Synthesis and Evaluation of Some Novel 2-(substituted amino) benzimidazoles as H_1-Receptor Blockers

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A variety of novel 2-(substitute amino) benzimidazoles have been synthesized by the cyclocondensation of o-phenylenediamine with a variety of dithiocarbamic esters. The title compounds were tested for their H_1 - antihistaminic activity on isolated guinea pig ileum. While all the test compounds exhibited antihistaminic activity, the compound IVa was found to be more potent than the standard pheniramine maleate.

Antihistamines receiving the major attention because of their utility in allergic diseases such as seasonal and perennial rhinitis, urticaria and pruritis[1-3]. Inspite of a large number of clinically useful antihistamines available[4], the benzimidazole-derived antihistamines such as astemizole, norastemizole, mizolastine, emadastine and mepinastine have attracted much attention, because of their potent antihistaminic and none or very low sedative, anticholinergic and cardiac toxicity[5]. These observations have prompted us to synthesize a variety of 2-(substituted amino) benzimidazole and evaluate these compounds for H_1-antihistaminic activity.

The title compounds, 2-(substituted amino) benzimidazoles (IV a-j) were synthesized in fair to good yields by the cyclocondensation of o-phenylenediamine with a variety of dithiocarbamic esters, the dithiocarbamic esters inturn were prepared by reacting primary amines (I) with carbondisulphide, sodium hydroxide and dimethylsulphate. Synthetic route depicted in Scheme-I outline the chemistry part of present work. The compounds synthesized were characterized by spectral data (IR, NMR and mass spectra) and the purity was ascertained by micro analysis.

Melting points were taken in open capillary tubes on a Thomas Hoover melting point apparatus and are uncorrected, IR spectra were recorded in KBr on Perkin Elmer-841 grating spectrometer; Mass spectra on a Varian Atlas CH-7 mass spectrometer at 70 eV and NMR spectra on a Varian A-60 or EM-360 spectrometer at 600 MHZ, using TMS as internal standard.

The dimethyl N-phenyldithiocarbamate (III) was prepared by adding carbondisulphide 1.6 ml and sodium hydroxide 2.4 ml (20 M) dropwise to a vigorously stirred solution of aniline 1.86 g (0.02 mol) in dimethylsulphoxide (10ml) at room temperature. After 30 min, dimethylsulphate 5 g (0.04 mol) was added dropwise under cooling with an ice bath. Stirring was continued for 2 h, the reaction mixture was then poured into ice water and the solid obtained was filtered, washed with water, dried and recrystallized from ethanol to obtain a pale yellow solid. Yield : 3.2 g (81%); m.p.: 73-75°; IR (KBr): 2750, 1400 (CH), 1680 (C=N); NMR ($CDCl_3$): δ ppm 2.3-2.6 (s, 6H, 2-SCH_3), 7.4-7.8 (m, 5H, Ar-H). Other compounds were prepared using the same methodology.

The title compound, 2-phenylaminobenzimidazole (IVa) was prepared by refluxing a mixture of o-phenylenediamine 1.08 g (0.01 mol) dimethyl N-phenyl dithiocarbamate 1.97 g (0.01 mol) in ethanol (30 ml) for 4 h. The reaction mixture on cooling was added to icewater and the solid separated was filtered, washed with water dried and recrystallized from ethanol to yield a white solid (Table -1); IR (KBr): 2876, 1513 (CG), 1620 (C=N); NMR ($CDCl_3$) δ ppm : 6.9-7.4 (m, 9H, Ar-H), 9.2 (S, 2H,2-NH). The compounds (IV a-j) were prepared using the same methodology.

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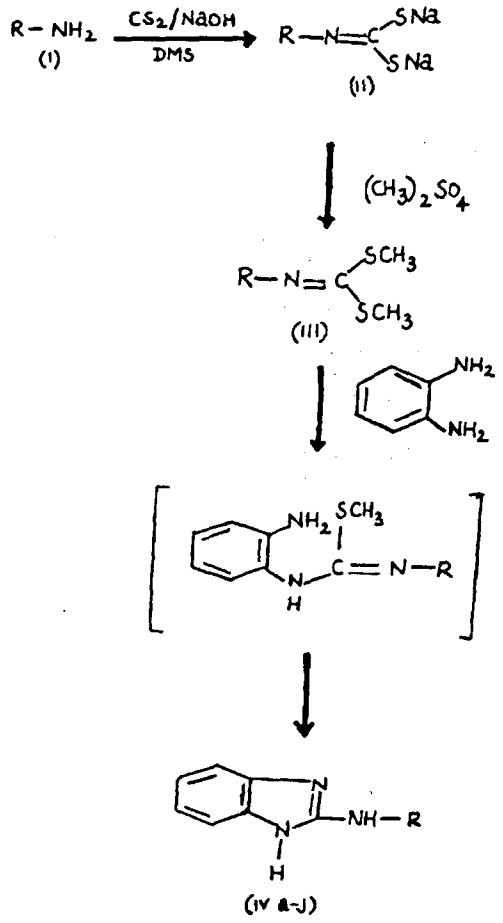
TABLE 1 : CHEMICAL CHARACTERISTICS AND ANTIHISTAMINIC ACTIVITY

