOH/PE	$C_{12}H_{10}ClN_3$	3.0×10^{-6}			
5	H	H	6-CF_3	170–171	85	EtOAc/PE	$C_{13}H_{10}F_3N_3$	4.6×10^{-6}			
6	C_2H_5	H	H	106–107	59	MeOH/EtOAc	$C_{14}H_{15}N_3 \cdot C_4H_4O_4$[f]	8.4×10^{-9}		$>10^{-4}$	1.0×10^{-5}
19	CH_2CO_2H	H	H	223–224		H_2O	$C_{14}H_{13}N_3O_2$	3.0×10^{-8}	$>10^{-4}$	$>10^{-4}$	
20	$CH_2CH_2CO_2H$	H	H	142–144	75	H_2O	$C_{15}H_{15}N_3O_2$	1.9×10^{-8}	$>10^{-4}$	$>10^{-4}$	$>10^{-5}$
21	$CH_2CH_2CO_2H$	CH_3	H	195–197	38	MeOH/EtOAc	$C_{16}H_{17}N_3O_2$	$(2.8 \pm 0.26) \times 10^{-8}$ (n = 8)	$>10^{-4}$	$>10^{-4}$	$>10^{-4}$
22	$CH_2CH_2CO_2H$	$CH(CH_3)_2$	H	200–202	37	H_2O	$C_{18}H_{21}N_3O_2$	8.2×10^{-9}	$>10^{-4}$		$>10^{-5}$
23	$CH_2CH_2CO_2H$	c-C_3H_5	H	156–158	44	MeOH/H_2O	$C_{18}H_{19}N_3O_2$	4.9×10^{-9}	$>10^{-4}$		
24	$CH_2CH_2CO_2H$	H	5-CH_3	178–179	45	EtOH	$C_{16}H_{17}N_3O_2$	4.2×10^{-8}	$>10^{-4}$		
25	$CH_2CH_2CO_2H$	H	5-OCH_3	189–190	78	EtOH	$C_{16}H_{17}N_3O_3$	4.3×10^{-8}	$>10^{-4}$		
26	$CH_2CH_2CO_2H$	H	5-Cl	188–189	48	EtOH	$C_{15}H_{14}ClN_3O_2$	2.1×10^{-8}	$>10^{-4}$		
27	$CH_2CH_2CO_2H$	H	5-Br	195–197	61	*g*	$C_{15}H_{14}BrN_3O_2$	1.2×10^{-8}	$>10^{-4}$		
28	$CH_2CH_2CO_2H$	H	5-$N(CH_3)_2$	158–159	48	EtOAc/PE	$C_{17}H_{20}N_4O_2$	8.2×10^{-8}	$>10^{-4}$		
29	$CH_2CH_2CO_2H$	H	6-CF_3	186–187	42	EtOH	$C_{16}H_{14}F_3N_3O_2$	1.0×10^{-8}	$>10^{-4}$		
30	(*E*)-CH=CHCO$_2$H	CH_3	H	228–230	44	*i*-PrOH	$C_{16}H_{15}N_3O_2$	7.0×10^{-8}	$>10^{-4}$		
31		(dazoxiben)						3.0×10^{-9}	$>10^{-4}$	$>10^{-4}$	$>10^{-4}$

[a] Each result represents the mean of two determinations unless otherwise indicated. [b] PE, petroleum ether, bp 60–80 °C. [c] All compounds gave C, H, and N analyses within 0.4% of the theoretical values. [d] Reference 11. [e] Previously reported bioassay figure 2×10^{-8} M.[11] [f] Maleate salt. [g] Purified by dissolving in dilute NaOH solution, filtering, and reacidifying (AcOH).

Table III. Inhibition of Serum TxB_2 Production following Intravenous Administration of 21 to Anesthetized Rabbits

dose, mg/kg	% inhibn postdose[a]		
	2 min	15 min	45 min
0.3		48 ± 14.6	49 ± 14.5
1.0	97 ± 0.4	94 ± 1.6	88 ± 2.6

[a] All results ± SEM (n = 4).

In summary, we have examined the effect of introduction of carboxylic acid substituents into a series of 3-(1*H*-imidazol-1-ylmethyl)-1*H*-indoles. In some, but not all, cases an increase in potency resulted. In the cases examined there was a decrease in activity against steroid 11β-hydroxylase relative to compounds lacking an acidic substituent. Compound **21** combined excellent potency and selectivity in vitro with high potency and a long duration of action in vivo.

