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An approach to hypertension crisis: Evaluation of new fused banzazoles; 2-arylethenyl and 2,4-bis(arylethenyl) derivatives derived from 2,4-dimethyl-pyrimido [*1,2-a*] benzimidazole

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ABSTRACT

In this manuscript, we investigated-in vivo- the hypotensive activity of the new derivatives related to the scaffold pyrimido-benzimidazole and compared the results with tolazoline. All of the reference; tolazoline and the tested derivatives are introduced in equimolar ratios in doses of (0.1 mg/kg iv) using anaesthetized-normotensive nonhuman primates (dogs). The new pyrimido [l,2-a] benzimidazole derivatives were synthesized from 2,4-dimethyl-pyrimido [1,2-a] benzimidazole ***(1)*** *which intern, obtained from condensing 2-aminobenzimidazole with acetyl-acetone. Precusor* ***1*** *was then condensed with the appropriate aldehyde* ***2a-f*** *to produce two series:* ***3a-f, and 4a-f****, as trans [E]-configurational geometry. The structure of the synthesized derivatives has been characterized by elemental microanalysis (CHN), IR, MS and NMR Spectroscopy, as well as physicochemical properties. In conclusion: Pyrimido-benzimidazole scaffold is a good target for antihypertensive activity.*

Keywords: Hypotensive activity, Anaesthetized-normotensive dogs, Pyrimido-benzimidazoles, Regioselectivity, E-isomer, geometrical isomerism.

INTRODUCTION

Essential hypertension affects about 10% of the world population and constitutes about 80% of the total cases of hypertension [1,2]. Satisfactory blood pressure control invariably requires chronic therapy, and the drug side effects must be minimal, consequently, clinical interest is improved and novel antihypertensive agents have been elaborated.

The antihypertensive activity of guanidine (or in general; amidine) congeners; a structural feature recognized and optimized for their neuronal receptor binding in several drugs is enhanced by the hydrophobic ring attachments [1]. This guanidine (or amidine) is found in several medicinally useful drugs such as alfuzosin®, prazosin®, doxazocin®, terazocin®, as well as tolazoline® which is used in this work as a reference. In continuation of our lab work [3-6], it was irrelevant to synthesize other derivatives of pyrimido [*1,2-a*] benzimidazoles to be investigated as potential antihypertensives. Historically, several biological activities were reported for this nucleus, such as antimicrobial [7-9], antiviral [10], antiulcer [11], analgesic and antinflammatory [12], antioxidants and centrally active agents [13-16], as well as potential anticancer activity [17-20]. In continuation to our work in fused

benzazoles [3-6, 21,23], this report describes the synthesis and evaluation of hypotensive effects of a two series; 4-methyl-2-(arylethenyl) pyrimido [1,2-a] benzimidazoles, and 2,4-bis (arylethenyl) pyrimido [1,2-a] benzimidazoles. By these derivatives we apt at pringing about the following structural modifications: a)- increasing the general lipophilic character of the parent molecule by insersion of an ethenyl (olefinic spacer) function between the pyrimidobenzimidazole nucleus and the aryl substituent, at C-2 on the expense of the 2-methyl or, in another seies, on the 2,4-dimethyl groups. b)- Augmenting the structural requirements found in selective α-$_1$-adrenergic receptor antagonists used to treat hypertension. c)- Ensuring possible electronic interactions by different substituents in the aryl groups. d)- Exploring the effect of isosteric replacement of the (un)substitutedphenyl-ethenyl group with furyl and thienyl ring structures on the hypotensive activity, if any.

