ACKNOWLEDGEMENT

The authors thank the Director, CDRI, Lucknow for anthelmentic screening. KA is also grateful to ICMR, for the award of a fellowship.

1. Skaging, K. and Zetterbery, B., *Antibiot. chemotherapy*, 1961, **9**, 37, (*Chem. Abstr.*, 1961, **55**, 14577).
2. Tewari, S. S. and Trivedi, G. L., *Indian J. Appl. Chem.*, 1971, **34**, 80.
3. Eldawy, M. A., Shans El-Dine, S. A. and El-Brembaly, K. M., *Pharmazie*, 1979, **34**, 248.
4. Harris, L. N. Spaun Ruediget, *Ger. Offen*, 1973, **2**, 258, 279, (*Chem. Abstr.*, 1973, **79**, 92236).
5. Kuppuswamy, N., Vishwa, P. A. and George Thomas, *S. African*, 1975, **7**, 405, 157 (*Chem. Abstr.*, 1978, **88**, 50855).
6. Magz oub, M., *Acta vet.*, 1973, **42**, 153 (*Chem. Abstr.*, 1974, **80**, 141506).
7. Raghu, S., Hoffman, A K. and Singh, B., *Ger. Offen.*, 1977, **2**, 718, 0582 (*Chem. Abstr.*, 1978, **88**, 62378).
8. Budde, P. B., *R.O., U.S.*, 1978, **4**,057,973 (*Chem. Abstr.*, 1978, **88**, 136622).
9. CIBA-GEIGY, Brit., A. G., 1977, 1474, 630, (*Chem. Abstr.*, 1977, **87**, 201533).
10. Vogel, A. I., *Textbook of practical organic chemistry*, III ed., ELBS and Longmans Group, 1971, 909.
11. Herbert and Shenin, *Organic Synthesis*, 1943, Coll. Vol. 2, p. 1.
12. Dakin, H. D., *J. Biol. Chem.*, 1929, **82**, 439.
13. Niender, J. B. and Zieruig, A., *J. Am. Chem. Soc.*, 1942, **64**, 885.
14. Steward, J. S., *Parasitology*, 1955, **45**, 255.

SYNTHESIS OF SOME NEWER. 1-HETEROCYCLIC AMINO/IMINOMETHYL-2-SUBSTITUTED BENZIMIDAZOLES AS A POTENT CNS; ANTICONVULSANT AND MONOAMINEOXIDASE INHIBITORY AGENTS

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ABSTRACT

A series of 1-heterocyclic amino/iminomethyl-2-substituted benzimidazoles (4-23) were synthesised and screened for their neuropharmacological and monoamineoxidase inhibitory properties. A number of such compounds showed CNS stimulant, anticonvulsant and monoamineoxidase inhibitory activity.

INTRODUCTION

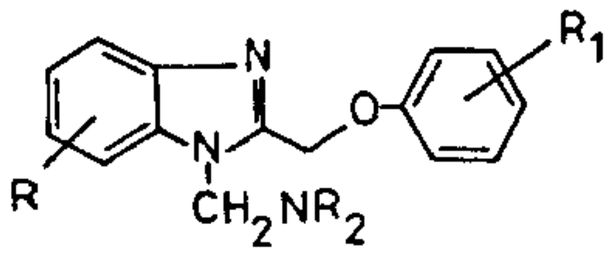
BENZIMIDAZOLE derivatives have become increasing important due to their psychotropic properties[1-3]. Heterocyclic amines are also reported to have chemotherapeutic value[4,5]. Hence it was anticipated that the combination of benzimidazole and heterocyclic amines may result in compounds of better CNS and monoamineoxidase inhibitory activity. The present paper describes the synthesis of 1-heterocyclic amino/iminomethyl-2-substituted benzimidazoles and their CNS, anticonvulsant and monoamineoxidase inhibitory activity.

SCHEME-1

Condensation of *o*-phenylenediamine (1) with different substituted phenoxy acetic acid (2)[6] gave 2-substituted phenoxy methyl benzimidazoles (3)[7]. Reaction of 3 with heterocyclic amines in presence of formaldehyde resulted in the formation of respective 1-heterocyclic amino/iminomethyl-2-substituted phenoxy methyl benzimidazoles (4-23) (Scheme 1).

EXPERIMENTAL

Melting points were recorded in an open capillary tube and are uncorrected. The IR spectra of the compounds were taken in Perkin-Elmer 137 and 177 spectrophotometers in KBr pellets and the mass spectra of the compounds were taken on JEOL-JMS-D-300 instrument.