Compd No	Substitution	Molecular Formula	Molecular Weight	MP°	Yield %	IC_{50} (μg)
IVa	-phenyl	$C_{13}H_{11}N_3$	209	270-71	77	0.04
IVb	-2-pyridyl	$C_{12}H_{10}N_4$	210	192-94	75	0.53
IVc	-4-methoxyphenyl	$C_{14}H_{13}N_3O$	239	218-19	81	5.32
IVd	-3-methylphenyl	$C_{14}H_{13}N_3$	223	280-83	78	45.12
IVe	-4-methylphenyl	$C_{14}H_{13}N_3$	223	276-79	80	53.32
IVf	-4-bromophenyl	$C_{13}H_{10}N_3Br$	288	255-57	70	41.11
IVg	-4-nitrophenyl	$C_{13}H_{10}N_4O_2$	254	262-64	73	55.56
IVh	-4-chlorophenyl	$C_{13}H_{10}N_3Cl$	243	251-55	71	62.77
IVi	-methyl	$C_8H_9N_3$	147	198-99	76	0.28
IVj	-^{n}Butyl	$C_{11}H_{15}N_3$	189	>290	79	51.42

IC_{50} of pheniramine maleate is 0.06 μg



SCHEME - 1

Antihistaminic activity of compounds IV a-j were performed on the isolated guinea pig ileum[6,7]. Concentration-dependent responses to histamine were recorded, after thorough wash with tyrode solution, the concentration-response curve of histamine in the presence of standard and test compounds (which were dissolved in dilute hydrochloric acid) were recorded. The IC_{50} values were calculated and shown in Table-1.

From the screening results it is evident that the compound with phenyl substitution (compound-IVa) showed antihistaminic activity (IC_{50}-0.04 μg) more potent than the standard, pheniramine maleate (IC_{50}-0.06 μg), and the pyridyl (compound - IVb) (IC_{50}-0.53 μg), methyl (compound-IVi IC_{50}-0.28 μg) substitution exhibited comparable antihistaminic activity to that of standard, while the other compounds exhibited slight to moderate antihistaminic activity.

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Effect of Selected Binders and Disintegrants on the Dissolution Rate of Nimesulide from Tablets

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Much variations in the disintegration and dissolution characteristics were observed when the effect of seven commonly used binders namely starch paste, acacia, sucrose, poly vinyl pyrrolidone (PVP), hydroxy propyl methyl cellulose (HPMC), methyl cellulose and gelatin and four disintegrants namely potato starch, micro crystalline cellulose (MCC), pregelatinized starch (PGS) and Primogel on the dissolution rate and other qualities of nimesulide tablets was studied. ANOVA of dissolution efficiency (DE_{30}) values and Duncan's Multiple Range Test were used to compare the performance of various binders and disintegrants. Based on DE_{30} values the order of performance of binders and HPMC>PVP> sucrose>acacia>starch paste>methyl cellulose>gelatin and that of disintegrants was Primogel>PGS> potato starch>MCC. Tablets formulated employing PVP-potato starch, HPMC-potato starch, starch paste-Primogel, PVP-PGS and PVP-Primogel as binder-disintegrant gave much higher dissolution rate and efficiency values than other, both formulated and commercial. The above tablets also fulfilled all other official requirements.

Nimesulide, is a relatively new non-steroidal antiinflammatory analgesic drug[1]. It is widely used for the treatment of inflammatory conditions associated with rheumatoid arthritis, respiratory tract infections, soft tissue and oral cavity inflammations. It is not yet official in any pharmacopoeia. Nimesulide is practically insoluble in water and aqueous fluids. Its solubility is reported as 0.01 g/l in water[2], 0.12 g/l in 0.1 N hydrochloric acid[3] and 0.10 g/l in phosphate buffer[3] of pH 7.5. As such its oral absorption is dissolution rate limited. The very poor aqueous solubility of the drug gives rise to difficulties in the formulation of dosage forms and may lead to variable dissolution rates and bioavailabilities. Though nimesulide tablets and suspensions are available commercially, no work was reported on the pharmaceutical formulation aspects of nimesulide. In the present work the effect of seven commonly used binders and four disintegrants on the dissolution rate of nimesulide from compressed tablets was studied. The results are reported in the present communication.

Nimesulide (gift sample from M/s. Aristo Pharmaceuticals Ltd., Mumbai), poly vinyl pyrrolidone (PVP, K-30) hydroxy propyl methyl cellulose (having a viscosity

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