MATERIALS AND METHODS

2-Aminobenzimidazole, acetylacetone, and arylcarbaldehydes are commercially available. Melting points were determined on an electro-thermal melting point apparatus [Stuart Scientific, UK], and are uncorrected. Precoated silica gel plates (kiesel gel 0.25 mm, 60G F254, Merk) were used for thin layer chromatography. Developing solvent system of chloroform/methanol (10:3) was used and the spots were detected by ultraviolet light; Spectroline ENF-240C/F (model CM-10) at short wavelength (λ = 254 nm) and/or iodine stain. All chemical yields are unoptimized and generally represent a single experiment. IR spectra (KBr disc) were recorded on IR-470 Shimadzu spectrometer, Japan. ^{1}H-NMR Spectra were scanned on a Varian EM-360 L NMR spectrometer (60 MHz) USA at Faculty of Pharmacy Assiut University. Chemical shifts are expressed in δ-values (ppm) relative to TMS as an internal standard, using $CDCl_3$ as a solvent. The microanalysis for C, H and N were performed on a Perkin Elmer 240 elemental analyzer, and were performed at the Department of Chemistry, Faculty of Science. Pharmacological screening was carried out at the department of pharmacology, faculty of medicine, El-Minia University, Al-Minia, Egypt.

1. Synthesis of precursor (1):
2-aminobenzimidazole (0.01 mole) and acetylacetone (0.01 mole) were dissolved in glacial acetic acid (10 mL) and the solution was refluxed for 3 hr. The reaction mixture after being cooled was poured in ice-cooled water and made basic to litmus with concentrated ammonia solution (27%). The precipitate was filtered off and crystallized from ethanol as yellowish-white needles. Yield: 85%, m.p. 233^{o}C, as reported [24].

2. Synthesis of 4-methyl-2-(2-arylethenyl)pyrimido [1,2-a] benzimidazole derivatives 3a-f, Table 1:
A mixture of 2,4-dimethyl-pyrimido[1,2-a] benzimidzole; **1** (5 mmole) and the appropriate arylcarbaldehyde, **2a-f** (5 mmole) was refluxed in glacial acetic acid (20 mL) for 24 h. The reaction mixture was cooled and poured into ice-cooled water. The formed precipitate was filtered off and crystallized from the ethanol.

3. **Synthesis of 2,4-Bis (2-arylethenyl) pyrimido [1,2-a] benzimidzole derivatives; 4a-f, Table 2.**
Method A: A mixture of 2,4-dimethyl-pyrimido[1,2-a] benzimidzole; **1** (5 mmole) and the appropriate arylcarbaldehyde; **2a-f** (11 mmole) was refluxed in glacial acetic acid (20 mL) for 24 hr. The reaction mixture was cooled and poured into ice-cooled water. The formed precipitate was filtered off and crystallized from the proper solvent.
Method B: A mixture of the appropriate 4-methyl-2-(2-arylethenyl) pyrimido [1,2-a] benzimidzole; **3a-f** (5 mmole) and the appropriate arylcarbaldehyde; **2a-f** (5 mmole) was refluxed in glacial acetic acid (20 mL) for 24 hr. The reaction mixture was cooled and poured into ice-cooled water. The formed precipitate was filtered off and crystallized from the proper solvent.

Table 1: The physicochemical data of 4-methyl-2-(2-arylethenyl)pyrimido [1,2-a] benzimidazoles; 3a-f.

Compd No.	R^1	Yield %	m.p.^{o}C	Formula (M. Wt)	Microanalysis		
						Calcd	Found
3a	C_6H_5-	60	150-3 ethanol	$C_{19}H_{15}N_3$ (285.35)	C H N	79.98 5.29 14.73	80.30 4.81 14.52
3b	*p*-Cl-C_6H_4-	80	290-2 ethanol	$C_{19}H_{14}ClN_3$ (319.79)	C H N	71.34 4.41 13.14	71.76 3.88 13.20
3c	*p*-CH_3O-C_6H_4-	56	113-5 ethanol	$C_{20}H_{17}N_3O$ (315.37)	C H	76.17 5.43	75.82 5.20

					N	13.32	13.00
3d	*m*-O_2N-C_6H_4-	71	240-1 ethanol	$C_{19}H_{14}N_4O_2$ (330.35)	C H N	69.08 4.27 16.96	69.64 4.78 16.80
3e	2-furyl	30	155-7 ethanol	$C_{17}H_{13}N_3O$ (275.31)	C H N	74.17 4.76 15.26	73.80 4.42 15.20
3f	2-thienyl	36	148-50 ethanol	$C_{17}H_{13}N_3S$ (291.37)	C H N	70.07 4.49 14.42	69.80 4.11 14.02