Experimental Section

Enzyme Assays. Methods used for the determination of activity against TxA_2 synthetase, PGI_2 synthetase, cyclooxygenase, and adrenal steroid 11β-hydroxylase in vitro have been described in the preceding paper.[19]

In Vivo Evaluation. (a) Intravenous Efficacy in Rabbits. Male New Zealand white rabbits (n = 4) were anesthetized and catheters introduced into a carotid artery and a jugular vein. Blood samples were taken from the carotid catheter 30 and 5 min prior to the administration of compound to establish control serum levels of TxB_2. A 0.3-mg/kg sample of the compound was administered via the jugular vein, and carotid blood samples were taken at 15 and 45 min after injection. Thirty minutes later a second dose of 1 mg/kg was given, and carotid blood samples were taken at 2, 15, and 45 min after injection. The blood samples were allowed to clot for 2 h at 37 °C and then centrifuged. Serum TxB_2 was determined by a specific RIA as described previously.[19] Results were calculated as the percentage reduction in serum TxB_2 levels following compound administration, relative to the control values prior to dosing.

(b) Oral Efficacy in Dogs. Blood samples were obtained from the external jugular vein of conscious male beagles prior to, and following, oral administration of compound. The determination of TxB_2 was carried out as described above except that the blood samples were allowed to clot for 1 h at 37 °C.

Chemistry. All melting points are uncorrected and were obtained with use of an Electrothermal capillary melting point apparatus. The structures of all compounds were confirmed by their IR and ^1H NMR spectra. The IR spectra were recorded on a Perkin-Elmer 197 or 237 spectrophotometer and the ^1H NMR spectra were obtained with a Perkin-Elmer R12B or a Varian XL-100 spectrometer using Me_4Si as internal standard.

5-Chloro-3-(1*H*-imidazol-1-ylmethyl)-1*H*-indole (4). A solution of 5-chloro-3-[(dimethylamino)methyl]-1*H*-indole (3.73 g, 0.018 mol) and imidazole (1.22 g, 0.022 mol) in xylene (20 mL) was heated under reflux for 3 h and then allowed to cool. The solid was filtered off and crystallized from IPA/petroleum ether (bp 60–80 °C) to give **4**, yield 3.50 g (84%); mp 195–197 °C. Anal. ($C_{12}H_{10}ClN_3$) C, H, N.

3-(1*H*-Imidazol-1-ylmethyl)-6-(trifluoromethyl)-1*H*-indole (5) was prepared similarly (Table II).

1-Ethyl-3-(1*H*-imidazol-1-ylmethyl)-1*H*-indole (6). Sodium hydride (1.50 g of 50% dispersion in mineral oil, 0.0315 mol) was added portionwise to a stirred solution of **1**[11] (5.92 g, 0.0315 mol) in dry DMF (60 mL) at 0 °C and the mixture was stirred below 5 °C for 1 h. A solution of diethyl sulfate (4.86 g, 0.0315 mol) in dry DMF (10 mL) was added dropwise and the mixture was stirred at room temperature for 18 h. The mixture was made alkaline with 5 N NaOH to destroy excess diethyl sulfate and then evaporated. The residue was partitioned between ethyl acetate and water and the organic phase was washed with water, dried (Na_2SO_4), and evaporated. The residue was chromatographed on silica gel. Elution with petroleum ether (bp 40–60 °C) gave mineral oil and further elution with $CHCl_3$/petroleum ether (bp 40–60 °C) (2:1) gave the product as an oil (4.40 g). The oil was treated with maleic acid in ethyl acetate and the resulting solid was crystallized from MeOH/EtOAc to give **6** maleate; yield 5.40 g (59%); mp 106–107 °C. Anal. ($C_{14}H_{15}N_3 \cdot C_4H_4O_4$) C, H, N.

3-(1*H*-Imidazol-1-ylmethyl)-1*H*-indole-1-ethanoic Acid Ethyl Ester (7). Compound **1** (3.94 g, 0.02 mol) in dry DMF (20 mL) was treated with NaH (0.98 g of 50% dispersion, 0.02 mol) as described above and ethyl bromoacetate (3.34 g, 0.02 mol) was added dropwise. The mixture was stirred at 25 °C for 2 h and then poured into water. Extraction with EtOAc gave an oil which was chromatographed on silica gel. Elution with $CHCl_3$ first gave mineral oil and some impurity followed by a solid which was crystallized from EtOAc/petroleum ether (bp 60–80 °C) to give **7**; yield 1.80 g (32%); mp 123–124 °C. Anal. ($C_{16}H_{17}N_3O_2$) C, H, N.

