SHORT COMMUNICATIONS

SYNTHESIS AND BIOLOGICAL EVALUATION OF SOME NOVEL N-[2-(PHENOXY/BROMO-SUBSTITUTED PHENOXY) ACETYL] MORPHOLINES/IMIDAZOLES

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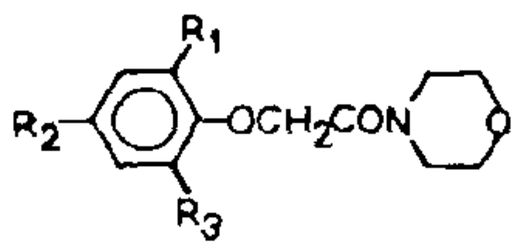
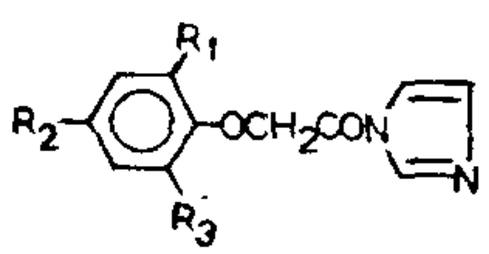
PHENOXY acetic acid and its various derivatives have been reported to possess a wide spectrum of biological activities[1,2]. These results prompted us to undertake the synthesis of some phenoxy and bromosubstituted phenoxy acetic acids with morpholine/imidazole moiety and to screen their pharmacological and anti-microbial properties.

The structure of all the synthesized compounds was checked by IR spectra and elemental analyses. Purity of the compounds was checked by TLC. Various phenoxy acetic acids and their bromosubstituted derivatives were synthesized by condensing the sodium salt of the appropriate phenols with $ClCH_2COONa$[3]. To a solution of aryloxy acid (0.025 M in 30 ml of dry benzene) was added thionyl chloride (0.04 M) and the mixture was refluxed on a waterbath for about 6 hr. The acid chlorides were added dropwise to an ice-cold solution of morpholine/imidazole (0.04 M in 35 ml of dry pyridine) and 25 ml of 1N NaOH solution with constant stirring. The separated amides were filtered, washed and purified over the coloumn of silica-gel. The melting points and analytical data of the compounds are shown in table 1. IR spectra displayed characteristic peaks at ≈2890, 1645, 1590, 1120 and 1030 cm^{-1}.

The synthesized compounds have the following structures.



(Compounds I_a–VI_a)



(Compounds VII_b–XII_b)