4-Methyl-2-(2-phenylethenyl) pyrimido [1,2-a] benzimidazole; 3a: IR, cm^{-1}: 3070 (Aromatic C-H stretch), 2960 (CH_3, C-H stretch), 1630, 1599, 1572 (C=C, C=N stretch), 980 (-CH=CH- trans bend), 775, 730, 690 (out-of-plane aromatic C-H bend of monosubstituted benzene ring). ^{1}H-NMR ($CDCl_3$): σ-value, ppm.: 3.00 (s, 3H, CH_3), 7.00 (1H, C_3-H), 7.20-7.60 (m, 7H, 2H of -CH=CH-, 5H of C_6H_5), 7.80-8.20 (m, 4H, fused benzo).

4-Methyl-2-(2-(*p*-chlorophenyl)ethenyl) pyrimido [1,2-a] benzimidazole; 3b: IR, cm^{-1}: 3060 (Aromatic C-H stretch), 2920 (CH_3, C-H stretch), 1628, 1584, 1570 (C=C, C=N stretch), 972 (-CH=CH- trans bend). MS: m/z (%): 319 (59.22, M+), 320 (70.8), 321 (43.09), 318 (100), 306 (36.33), 305 (45.7), 304 (87.07), 269 (11.69), 210 (14.97) , 90 (15.34)

4-Methyl-2-(2-(*p*-methoxyphenyl)ethenyl)pyrimido[1,2-a]benzimidazole; 3c: IR, cm^{-1}: 3055 (Aromatic C-H stretch), 2980 (CH_3, C-H stretch), 1624, 1589, 1560 (C=C, C=N stretch), 980 (-CH=CH- trans bend), 767, 729 (out-of-plane bend). ^{1}H-NMR ($CDCl_3$): σ-value, ppm.: 2.97 (s, 3H, CH_3), 6.65 (1H, C_3-H), 6.70-8.10 (m, 10H, 2H of -CH=CH-, 4H of C_6H_4-p), 4H, fused benzo).

4-Methyl-2-(2-(*m*-nitrophenyl) ethenyl) pyrimido [1,2-a] benzimidazole; 3d: IR, cm^{-1}: 3050 (Aromatic C-H stretch), 2950 (CH_3, C-H stretch), 1670, 1630, 1525 (C=C, C=N stretch and asymmetric nitro stretch), 1348 (symmetric nitro stretch), 970 (-CH=CH- trans bend), 735 (out-of-plane bend).

4-Methyl-2-(2-(2-furyl)ethenyl)pyrimido[1,2-a]benzimidazole; 3e: IR, cm^{-1}: 3060 (Aromatic C-H stretch), 2950 (CH_3, C-H stretch), 1670, 1630, 1525 (C=C, C=N stretch), 1091 (-C-H bend), 1005 (-CH=CH- trans bend), 760 (out-of-plane bend).

2-Phenyl-4-(2-(2-thienyl)ethenyl)pyrimido[1,2-a]benzimidazole; 5f: IR, cm^{-1}: 3050 (Aromatic C-H stretch), 2915 (CH_3, C-H stretch), 1668, 1595 (C=C, C=N stretch), 1091 (-C-H bend), 1010 (-CH=CH- trans bend), 760 (out-of-plane bend). ^{1}H-NMR ($CDCl_3$): σ-value, ppm.: 3.00 (s, 3H, CH_3), 6.72 (1H, C_3-H), 6.80-8.35 (m, 9H, 2H of -CH=CH-, 3H of thienyl, 4H, fused benzo).

