Synthesis and anti-inflammatory activity of novel 2-(Substituted alkyl or aryl pyridynyl) benzimidazole derivatives

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Abstract:

Benzimidazole derivatives belong to a crucial structural design that is seen in many pharmaceutically and biologically interesting molecules. Benzimidazole have shown potential for application in a variety of pharmacological targets. They have been intensively used in medicinal chemistry as drugs such as antihistaminic, antiulcerative, antihelmentic, antipsychotic etc. The preparation and investigation of nitrogen heterocycles is one of our main projects. We have already developed some procedures to gain access to diverse structures of benzimidazoles. It has been reported that 2-(Substituted pyridynyl) benzimidazole possess anti-inflammatory activity. At the same time alkyl or aryl substitution at second position of benzimidazole is not yet reported, which may possess same activity as that of benzimidazole substituted with pyridynyl. The series of new 2-(Substituted alkyl and aryl pyridynyl) benzimidazole derivatives have been prepared. In this case, corresponding eight ortho phenylene diamine derivatives were prepared and these results prompted us to extend this methodology for a similar synthesis of benzimidazole derivatives. Compounds 1, 7 and 8 were exclusively isolated and characterized with other five derivatives and tested for anti-inflammatory activity. Anti-inflammatory activity evaluated by using carrageenan induced rat paw edema method because heterocyclic nucleus and substitution at 2-position of the benzimidazole were reported to be associated with potent anti-inflammatory activity. Carrageenan induced rat paw edema is the most widely used, primary test to screen inflammation which measures the ability of the compounds to reduce local edema induced in the rat paw by carrageenan. Therefore it was thought that preparing such derivatives as 2-substituted benzimidazoles would probably result in compounds of having high biological

activity like anti-inflammatory with low toxicity toward many diseases. Most of the obtained compounds exhibit anti-inflammatory activity, especially compound 1, 7 and 8 showed significant activity when compared with that of ibuprofen used as standard drug. Further development of benzimidazole derivatives should make these molecules significantly accessible to permit their widespread use in medicinal synthesis and for pharmacological screening.

Keywords: substituted benzimidazoles, 2-(subtituted pyridynyl) benzimidazole, anti-inflammatory activity, carrageenan induced rat paw edema

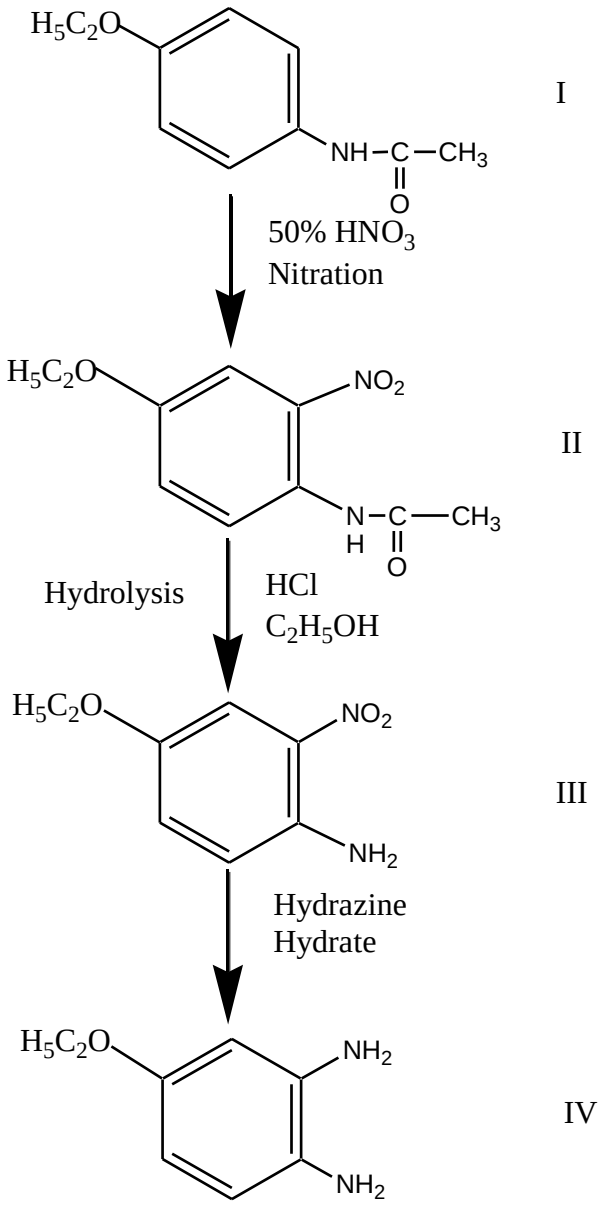
Introduction:

The extensive literature survey of the benzimidazole nucleus revealed that substituted benzimidazole possesses diversified pharmacological activity; Benzimidazoles are a group of molecules which have shown potential for application in a variety of pharmacological targets. They are of wide interest because of their diverse biological activity and clinical applications. A large variety of 2-substituted benzimidazoles have been found to possess anti-inflammatory[1], antispasmodic[2], antihistaminic[3], antimicrobial[4,5,6], antitumour[7], anticancer[8] and cycloxygenase inhibitors[9] activities. In addition benzimidazoles have also been investigated for their analgesic [10] and ant tubercular [11], activity. Although a variety of benzimidazole derivatives are known, the development of new and convenient strategies to synthesize new biologically active benzimidazoles is of considerable interest. Anti-inflammatory activity is evaluated by studying inflammatory responses produced in the animals by injecting carrageenan which produce edema or granuloma. Drugs which suppress these responses are designed as “anti-inflammatory drugs”.

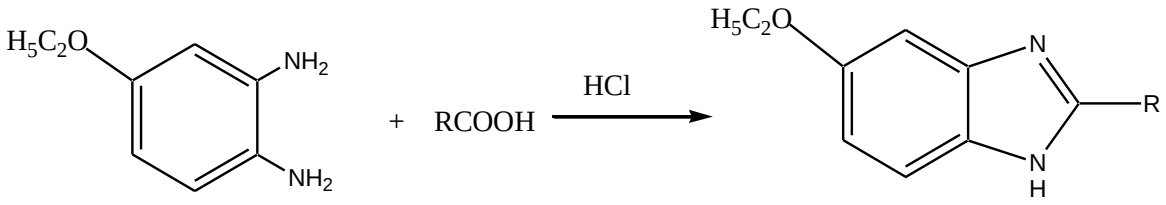
Experimental work:

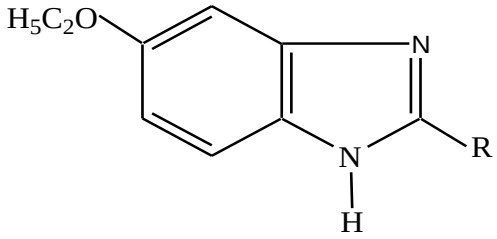
In the present investigation different compounds were synthesized as, a series of 5-ethoxy-2-substituted benzimidazole, were synthesized using appropriate synthetic route and screened for anti-inflammatory activity. N-(2-nitro-5-ethoxyphenyl) acetamide (I) was synthesized in an excellent yield by electrophilic aromatic nitration on phenacetin by concentrated nitric acid (50%) under refluxed condition. Compound (I) hydrolysis with alcohol under reflux condition afforded 5-Ethoxy-2-nitroaniline (II). Compound (II) on reduction with ethanol and hydrazine hydrate by using raney nickel as catalyst afforded 5-Ethoxy ortho Phenylene diamine (III). Reaction of compound (III) with appropriate carboxylic acid gives corresponding 5-ethoxy-2-substituted benzimidazole derivatives. The homogeneity and purity of synthesized compounds were preliminary confirmed by physical constant and thin layer chromatography. Structures of synthesized compounds were confirmed by elemental analysis ,IR.^{1}H-NMR,FAB-MS analysis.

Scheme I:



Scheme II:





5-ethoxy-2-substituted benzimidazole

Compound	R	Molecular formula	M. P. (°C)	NMR (δppm)	IR (KBr)cm-1	Mass
1	Hydrogen	$C_9H_9N_2O$	82-85	7.21, δ 6.77, δ 7.59 (Ar-H), δ 5.0 (-NH-),δ 3.9 (>CH_2), δ. 3.98(-CH_3).	3348cm^{-1} (-NH-), 1251 cm^{-1} (C=N), 2982 cm^{-1} (Ar–H), 835 cm^{-1} (C=C), 2810 cm^{-1} (C-H), 1043 cm^{-1} (ether group in ring).	161
2	Methyl	$C_{10}H_{11}N_2O$	82-85	δ 7.21, δ 6.77, δ 7.59 (Ar-H), δ 5.0 (-NH-), δ 3.9 (>CH_2), δ 3.98 , δ2.42(-CH_3)	3340 cm^{-1} (-NH-), 1250 cm^{-1} (C=N), 3010 cm^{-1} (Ar–H), 1040 cm^{-1} (ether group in ring); 2950 cm^{-1} (CCH_3).	174
3	Ethyl	$C_{11}H_{13}N_2O$	85-90	7.21, δ 6.77, δ 7.59, (Ar-H), δ 5.0 (-NH-), δ 3.9, 2.59 (>CH_2), δ 3.98 and δ2.42 (-CH_3).	3327 cm^{-1} (-NH-), 1248 cm^{-1} (C=N), 3010 cm^{-1} (Ar–H); 1039 cm^{-1} (ether group in ring); 2990 cm^{-1} (CC_2H_5).	189