Synthesis of substituted phenoxy acetic acids

The substituted phenoxy acetic acids were synthesised by the method reported in literature[6].

Synthesis of 2-(substituted phenoxymethyl)benzimidazoles

The 2-(substituted phenoxymethyl) benzimidazoles were prepared according to the known method[7].

Synthesis of 1-pyrrolidinyl methyl-2-(p-nitrophenoxy methyl) benzimidazole (7)

A solution of 2-(*p*-nitrophenoxy methyl) benzimidazole (2.72 g, 0.01 mol) in ethanol (25 ml) was added dropwise to a stirred solution of pyrrolidine (0.7 g, 0.01 mol) and formaldehyde (0.3 g, 0.01 mol) in ethanol (50 ml) at room temperature. Stirring was continued for 1 hr and the reaction mixture was then refluxed for 3 hr. The solvent was distilled off under reduced pressure. The residual solid was crystallized from ethanol to give 7.

m.p. 125° C; Yield—2.2 g (60%)

		Calcd.	Found
For $C_{19}H_{20}N_4O_3$	C =	64.77%	64.54%
	N =	15.91%	15.79%
	H =	5.68%	5.86%

I.R. (KBr): 2900 cm^{-1} ($-CH_2$)
1500 cm^{-1} ($-NO_2$)
1600 cm^{-1} ($C=N$)

Mass : M^+ at m/e = 352

Similarly other compounds were also synthesized and their physical data are given in table 1.

TABLE 1

Physical data of 1-heterocyclic amino/iminomethyl-2-substituted benzimidazoles (4-23)

No.	R	R_1	NR_2	m.p. (° C)	Molecular* formula†
4.	H	*p*-NO_2	pyridl-2-amino	198	$C_{20}H_{17}N_5O_3$
5.	H	*p*-NO_2	thiazolyl-2-amino	170	$C_{18}H_{15}N_5O_3S$
6.	H	*p*-NO_2	thiazolyl-2-amino	137	$C_{18}H_{16}N_4O_3S$
7.	H	*p*-NO_2	pyrrolidinyl	125	$C_{19}H_{20}N_4O_3$
8.	H	H	pyridyl-4-amino	115	$C_{20}H_{18}N_4O$
9.	6-Cl	*p*-NO_2	pyridyl-2-amino	194	$C_{20}H_{16}ClN_5O_3$
10.	6-Cl	*p*-NO_2	thiazolyl-2-amino	191	$C_{18}H_{14}ClN_5O_3S$
11.	6-Cl	H	pyridyl-4-amino	200	$C_{20}H_{17}ClN_4O$
12.	H	*p*-OCH_3	thiazolyl-2-amino	90	$C_{19}H_{18}N_4O_2S$
13.	6-Cl	*p*-NO_2	pyridyl-4-amino	118	$C_{20}H_{16}ClN_5O_3$
14.	H	*o*-Cl	thiazolyl-2-amino	121	$C_{18}H_{15}ClN_4OS$
15.	6-Cl	H	thiazolyl-2-amino	131	$C_{18}H_{15}ClN_4OS$
16.	H	*p*-OCH_3	pyridyl-4-amino	117	$C_{21}H_{20}N_4O_2$
17.	H	*o*-Cl	pyridyl-4-amino	128	$C_{20}H_{17}ClN_4O$
18.	H	*p*-OCH_3	pyridyl-2-amino	112	$C_{21}H_{20}N_4O_2$
19.	H	*o*-Cl	pyridyl-2-amino	151	$C_{20}H_{17}ClN_4O$
20.	H	*p*-OCH_3	pyrrolidinyl	142	$C_{20}H_{23}N_3O_2$
21.	H	*o*-Cl	morpholinyl	162	$C_{19}H_{20}ClN_3O$
22.	H	*p*-NO_2	morpholinyl	155	$C_{19}H_{20}N_4O_4$
23.	H	*p*-OCH_3	morpholinyl	148	$C_{20}H_{23}N_3O_3$

* Yield within the range of 50–60%.

† The analytical results for carbon, hydrogen and nitrogen agreed with the calculated values and within the limits of experimental errors.

Pharmacological activity

Toxicity study was performed with the benzimidazoles. The test compounds were administered intraperitoneally in albino mice weighing 25–30 g in 5% aqueous suspension of gum acacia at different doses and approximate LD_{50} were determined[8]. The ALD_{50} values of all the compounds were found in the range of 600–1000 mg/kg.