Table 2: The physicochemical 2,4-Bis (2-arylethenyl) pyrimido [1,2-a] benzimidzole derivatives; 4a-f

Compd No.	R^1	Yield %	m.p.°C	Formula (M. Wt)	Microanalysis		
						Calcd	Found
4a	C_6H_5-	30	145-7 ethanol	$C_{26}H_{19}N_3$ (373.46)	C H N	83.62 5.13 11.25	83.25 5.14 10.78
4b	*p*-Cl-C_6H_4-	76	280-3 acetic acid	$C_{26}H_{17}Cl_2N_3$ (442.35)	C H N	70.59 3.87 9.49	70.21 4.00 9.20
4c	*p*-CH_3O-C_6H_4-	45	228-30 ethanol	$C_{28}H_{23}N_3O_2$ (433.51)	C H N	77.58 5.35 9.69	77.30 4.93 10.00
4d	*m*-O_2N-C_6H_4-	85	292-5 acetic acid	$C_{26}H_{17}N_5O_4$ (463.45)	C H N	67.38 3.69 15.11	67.20 3.92 15.30
4e	2-furyl	32	115-7 ethanol	$C_{22}H_{15}N_3O_2$ (353.38)	C H N	74.78 4.28 11.89	74.40 4.04 11.34
4f	2-thienyl	30	126-8 ethanol	$C_{22}H_{15}N_3S_2$ (385.50)	C H N	68.54 3.92 10.90	69.06 4.20 10.92

2,4-Bis(2-phenylethenyl) pyrimido [1,2-a] benzimidazole; 4a: ^{1}H-NMR ($CDCl_3$): σ-value, ppm.: 6.97 (s, 1H, C3-H), 7.10-8.10 (m, 18H, 4H of two CH=CH of ethenyl, 10H of two C_6H_5, and 4H of C_6H_4 fused benzo.).

2,4-Bis(2-(p-chlorophenyl)ethenyl)pyrimido[1,2-a]benzimidazole; 4b: IR, cm^{-1}: 3040 (Aromatic C-H stretch), 1630, 1595 (C=C, C=N stretch), 955 (-CH=CH- trans bend). MS: m/z (%): 441 (79.3, M+), 442 (77.8, M+1), 443 (56.3, M+3), 440 (100), 330 (28.1), 318 (24.9), 304 (24.7), 279 (22.1).

2,4-Bis(2-(p-methyoxyphenyl)ethenyl) pyrimido [1,2-a] benzimidazole; 4c: IR, cm^{-1}: 3030 (Aromatic C-H stretch), 2900 (CH_3, C-H stretch), 1628, 1575, 1510 (C=C, C=N stretch), 1251, 1174 (C-O-C, stretch), 995 (-CH=CH- trans bend). ^{1}H-NMR ($CDCl_3$): σ-value, ppm.: 3.60 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3),6.80 (s, 1H, C3-H), 6.85-8.25 (m, 16H, 4H of two –CH=CH- ethenyl, 8H of two C_6H_4-p-, and 4H of C_6H_4 fused benzo.).

2,4-Bis(2-(m-nitrophenyl)ethenyl) pyrimido [1,2-a] benzimidazole; 4d: IR, cm^{-1}: 3085 (Aromatic C-H stretch), 1630, 1587, 1522 (C=C, C=N stretch, and/or the asymmetric absorption of NO_2), 1350 (Symmetric stretch of NO_2), 985 (-CH=CH- trans bend).

Pharmacology [4-6,28-29]

1- Groups of dogs (each of 3 animals) were anaesthetized with an i.p. injection of urethane solutions. The right common carotid artery as well as the left jugular vein was used for intravenous injection of the drugs under investigation, while the arterial catheter was connected to a PT 400 blood pressure transducer and a CD10 amplifier of a two channel oscillograph (MD2 Bioscience, Palmer-George, Washington, USA). The transducer was first calibrated, the animal left for a thirty minute-period for stabilization and pretreatment (basal) mean blood pressure was then measured. The calculated doses of the tested compounds were injected intravenously through the jugular vein and the blood pressure was recorded directly (D) and through 1, 3, 10, 15, 30, 45 and 60 minutes following the injection of each drug (**Tables 3,4**). The same procedure was performed for evaluation of the effect of the reference antihypertensive agent (**Table 5**).

2- In an another group of dogs, the solvent system was injected intravenously in the same volume used as for the tested compounds and the change in blood pressure was recorded which proved of non-significant, if ever.