Table 1 *Characterization data of the compounds*

Compound No.	R_1	R_2	R_3	Mol. formula	Solvents used for crystallization	M P. (°C)	Yield (%)	Composition % C	H	Calculated (Found) N	Br
Ia	H	H	H	$C_{12}H_{15}NO_3$	Pet. ether	89–91	80	65.15	6.78	6.33	—
								(65.1)	(6.55)	(5.82)	—
IIa	Br	Br	Br	$C_{12}H_{12}NO_3Br_3$	Acetone	115–17	78	31.44	2.62	3.05	52.40
								(31.39)	(2.60)	(3.01)	(53.37)
IIIa	Br	Br	H	$C_{12}H_{13}NO_3Br_2$	Ethyl acetate	94–95	74	37.99	3.43	3.69	42.21
								(37.86)	(3.41)	(3.60)	(42.16)
IVa	Br	H	Br	$C_{12}H_{13}NO_3Br_2$	Methanol	102–04	69	37.99	3.43	3.69	42.21
								(37.91)	(3.40)	(3.62)	(42.14)
Va	Br	H	H	$C_{12}H_{14}NO_3Br$	Acetone	82–84	82	48.00	4 66	4.66	26.66
								(47.91)	(4.58)	(4 61)	(26.60)
VIa	H	Br	H	$C_{12}H_{14}NO_3Br$	Acetone	88–90	70	48.00	4.66	4.66	26.66
								(47.43)	(4.61)	(4.61)	(26.67)
VIIb	H	H	H	$C_{11}H_{10}O_2N_2$	Benzene	102–04	78	65.34	4.95	13.86	—
								(65.31)	(4.94)	(13.83)	—
VIIIb	Br	Br	Br	$C_{11}H_7O_2N_2Br_3$	Sol. ether	115–17	74	30.06	1.59	6.37	54 66
								(30.04)	(1.59)	(6.36)	(54 61)
IXb	Br	Br	H	$C_{11}H_8O_2N_2Br_2$	Chloroform	112–14	72	36.66	2.22	7.77	44 44
								(36.62)	(2.22)	(7 75)	(44 00)
Xb	Br	H	Br	$C_{11}H_8O_2N_2Br_2$	Chloroform	98	81	36.66	2.22	7.77	44 44
								(36 62)	(2.21)	(7.77)	(44.41)
XIb	Br	H	H	$C_{11}H_9O_2N_2Br_1$	Ethyl acetate	126	74	46.97	3.20	9 96	28.46
								(46.93)	(3.21)	(9.94)	(28 40)
XIIb	H	Br	H	$C_{11}H_9O_2N_2Br$	Benzene	142	73	46.97	3.20	9.96	28.46
								(46.90)	(3.26)	(9.92)	(28 40)

Table 2 *Anti-inflammatory activity of compounds Ia–VIa*

Group	Dose mg/kg per os	Mean volume (±S.E.) paw after carrageenin administration (ml) 0 hr	1 hr	2 hr	3 hr	Total increase in paw volume after 3 hr	Per cent Inhibition
Control	—	0.63 ± 0.07	0.79 ± 0.01	0.88 ± 0.06	0.95 ± 0.04	0.32 ± 0.002	—
Compd. Ia	100	0.72 ± 0.05	0.81 ± 0.02	0.96 ± 0.05	1.00 ± 0.04	0.28 ± 0.02	12.50
Compd. IIa	100	0.76 ± 0.09	0.82 ± 0.07	0.84 ± 0.06	0.86 ± 0.08	0.10 ± 0.09	68.75
Compd. IIIa	100	0.75 ± 0.08	0.80 ± 0.02	0.87 ± 0.06	0.94 ± 0.01	0.19 ± 0.07	40.62
Compd. IVa	100	0.77 ± 0.01	0.83 ± 0.09	0.90 ± 0.04	0.95 ± 0.08	0.18 ± 0.03	56.25
Compd. Va	100	0.76 ± 0.08	0.88 ± 0.02	0.92 ± 0.03	0.97 ± 0.05	0.21 ± 0.04	34.37
Compd. VIa	100	0.76 ± 0.03	0.85 ± 0.01	0.89 ± 0.01	0.98 ± 0.06	0.22 ± 0.05	31.25
Ibu-profen	100	0.74 ± 0.03	0.77 ± 0.07	0.80 ± 0.07	0.83 ± 0.06	0.09 ± 0.01	71.87

The biological assay was carried out on albino mice of either sex. All the compounds were relatively less toxic as their LD_{50} values ranged from 650–1000 mg/kg. P.O.

Compounds Ia–VIa were tested for the anti-inflammatory and plant growth-promoting activities while compounds VIIb–XIIb were studied for the anti-microbial and CNS-depressant properties.

Anti-inflammatory activity of compounds Ia–VIa was tested by adopting the method of Winter *et al*[4]. The per cent inhibition of inflammation was calculated by the method of Newbould[5] (table 2).

Compounds Ia, IIIa and IVa were found to possess plant growth-promoting properties. A solution of 100 mg of each compound in 100 ml of water when applied to the germinating seeds of *Zea mays* showed shoot length after 6 days (table 3).