3-(1*H*-Imidazol-1-ylmethyl)-1*H*-indole-1-propanenitrile (8). Benzyltrimethylammonium hydroxide (0.5 mL of 40% solution in MeOH) was added to a suspension of **1** (1.97 g, 0.01 mol) and acrylontrile (2.2 mL) in dioxane (25 mL) at 25 °C. The resulting solution was warmed at 50–60 °C for 30 min, allowed to stand at 25 °C for 18 h, and then poured into water. The mixture was extracted with EtOAc (3 × 50 mL), and the combined extracts were washed with water and dried (Na_2SO_4). The solvent was evaporated and the residue was chromatographed on silica gel. Elution with $CHCl_3$ gave **8** as an oil; yield 1.58 g (67%); IR 2250 (C≡N). The fumarate salt had mp 167–169 °C (from butan-2-one/petroleum ether, bp 60–80 °C). Anal. ($C_{15}H_{14}N_4 \cdot C_4H_4O_4$) C, H, N.

Other propanenitrile derivatives **9**–**17** (Table I) were prepared similarly.

(*E*)-3-[3-(1*H*-Imidazol-1-ylmethyl)-2-methyl-1*H*-indol-1-yl]propenoic Acid Ethyl Ester (18). Tetrabutylammonium fluoride (50 mL of a 1 M solution in THF) was added dropwise to a stirred solution of **3**[11] (10.55 g, 0.05 mol) and ethyl propiolate (4.90 g, 0.05 mol) in dry THF (150 mL) at 25 °C and the solution was stirred at this temperature for 2 h and then poured into water. Extraction with ethyl acetate gave an oil which was chromatographed on silica gel. Elution with $CHCl_3$ first gave impurity followed by product. Evaporation of the product fractions gave a solid which was crystallized from $CHCl_3$/petroleum ether (bp 40–60 °C) to give **18**; yield 8.00 g (52%); mp 121–122 °C; 100-MHz ^1H NMR ($CDCl_3$) δ 1.36 (t, 3 H, J = 7 Hz, CH_2CH_3), 2.54 (s, 3 H, 2-CH_3), 4.30 (q, 2 H, J = 7 Hz, CH_2CH_3), 5.22 (s, 2 H, CH_2), 6.25 (d, 1, H, J = 14.3 Hz, =CH), 6.88 (br s, 1 H; imidazole CH), 7.03 (br s, 1 H, imidazole CH), 7.18–7.41 (m, 3 H, indole CH), 7.53 (br s, 1 H, imidazole CH), 7.65–7.75 (m, 1 H, indole CH), 8.17 (d, 1 H, J = 14.3 Hz, =CH). Anal. ($C_{18}H_{19}N_3O_2$) C, H, N.

3-(1*H*-Imidazol-1-ylmethyl)-1*H*-indole-1-ethanoic Acid (19). A mixture of **7** (0.98 g, 0.0035 mol), NaOH (0.25 g), EtOH (10 mL), and water (2 mL) was heated under reflux for 2 h and then evaporated. The residue was dissolved in H_2O (5 mL) and the solution was made just acidic with AcOH and evaporated. The residue was stirred with a little H_2O and filtered. The solid was crystallized from H_2O to give **19**; yield 0.65 g (73%); mp 223–224 °C. Anal. ($C_{14}H_{13}N_3O_2$) C, H, N.

(*E*)-3-[3-(1*H*-Imidazol-1-ylmethyl)-2-methyl-1*H*-indol-1-yl]propenoic Acid (30). This compound was prepared similarly from the ester **18**.

3-(1*H*-Imidazol-1-ylmethyl)-1*H*-indole-1-propanoic Acid (20). A mixture of **8** (1.0 g, 0.004 mol), KOh (1.0 g), EtOH (5 mL), and H_2O (10 mL) was heated under reflux for 4 h. The solution was evaporated to a small volume, filtered, and acidified with AcOH. The solid which crystallized on standing was filtered off, washed with H_2O, and dried to give **20**; yield 0.75 g, 70%; mp 142–144 °C (from H_2O). Anal. ($C_{15}H_{15}N_3O_2$) C, H, N.

Compounds **21**–**29** (Table II) were prepared similarly.