Table 3: Hypotensive activity of compounds (3a-f)

C. No.	T. (min)	Dog 1			Dog 2			Dog 3			Mean %Dec.	±S.E.
		Mean B.P.	Dec.	%Dec.	Mean B.P.	Dec.	%Dec.	Mean B.P.	Dec.	%Dec.		
3a	**0**	**98**	-	-	**98**	-	-	**100**	-	-	-	
	D		52	53.1		52	53.1		41	41	**49.0**	
	3		14	14.3		9	9.2		20	20	14.2	
	10		9	9.2		9	-11		8	8	8.8	
	15		4	4.1		6	-4		5	5	5	
	30		0	0		6	6.1		5	5	3.7	
	45		0	0		6	6.1		7	7	4.4	
	60		0	0		6	6.1		7	7	4.4	2.19
3b	**0**	**102**	-	-	**103**	-	-	**102**	-	-	-	
	D		28	27.5		39	37.8		24	25.5	**29.6**	
	3		21	20.5		22	21.4		18	17.6	19.8	
	10		19	18.6		9	8.7		4	3.9	10.4	
	15		19	18.6		10	9.7		5	4.9	11.6	
	30		18	17.6		10	9.7		5	4.9	10.7	
	45		18	17.6		10	9.7		4	3.9	10.4	
	60		18	17.6		10	9.7		4	3.9	10.4	3.97
3c	**0**	**98**	-	-	**100**	-	-	**100**	-	-	-	
	D		34	34.7		31	31		35	35	**33.5**	
	3		-2	-2.04		6	6		2	2	2	
	10		-4	-4.1		-4	-4		-4	-4	-4	
	15		0	0		2	2.04		0	0	1.3	
	30		0	0		0	0		0	0	1.3	
	45		3	3.1		0	0		0	0	1.3	
	60		2	0		0	0		0	0	0.7	1.33
3d	**0**	**95**	-	-	**106**	-	-	**98**	-	-	-	
	D		41	43.2		78	73.6		46	50	**54.6**	
	3		-10	-4.1		5	4.7		10	10.2	1.5	
	10		-10	-10.5		4	3.8		7	7.1	2.6	
	15		8	8.4		6	5.7		12	12.1	8.8	
	30		12	12.6		16	15.1		11	11.1	12.9	
	45		12	12.6		16	15.1		20	20.4	16	
	60		12	12.6		16	15.1		13	13.3	13.7	0.7
3e	**0**	**98**	-	-	**98**	-	-	**97**	-	-	-	
	D		34	34.7		33	33.7		33	34	**34.1**	
	3		8	8.2		10	10.2		9	9.3	5.1	
	10		-4	-4.1		0	0		-1	-1.03	-1.7	
	15		0	0		1	1.02		0	0	0.3	
	30		2	2.04		2	2.04		2	2.1	2	
	45		4	4.1		3	3.1		3	3.1	3.4	
	60		4	4.1		3	3.1		3	3.1	3.4	0.33
3f	**0**	**98**	-	-	**98**	-	-	**98**	-	-	-	
	D		39	39.8		34	34.7		33	33.7	**36.1**	
	3		2	2.04		4	4.1		1	1.02	2.4	
	10		-4	-4.1		-11	-11.2		6	6.1	-0.3	
	15		0	0		-5	-5.1		2	2.04	-1	
	30		2	2.04		1	1.02		3	3.1	2	
	45		4	4.1		3	3.1		4	4.1	3.7	
	60		4	4.1		3	3.1		4	4.1	3.7	0.33

(C.No. = compound No., T. = Time, S.E. = standard error, Dec. = decrease), Negative values signify an increase in blood pressure

Table 4: Hypotensive activity of compounds (4a-f)