Gross-behaviour activity was determined according to the method of Irwin[9]. The test compounds were administered intraperitoneally in albino mice at the dose of 1/5th of ALD_{50}. *In vivo* studies indicate that all the benzimidazoles exhibited CNS stimulant action by increasing of reactivity towards sound, touch, body and limbs.

Anticonvulsant activity[1] against pentylene tetrazol induced seizures was determined in albino mice of either sex weighing 25–30 g. The test compounds were administered intraperitoneally to a group of 10 animals in 5% aqueous suspension of gum acacia at a dose of 100 mg/kg. The results of anticonvulsant activity exhibited by these substituted benzimidazoles are shown in table 2. All the compounds afforded protection ranging from 0 to 60%. Maximum protection was observed with compound 23. These compounds, however, were unable to provide protection against death; 40–100% mortality was observed during 24 hr in pentylene tetrazol-treated animals.

TABLE 2

Pharmacological and monoamine oxidase inhibitory activity of 1-hetrocyclic amino/iminomethyl-2-substituted benzimidazoles (4-23)

No.	Approximate LD_{50}	Anticonvulsant activity: protection [%]	Anticonvulsant activity: morality [%]	M.A.O. inhibition
4.	1000	20	80	41.0
5.	800	20	80	42.5
6.	1000	30	70	45.4
7.	750	20	80	40.5
8.	850	30	70	47.0
9.	1000	10	90	41.5
10.	900	10	100	40.0
11.	750	10	90	42.5
12.	1000	40	60	50.0
13.	1000	0	100	40.0
14.	600	10	90	43.2
15.	1000	20	80	47.5
16.	650	40	60	64.5
17.	850	40	60	65.5
18.	800	20	80	44.5
19.	1000	10	90	75.0
20.	900	20	80	43.2
21.	1000	10	80	43.2
22.	1000	10	90	40.0
23.	950	60	40	52.5

*The value of M.A.O. inhibition given above are the mean values of the two experiments.

Monoamineoxidase activity

The spectrophotofluorometric method was used for the determination of monoamineoxidase activity of rat brain homogenate using Kynuramine as a substrate[1]. The 4-hydroxy quinoline formed during oxidative deamination of Kynuramine was determined. The compounds were dissolved in propylene glycol at a final concentration of 1×10^{-5} M. The results are summarised in table 2. All the substituted benzimidazoles produced inhibition of rat brain monoamineoxidase ranging from 40 to 75%. The maximum inhibition was observed with compound 19 and minimum in compounds 10, 13 and 22. As is evident from the table, the compounds having hydrogen at *R* position produced greater degree of inhibition than chloro group but the change in the position of *R* by different groups did not reveal any alteration in the inhibition.

ACKNOWLEDGEMENT

The authors wish to express their thanks to Dr. B. N. Dhawan, C.D.R.I., Lucknow for facilities in evaluating the activity. Two of them (SS) and (RR) are grateful to C.S.I.R. for the award of fellowships.

1. Parmar, S. S., Misra, R. S. Chaudhary, A. and Gupta, T. K., *J. Pharm. Sci.*, 1972, **61**, 1322.
2. Arora, G. L. and Singh, R. B., *Indian J. Exp. Biol.*, 1973, **11**, 243.
3. Loev, B., Bender, E. P., Bowman, H., Nelean, A. A. R. and Jen, T., *J. Med. Chem.*, 1972, **15**, 1024.
4. Dwivedi, C., Gupta, T. K. and Parmar, S. S., *J. Med. Chem.*, 1972, **15**, 553.
5. Elslager, E. F., Tendick, P. H., Warkel, I. M. and Worth, D. F., *J. Med. Chem.*, 1969, **12**, 970.
6. Woop, J. W. and Fontaine, T. D., *J. Org. Chem.*, 1952, **17**, 89.
7. Moyle, C. L. and Chern, D. M., U.S. Patent, 3, 182, 070, 1965, *Chem. Abstr.*, 1965, **65**, 4304d.
8. Verma, D. R., Sareen, K. N. and Gujral, M. L., *Indian J. Physiol. Parmacol.*, 1967, **17**, 409.
9. Irwin, S., *Evoluation of drug activities pharmacometrics*, (eds), D. R. Laurance and A. L. Bacharach, 1964, **1**, 33.