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Registry No. 1, 19714-15-9; 3, 72818-37-2; 4, 76894-60-5; 5, 72818-58-7; 6, 72818-64-5; 6·maleate, 72818-65-6; 7, 76894-74-1; 8, 76894-54-7; 8·formate, 76894-55-8; 9, 99838-23-0; 10, 76894-91-2; 11, 99838-24-1; 12, 10075-50-0; 13, 76894-59-2; 14, 99838-26-3; 15, 99838-27-4; 16, 99838-28-5; 17, 99838-29-6; 18, 85602-48-8; 19,

76894-86-5; **20**, 76894-75-2; **21**, 76894-77-4; **22**, 76894-78-5; **23**, 76894-79-6; **24**, 76894-80-9; **25**, 76894-81-0; **26**, 76894-82-1; **27**, 76894-83-2; **28**, 76894-84-3; **29**, 76894-85-4; **30**, 85602-50-2; 5-chloro-3-[(dimethylamino)methyl]-1*H*-indole, 830-94-4; 2-methyl-1*H*-indole, 95-20-5; 2-cyclopropyl-1*H*-indole, 40748-44-5; 5-methyl-1*H*-indole, 614-96-0; 5-methoxy-1*H*-indole, 1006-94-6; 5-bromo-1*H*-indole; 5-(dimethylamino)-1*H*-indole, 6843-23-8; imidazole, 288-32-4; ethyl bromoacetate, 105-36-2; acrylonitrile, 107-13-1; ethyl propiolate, 623-47-2; thromboxane synthetase, 61276-89-9.

Ribose-Modified Adenosine Analogues as Adenosine Receptor Agonists

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Analogues of the potent adenosine receptor agonist (*R*)-*N*-(1-methyl-2-phenylethyl)adenosine (*R*-PIA), modified at N9, were prepared and evaluated for adenosine A_1 and A_2 receptor binding and in vivo central nervous system and cardiovascular effects. The modifications at N9 include deoxy sugars, 5′-substituted-5′-deoxyriboses, non-ribose sugars, sugar ring homologues, and acyclic sugar analogues. Most of the derivatives have poor affinity for adenosine receptors. Only minor modifications at C5′ and C3′ maintain potent binding. In general, those derivatives exhibiting in vivo behavioral or cardiovascular effects also have the highest affinity for adenosine receptors.

A wealth of recent evidence has revealed the prominent role of endogenous adenosine as a regulatory substance, distinct from endocrine hormones and the common neurotransmitters.[1] The number and variety of effects attributable to adenosine are remarkable, particularly since it may elicit opposite effects in different tissues. For example, adenosine causes vasodilation and hypotension in peripheral blood vessels[2] while in the kidney vasoconstriction results.[3] Other smooth muscle tissues are sensitive to adenosine including lung,[4] ileum,[5] and taenia coli.[6] Effects on coronary blood flow,[7] contractility of cardiac muscle,[8] and fat metabolism[9] are well documented. Some evidence suggests that adenosine may act as a neurotransmitter or neuromodulator in the brain.[10]

The observed physiological effects of adenosine are the result of its interaction with specific receptors. Direct binding studies with radiolabeled ligands with high affinity for adenosine receptors[11] have facilitated the identification of receptors in various tissues. At least two extracellular adenosine receptors are coupled to adenylate cyclase. One, termed A_1, is a high-affinity site that exerts an inhibitory effect on adenylate cyclase. The second, A_2, is a low-affinity site that activates adenylate cyclase.[12]

Antagonists of adenosine such as theophylline have long been known and considerably more potent derivatives such as 8-(2-amino-4-chlorophenyl)-1,3-dipropyl-1*H*-purine-2,6-dione have been developed.[13] No significant selectivity for either receptor subtype has been reported. Similarly, a number of adenosine analogues, particularly N^6-alkyl derivatives, are potent adenosine agonists. Several, such as (*R*)-*N*-(1-methyl-2-phenylethyl)adenosine (*R*-PIA, **1**),[12,14] produce dramatic hypotensive and negative chronotropic effects in vivo.[15] These derivatives are generally selective for A_1 receptors.

Our efforts in this area are directed toward the development of novel, selective adenosine agonists as potential therapeutic agents. Recently, we reported adenosine analogues having modified heterocyclic ring systems.[16] In this report, we detail the preparation and evaluation of *R*-PIA analogues modified at the ribose moiety. The modifications at N9 include deoxy sugars, 5′-substituted-5′-deoxyriboses, non-ribose sugars, sugar ring homologues, and acyclic sugar analogues. This work differs from previous structure–activity relationship studies in two ways. First, evaluating *R*-PIA analogues rather than adenosine analogues should eliminate the potential complicating effect of adenosine deaminase in the biological preparations and utilizes a substitution at N^6 known to improve affinity for the adenosine receptor. Second, affinity for adenosine receptors was determined by displacement of

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