C. No.	T. (min)	Dog 1			Dog 2			Dog 3			Mean %Dec.	±S.E.
		Mean B.P.	Dec.	%Dec.	Mean B.P.	Dec.	%Dec.	Mean B.P.	Dec.	%Dec.		
4a	**0**	**102**	-	-	**102**	-	-	**102**	-	-	-	
	D		70	68.6		70	68.6		60	58.5	**65.2**	
	3		-7	-6.8		-8	-7.8		-8	-7.8	-7.4	
	10		-5	-4.9		-1	-0.98		-1	-0.98	-2.2	
	15		-4	-3.9		-1	-0.98		-1	-0.98	-1.9	
	30		6	5.8		4	3.9		5	4.9	1.1	
	45		1	0.98		4	3.9		4	3.9	2.9	
	60		1	0.98		0	0		0	0	0.3	0.33
4b	**0**	**100**	-	-	**98**	-	-	**99**	-	-	-	
	D		60	60		66	67.3		54	54.5	**60.6**	
	3		-4	-4		-8	-8.1		-4	-4	-5.4	
	10		-4	-4		-9	-9.2		-6	-6.1	-6.4	
	15		0	0		-6	-6.1		1	1.01	-1.7	
	30		4	4		2	2.04		2	2.02	2.6	
	45		3	3		2	2.04		2	2.02	2.4	
	60		2	2		2	2.04		3	3.03	2.4	0.34
4c	**0**	**109**	-	-	**111**	-	-	**110**	-	-	-	
	D		41	37.6		51	45.9		51	46.4	**43.3**	
	3		-5	-4.6		-1	-0.9		0	0	-1.8	
	10		-5	-4.6		-5	-4.5		-5	4.5	-4.5	
	15		-4	-3.7		-5	-4.5		-7	-6.4	-4.9	
	30		3	2.8		5	4.5		1	0.9	2.7	
	45		3	2.8		0	0		8	7.3	3.4	
	60		0	0		2	1.8		9	8.2	3.3	2.5
4d	**0**	**104**	-	-	**108**	-	-	**96**	-	-	-	
	D		68	65.4		48	44.4		38	39.6	**58.3**	
	3		6	5.6		1	10.2		2	2.1	2.9	
	10		4	3.9		3	15.3		-2	-2.1	1.5	
	15		2	1.9		7	10.2		1	1.04	1.5	
	30		1	0.96		8	21.4		3	3.1	3.8	
	45		2	1.9		7	24.5		4	4.2	4.2	
	60		-1	-0.96		0	24.5		4	4.2	1.1	1.6
4e	**0**	**102**	-	-	**98**	-	-	**98**	-	-	-	
	D		72	70.6		44	44.9		26	26.5	**47.4**	
	3		6	5.9		8	8.2		8	8.2	7.4	
	10		2	1.9		1	1.02		5	5.1	2.7	
	15		2	1.9		9	9.2		6	6.1	5.7	
	30		2	1.9		4	4.1		1	1.02	2.3	
	45		2	1.9		4	4.1		4	4.1	3.4	
	60		2	1.9		4	4.1		3	3.1	3	0.64
4f	**0**	**102**	-	-	**103**	-	-	**104**	-	-	-	
	D		59	57.8		62	60.2		42	40.4	**52.8**	
	3		-6	-5.9		1	0.9		-4	-3.8	-2.9	
	10		-4	-3.9		2	1.9		4	3.8	-1.9	
	15		2	1.9		2	1.9		4	3.8	2.5	
	30		3	2.9		3	1.9		5	4.8	3.5	
	45		3	2.9		3	2.9		4	3.8	3.2	
	60		5	4.9		3	2.9		4	3.8	3.9	0.58

(C.No. = compound No., T. = Time, S.E. = standard error, Dec. = decrease), Negative values signify an increase in blood pressure

Table 5: The hypotensive activity of the reference clonidine hydrochloride under the same conditions

C. No.	T. (min)	Dog 1			Dog 2			Dog 3			Mean %Dec.	±S.E.
		Mean B.P.	Dec.	%Dec.	Mean B.P.	Dec.	%Dec.	Mean B.P.	Dec.	%Dec.		
	0		-	-		-	-		-	-	-	
	D		-4	-4.12		-1	-1		-2	-1.92	**--2.4**	
	3		-13	-13.4		-12	-12		-24	-23.8	-16.4	
	10	**97**	14	14.4	**100**	9	9	**104**	7	6.8	10.1	
	15		17	17.5		21	21		13	12.8	17.1	
	30		19	19.5		17	17		24	23.6	20	
	45		20	20.2		21	21		24	23.6	21.6	
	60		25	25.8		20	20		25	24	23.3	2.5

