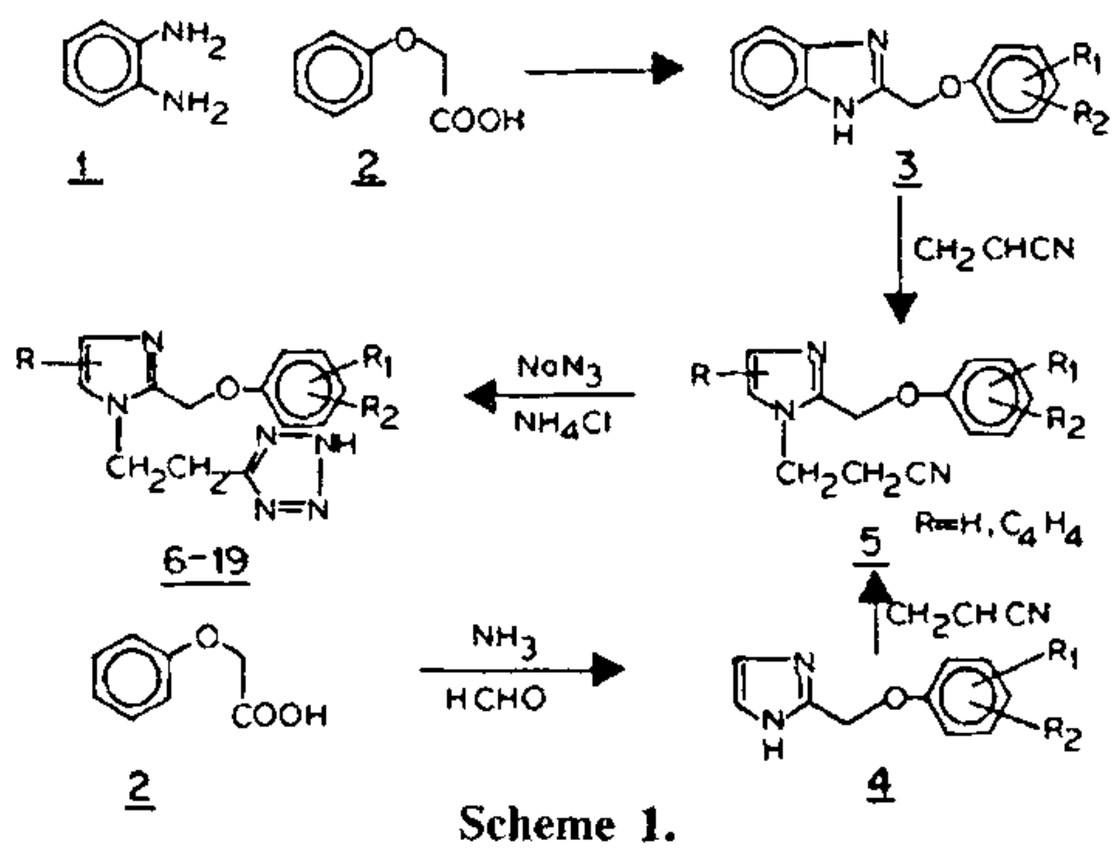
SHORT COMMUNICATIONS

SYNTHESIS AND ANTI-INFLAMMATORY ACTIVITY OF SOME 5-SUBSTITUTED TETRAZOLES

J. S. SHUKLA, R. MISRA and R. RASTOGI
Department of Chemistry, Lucknow University, Lucknow 226 007, India.

CYANOETHYLATION of some heterocyclic compounds containing an amino or imino hydrogen has been specially used for building up novel heterocyclic systems and it has also been achieved with benzimidazole and imidazoles respectively[1]. Tetrazole and their derivatives exhibit a wide range of biological activity and their therapeutic use is also well-established[2,3]. Anti-inflammatory activity has also been reported in 5–(2–anilino phenyl) tetrazoles and 5–[2–(3,4–dichlorophenyl carbonyl) phenoxy methyl] tetrazoles[4,5]. These observations have prompted us towards the synthesis of benzimidazole/imidazole derivatives containing tetrazole nucleus by cyclization of cyanoethylated benzimidazole/imidazoles. The present paper describes the synthesis and anti-inflammatory activity of 5–{β–[N–(2–substituted phenoxy methyl benzimidazolyl/imidazolyl)ethyl] } tetrozoles (**6–19**).

Condensation of *o*-phenylenediamine (**1**) with different substituted phenoxy acetic acid (**2**)[6] gave 2–substituted phenoxy methyl benzimidazoles (**3**)[7]. Similarly reaction of substituted phenoxy acetic acid (**2**) with ammonia and formaldehyde gave 2–substituted phenoxy methyl imidazoles (**4**). Reaction of **3/4** with acrylonitrile in the presence of sodium ethoxide yielded N–(β–cyanoethyl)–2–(substituted phenoxy methyl) benzimidazole/imidazoles (**5**)[8]. They were subjected to cyclization with sodium azide to give 5–{β–[N–(2–substituted phenoxy methyl benzimidazolyl/imidazolyl) ethyl]} tetrazoles (**6–19**) (scheme 1).



Scheme 1.