4	2-subst.phenol	$C_{15}H_{13}N_2O_2$	80-85	7.21, δ 6.77, δ 7.59, (Ar-H), δ 6.79, δ 7.05, δ 6.88,δ 7.31(substituted phenyl), δ 5.0 (-OH), δ 3.9 (>CH_2), δ 1.33(-CH_3).	3324 cm^{-1} (-NH-), 1248 cm^{-1} (C=N), 3034 cm^{-1} (Ar–H); 1039 cm^{-1} (ether group in ring); 3634 cm^{-1}(C-OH).	253
5	Phenyl	$C_{15}H_{13}N_2O$	90-93	7.21, δ 6.77, δ 7.59, (Ar-H), δ 3.9 (>CH_2), δ 1.33(-CH_3), 7.29 , δ 7.03(phenyl)	3324 cm^{-1} (-NH-), 1250 cm^{-1} (C=N), 3020 cm^{-1} (Ar–H); 1043 cm^{-1} (ether group in ring)	237
6	2-subst-acetic acid phenyl ester	$C_{17}H_{16}N_2O_3$	110-115	7.21, δ 6.77, δ 7.59, (Ar-H), δ 3.9 (>CH_2), δ 1.33, 2.08(-CH_3), δ 7.29 and δ 7.03(substituted phenyl)	3320 cm^{-1} (-NH-), 1240 cm^{-1} (C=N), 3010 cm^{-1} (Ar–H); 1047 cm^{-1} (ether group in ring), 1730 cm^{-1} (C=O)	296
7	2-subst.ethanol	$C_{11}H_{13}N_2O_2$	90-95	7.21, δ 6.77, δ 7.59, (Ar-H), δ 3.9 (>CH_2), δ 1.33, 1.49(-CH_3), δ 5.0(-NH-),δ 2.0(-OH)	3330 cm^{-1} (-NH-), 1245 cm^{-1} (C=N), 3010 cm^{-1} (Ar–H); 1044 cm^{-1} (ether group in ring), 3634 cm^{-1}(C-OH).	205
8	Subst. methanol	$C_{10}H_{12}N_2O_2$	106-108	7.21, δ 6.77, δ 7.59, (Ar-H), δ 3.9, 4.79 (>CH_2), δ 1.33(CH_3), δ 5.0(-NH-),δ 2.0(-OH)	3320 cm^{-1} (-NH-), 1240 cm^{-1} (C=N), 3010 cm^{-1} (Ar–H); 1040 cm^{-1} (ether group in ring), 3630 cm^{-1}(C-OH)	192

Result and discussion:

Structures of synthesized compounds were confirmed by elemental analysis ,IR.^{1}H-NMR,FAB-MS analysis. The aromatic Ar–H stretching for all the derivatives was found to be at the range of 3050-3200 cm^{-1}.The presence of ethoxy group was confirmed by the peak between 1000-1050 cm^{-1}. The presence of N-H stretching was confirmed by the peaks at the range 3350-3390 cm^{-1}. Also ^{1}H-NMR spectra's revels the chemical structure ,δ 7.30-8.0 indicates the presence of phenyl ring protons, peak at δ 5.0 shows that presence of amine linkage peak at δ 3.98 δ2.42 shows the presence of methyl groups in the compound. And a mass spectrum of the compounds gives mass of compounds.

Cut-off LD^{50} was determined for all the test compounds. Cut-off LD^{50} of test compounds were found to be 2000mg/kg. The anti-inflammatory activity was determined using Carrageenan induced rat paw edema method and it was found that the compound no. I, VII and VIII possess significant anti-inflammatory activity, while compound no. II, III, IV, V and VI possess moderate activity as compared with the standard drug Ibuprofen. Thus substitution at 2 position of benzimidazole ring showed anti-inflammatory activity, however there is no clear cut relationship between the structure and activity. Compound no. I.VII, VIII possess good anti-inflammatory activity.

Conclusion:

A series of 5-ethoxy-2-substituted benzimidazoles, were synthesized using appropriate synthetic route and screened for anti-inflammatory activity. The purity and homogeneity of compounds synthesized were determined by their sharp melting points and TLC, IR spectra. Structures of synthesized compounds were confirmed by IR, NMR, Mass and elemental analysis. Preliminary pharmacological screening was performed, which includes acute toxicity testing (LD_{50}) and anti-inflammatory activity. The LD_{50} of the test compounds performed on the rats as per the OECD guidelines for selecting the dose. The test compounds showed significant antiinflammatory activity compared with the standard drug Ibuprofen. The Compound no. 1^{st} and 7^{th} possess good antiinflammatory activity with reduced toxicity. We reported a convenient synthetic method for the synthesis of new compounds and the results of antibacterial and antifungal screening were encouraging. Further investigations with appropriate structural modifications of title compounds may result in therapeutically useful products.

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