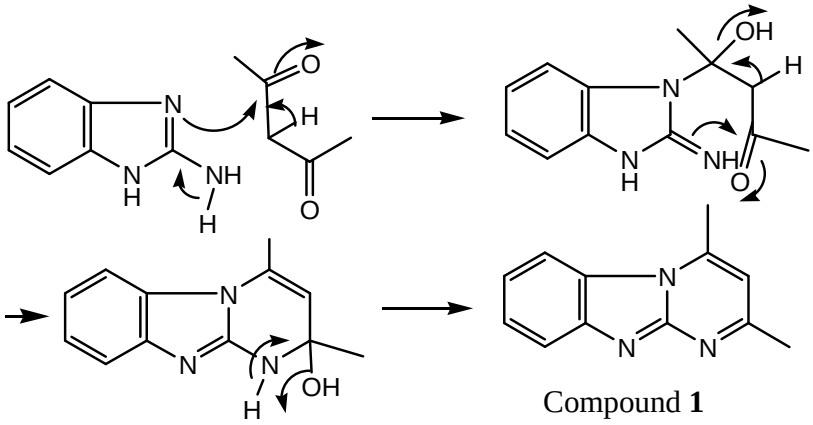
(C.No. = compound No., T. = Time, S.E. = standard error, Dec. = decrease), Negative values signify an increase in blood pressure

RESULTS AND DISCUSSION

CHEMISTRY:

The condensation was carried out by refluxing equimolar amounts of 2-aminobenzimidazole and acetylacetone (2,4-pentanedione) in glacial acetic acid for 3 hr. to afford 1 in 85% yield [6, 24,25]. Fusion of equimolar amounts of 2-aminobenzimidazole and acetylacetone at 150-170 ^{0}C for 5 hr. Diphenyl carbonate (DPC) did not improve the yield, rather than forming tarry products [26]. Separation and purification of the product was effected through hydrochloride salt formation followed by regeneration of the free base.

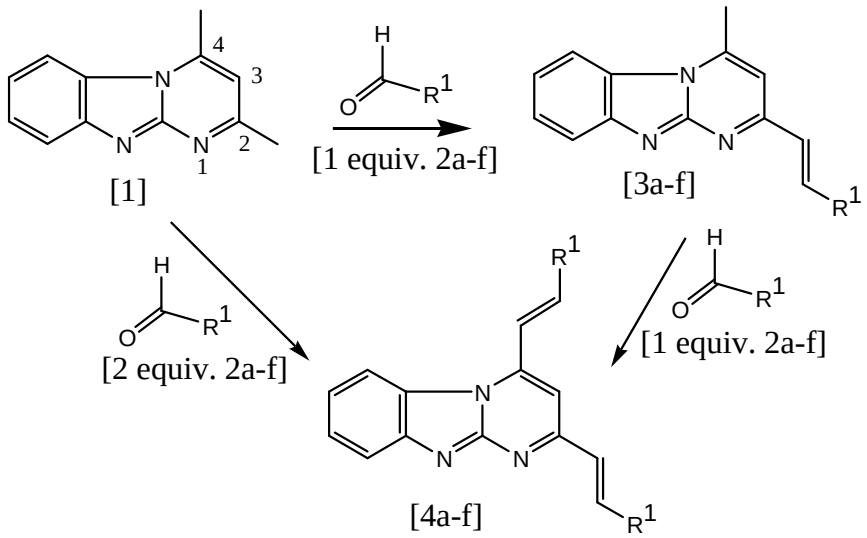
Scheme 1: The synthetic pathway for the precursor; compound 1



Compound **1**

The precursor 2,4-dimethylpyrimido [1,2-a] benzimidazole; **1** was obtained by condensation of 2-aminobenzimidazole and acetylacetone (2,4-pentane-dione) in acetic acid. 2-(Arylethenyl)-4-methyl-pyrimido[1,2-a]benzimidazoles (**3a-f**, **Scheme 2**) were obtained regioselectively, by condensation of one equivalent of aldehyde with **1**, however, two equivalents of aldehyde resulting in the formation of the bis derivatives; **4a-f**. Pharmacological investigations of all derivatives were shown and claimed with appreciable initial hypotensive activity which didn't persist for longer times, **tables 3-5** (c.f. 2-aryl substituents [3-6]).