Melting points were recorded in an open capillary tube and are uncorrected. The IR and PMR spectra of the compounds were taken in Perkin Elmer 137 (ν_{max} in cm^{-1}) and Varian A–60D spectrophotometers (chemical shifts in δ–scale downfield from TMS as internal standard) respectively.

Synthesis of 5–{β–[N–2–(2'–chlorophenoxy methyl) benzimidazolyl] ethyl } terazole (6)

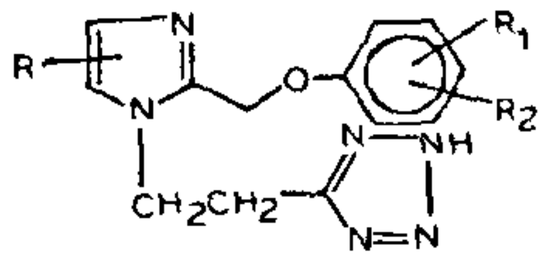
A mixture of N–(β–cyanoethyl)–2–(2'–chloro phenoxy methyl) benzimidazole (6.23 g, 0.02 mol), sodium azide (1.40 g, 0.02 mol) and ammonium chloride (1.5 g, 0.02 mol) in dimethylformamide (25 ml) was heated with constant stirring at 127°C for 17 hr. The solvent was removed under reduced pressure and the residual mass was suspended in cold water. The filtrate was acidified and the solid mass thus obtained was crystallized from ethyl alcohol. Yield: 4.25 g (60%); m.p. 259°C; [Found: C, 57.2, H, 4.00; N, 23.45; $C_{17}H_{15}ClN_6O$ requires C, 57.54; H, 4.23; N, 23.69%] IR (KBr): 1650 (C=N), 2900 (CH_2); PMR ($CDCl_3$): 2.50 3.80 (**m**, 4H, CH CH), 3.82 (**s**, 2H, OCH_2), 6.51–8.30 (**m**, 9H, ArH, NH).

Similarly other compounds (**7–19**) were also synthesized and their physical data are given in table 1.

Anti-inflammatory activity

All the compounds were tested for their anti-inflammatory activity on albino mice at the oral dose of 1/5 ALD_{50} (approximate lethal dose in 50% of animals) according to the technique of Srimal and Dhawan[9]. Carrageenin-induced oedema in mice was a well-established method for the testing of anti-inflammatory activity. Phenylbutazone and cortisone were used as standard drugs for activity. The results, expressed as the percentage inhibition of oedema are shown in table 1, and it is evident that all tested tetrazoles afforded inhibition of oedema ranging from 20–50%. Maximum inhibition was observed with compound **8** and minimum was exhibited with compound **6**. The result also shows that the introduction of nucleophile at *R* position decreases the degree of inhibition while electrophile increases the degree of inhibition. The free hyd-

Table 1 *5-{β-[N-(2-substituted phenoxy methyl benzimidazolyl/imidazolyl) ethyl]} tetrazoles* (**6–19**)



Sl. No	R_1	M.P. °C	Molecular formula*	Yield	Anti-inflammatory activity (P.O.) % inhibition
	$R \simeq C_4H_4$				
6.	*o*-chloro	259	$C_{17}H_{15}ClN_6O$	60	20
7.	*m*-methyl	228	$C_{18}H_{18}N_6O$	65	44
8.	*p*-methyl	210	$C_{18}H_{18}N_6O$	55	50
9.	*o*-methyl	250	$C_{18}H_{18}N_6O$	58	40
10.	*p*-nitro	234	$C_{17}H_{15}N_7O_3$	60	35
11.	H	270	$C_{17}H_{16}N_6O$	58	39
12.	*p*-chloro	280	$C_{18}H_{17}ClN_6O$	62	33.5
	$R = H$				
13.	*o*-chloro	110	$C_{13}H_{13}ClN_6O$	55	22.5
14.	*m*-methyl	140	$C_{14}H_{16}N_6O$	48	45
15.	*p*-methyl	160	$C_{14}H_{16}N_6O$	50	47
16.	*o*-methyl	120-123	$C_{14}H_{16}N_6O$	42	42
17.	*p*-nitro	173	$C_{13}H_{13}N_7O_3$	40	30
18.	H	132	$C_{13}H_{14}N_6O$	45	37
19.	*p*-chloro	198	$C_{14}H_{15}ClN_6O$	58	31

R_2 = o-methyl (12 and 19); R = C_4H_4 (8–14); R = H (1–7); *Satisfactory analysis for C, N and H was obtained.

rogen atom on tetrazole nucleus is also responsible for anti-inflammatory activity[10].

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EFFECT OF POLYCHLORINATED DIBENZOFURANS (PCDFs) ON GLUTATHIONE, GLUTATHIONE PEROXIDASE AND LIPID PEROXIDATION IN RAT LIVER

P. S. DEVAMANOHARAN, R. SANKAR and C. S. SHYAMALA DEVI

Department of Biochemistry, University of Madras, Madras 600 025, India.

HALOGENATED aromatic hydrocarbons such as polychlorinated dibenzofurans (PCDFs), dibenzodioxins (PCDDs) and biphenyls (PCBs) are a class of widespread and persistent environmental pollutants[1]. PCDFs are found as contaminants in commercial PCBs[2], as well as in certain widely used