Compounds VIIb–XIIb were screened for the anti-bacterial and anti-fungal activities against various pathogenic bacteria *Pseudomonas ovalis*; *Bacillus migaterium*; *Vibro cholera* and fungi *Candida albicans*; *Aspergillus fumigatus* and *Curvularia lunata* using standard methods[6,7]. Only compounds IXb and Xb were found to possess significant anti-microbial activity whereas other compounds were found to be mild to moderately active against the various bacteria and fungi tested.

Table 3 *Plant growth-promoting properties of compounds I–VIa*

Compound	Length (cm)
Control	6
Ia	7.6
IIa	6.1
IIIa	7.4
IVa	7.8
Va	6.3
VIa	5.8

Compounds VIIb–XIIb were also tested for CNS-depressant activity. All the tested compounds exhibited $LD_{50} > 1000$ mg/kg. One fifth of LD_{50} doses of all the compounds were found to possess CNS depressant activity in mice.

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PREHISTORIC RESEARCH IN KERALA

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RESEARCH on prehistoric evidences in Kerala has brought to light for the first time several Lower Palaeolithic and Mesolithic sites in various parts of Kerala which lies in the south-west coast of India. The Lower Palaeolithic industry is devoid of Acheulian elements, consists of massive chopper-scraper-flake assemblages while the mesolithic industry is represented by small tools such as scrapers, points, blades, borers, burins, lunates, knives, discoids and choppers. Evidences are found to occur as surface finds, in stratified contexts and also inside the rock-shelters. The locally available quartz raw material was exclusively utilized for tool fabrication in both the industries.

Recently one of the rock-shelters at Tenmalai in Quilon District of Kerala has been excavated and Mesolithic implements and wood charcoal stratified in primary context was found in a deposit of 35 cm thickness. The wood charcoal from the depths 30, 35 and 20–35 cm from trench T1, T2 and T3 have been dated by C^{14} in the Birbal Sahni Institute of Palaeobotany, Lucknow, India to 5120 ± 120, 5210 ± 110 and 4420 ± 110 Y.B.P. respectively. These are not only the first absolute dates for any stone age cultures in Kerala or in South India but also the first dates for any Indian coastal mesolithic industry.

The above dates clearly show that it was a Mesolithic culture which had existed in the monsoonal tropical evergreen forests of Kerala in the Late Holocene period. Tenmalai rock-shelter also has an incised motif on its exterior surface and possibly it might be contemporary with the dated mesolithic culture. It is to be noted that the Mesolithic culture. It is to be noted that the mesolithic industries in Kerala are non-geometric, implements of non-microlithic nature and similar characteristics have been noticed all over South India, especially along the coasts.

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PEROXIDASE ISOENZYMES—A DEVICE OF GENIC DIFFERENCES IN FOUR FORMS OF *DATURA METEL* LINN

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THE important role that peroxidases play in plant oxidation processes has been worked out by several investigators[1,2]. These enzymes require both electron-donor and electron-acceptor properties and show different activities with different electron donors. Isoperoxidases in organs of two species of *Datura* have been examined[3].

The four forms of *D. metel* exhibit distinct morphological characters and breed true[4]. The peroxidases were studied in the leaves at different ontogenetic stages. Samples were collected from individual plants at particular ontogenetic stages in order to obtain reproducible zymograms for making comparisons among four forms, e.g the fourth leaf (AL 4) below from the shoot apex was collected when the youngest leaf (AL 1) was 2 cm long. The second (AL 2) and third (AL 3) leaves were similarly collected to ensure that the leaves are at the same ontogenetic stages. For qualitative studies only the fourth leaf was taken. Samples were homogenized in prechilled distilled water and centrifuged at 6000 g at 2°C. The supernatant was precipitated with acetone (10:1) at–10°C. The precipitate was dried and kept at 4°C. This powder was redissolved in a known volume of chilled phosphate buffer (pH 6.4, 0.02 M)[5]. Polyacrylamide gel electrophoretic