Scheme 2: The synthetic pathway for compounds 3a-f & 4a-f



3a-f R = H, a (R^1= C_6H_5-); b (R^1= p-Cl-C_6H_4-); c (R^1= p-CH_3O-C_6H_4-);
d (R^1= p-O_2N-C_6H_4-); e (R^1= 2-furyl); f (R^1= 2-thienyl)

4a-f R = Cl, a (R^1= C_6H_5-); b (R^1= p-Cl-C_6H_4-); c (R^1= p-CH_3O-C_6H_4-);
d (R^1= p-O_2N-C_6H_4-); e (R^1= 2-furyl); f (R^1= 2-thienyl)

Synthesis of the target compounds **3a-f** was achieved by condensing **1** with various (un)substituted-benzene, furan and thiophene carbaldehyde derivatives under proper catalysis (**Scheme 2**). The rate limiting step in such a reaction is associated with, not only the generation of a carbanion from the methyl groups, but also with the reactivity the resulted anion. Anion at C-2 is more reactive and more available, than that at C-4, which is less available on account of its vicinity (α) to the electron-deficient bridgehead nitrogen atom. The second fast step involves attack of the carbonyl-carbon of the aldehyde component to give ultimately the ethylenic derivative. Comparative study with the spectra of the precursor compounds easily revealed the disappearance of one or the two methyl group(s) depending on the equivalent of aldehydes.

For most of the synthesized ethenyl derivatives, compounds (**3a-f, 4a-f, Tables 1,2**) the assignment of the configuration of the olefinic linkage could be established by IR. The trans configuration of these compounds can be suggested on the basis of their IR spectra on account of the presence of strong absorption at 850-990 cm^{-1} [27]

PHARMACOLOGY

All of the synthesized derivatives were tested for their hypotensive effect in anaesthetized normotensive dogs [4-6,28-29]. The calculated weight of each compound was dissolved in 3 mL of a solution [composed of (v/v) ethanol and dimethylformamide in (3:1) ratio], then completed to 20 mL with 50% aqueous ethanol so as to afford 10^{-3} molar test solutions. Adult healthy male dogs (8-10 kg) were used as provided by the department of pharmacology. Urethane (ethyl carbamate, Aldrich Chemical Company, USA) was used as 25% solution in water. Pure reference standard clonidine hydrochloride (Sigma Chemical Company, USA) was used as a reference antihypertensive agent in the same molar concentration as used for the tested compounds (10^{-3} mmole/kg). The animals were injected i.v. with a dose of 1 mL of the prepared solution per kg. animal body weight (10^{-3} mmole/kg). Results are recorded directly (D) and every few minutes for a period of 1 hour (**Tables 3-5**). An appreciable initial hypotensive effect (~30-60%) was noticed in all tested derivatives, however. The initial hypotensive effect doesn't persist in this level, after which, no more than 12% reduction is recorded. Derivatives **3a-f** are of activity higher than the corresponding bis structures; **4a-f**. Clonidine hydrochloride; the reference standard causes initial hypertension persists for three minutes after i.v. administration, followed by persistant reduction of about 23%. However, the tested derivatives (**3a-f and 4d-f**) start by initial hypotensive effect (30-60%) persists for 2-3 minutes, followed by hypotension (3-12%) that might reflect a possible consideration in hypertension crisis, rather than chronic hypertension.

CONCLUSION

In conclusion, the results obtained in this study strongly suggest that pyrimido-benzimidazole target can be considered as a good scaffold for antihypertensive activity as emergency in cases of hypertension crisis. This finding can allow for further investigation and modification.

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