

Pharmacological and Toxicological Screening of Novel Benzimidazole-Morpholine Derivatives as Dual-Acting Inhibitors

Abstract

The end of this study was to probe acetylcholinesterase (AChE), monoamine oxidase A (MAO-A), monoamine oxidase B (MAO-B), cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) enzyme inhibitory, and antimicrobial conditioning of a new series of 2-(4-substituted phenyl)-1-(2-(morpholin-4-yl) ethyl)-1H-benzimidazole derivations, for their possible use as multi-action remedial agents. Target composites (n = 15) were synthesized under microwave oven irradiation conditions in two ways, and their structures were illustrated by FT-IR, ¹H-NMR, ¹³C-NMR and high resolution mass spectroscopic analyses. Pharmacological webbing studies revealed that two of the composites (2b and 2j) have inhibitory eventuality on both COX-1 and COX-2 enzymes. In addition, cytotoxic and genotoxic parcels of the composites 2b, 2j and 2m were delved via the well-known MTT and Ames tests, which revealed that the mentioned composites are non-cytotoxic and non-genotoxic. As a terse conclusion, two new composites were characterized as implicit campaigners for treatment of constantly encountered seditious conditions.

Keywords: Benzimidazoles • Morpholines • Cytotoxic

Introduction

One of the promising advances in medicine discovery is the contemporaneous combination of two or further salutary chemical halves on the same emulsion, especially for treatment of a certain complaint. Any pharmaceutical benefit that reduces the demand on polypharmacy, e.g., treatment while dwindling side goods, barring symptoms, or addition of an adjuvant remedial exertion is accepted as an ideal starting-point that may lead to the development of new composites with multiple pharmacological goods [1]. There's an agreement that multifactorial diseases can appear from numerous sources, so searching for new mongrel composites with multiple pharmacological biographies that can be expressed through further than one biochemical pathway would be useful for treating numerous kinds of conditions. Despite the great challenge in the design and optimization of similar composites, this strategy possesses clear advantages over medicine fusions or multicomponent medicines owing to minimization of medicine-medicine commerce pitfalls [2, 3]. Some available medicines present the capability to modulate further than one bioreceptor, as instanced by the atypical antipsychotics olanzapine, risperidone and aripiprazole, which act substantially as dopamine and serotonin receptor antagonists and have lower affinity to histamine, cholinergic muscarinic and α -adrenergic receptors. Ladostigil is another illustration of binary monoamine oxidase B (MAO-B) and acetylcholine esterase (AChE) asset [4]. Despite their great pledge in the clinical operation, any implicit threat of side goods shouldn't be neglected. The binary impediments are frequently characterized by high molecular weight that may reduce the chance of their medicine capacities [5]. Thus, the safety biographies as well as pharmacokinetic parcels need to be completely considered in the design of binary impediments. Benzimidazole derivations have a prominent position in medicinal chemistry, which are always used as one of the essential starting accoutrements for discovery of new rectifiers [6, 7]. The origin

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of the special interest towards benzimidazole derivations has been the,6- dimethyl- 1-(α -d- ribofuranosyl)- benzimidazole structure, which is an introductory part of vitamin B12. Likewise, the benzimidazole ring is a structural bioisostere of some of the nucleobases being in natural nucleotides, which can interact fluently with the biopolymers in living systems [8]; this point is frequently accepted as the responsible for its natural significance, either alone or as incorporated into different templates. It has been reported to show numerous pharmacological conditioning including antimicrobial, MAO or cyclooxygenase (COX) inhibitory, or anticholinesterase [9, 10].

Discussion

The antimicrobial and COX inhibitory eventuality of benzimidazole and morpholine-grounded composites may be favorable in the design of binary COX inhibitory- antibacterial agents because inflammation and infection are conditions which are constantly encountered together [11, 12]. A drop of fever besides elimination of a contagious microorganism or treatment of inflammation besides junking of pain are binary issues of similar agent [13, 14]. Either, the inhibition energy of benzimidazole and morpholine derivations against pang and MAO enzymes may be salutary in the design of new anti-Alzheimer's complaint agents [15]. Inhibition of pang increases neurotransmission in the cholinergic synapses and temporally decreases the cognitive deficiency. Pang also contributes in other functions related to neuronal development [16], isolation, adhesion and β -amyloid protein processing. Also, MAO-B inhibition retards further deterioration of cognitive functions [17,18]. Therefore, discovery of a binary asset of these enzymes are anticipated to have implicit for the treatment of Alzheimer's complaint [19]. It's clear that, the benzimidazole- morpholine combination has the implicit to serve as a pharmaceutical source for remedy. With the end of producing safer and more active mongrel composites, the conflation and pharmacological evaluation of some new notes that include bioactive benzimidazole and morpholine halves have been presented in this study. The genotoxicity of named composites (2b, 2j, 2m) was determined by Ames assay using Ames MPF98/100 mutagenicity assay sample tackle (Xenometrix AG, Allschwil, Switzerland) as preliminarily described away. Salmonella typhimurium strains, TA98 (frameshift

mutations) and TA100(base- brace negotiations) were used in the assay. The attention of the composites was between 16 and 5000 μ g/ mL, in agreement with the guideline. Composites were prepared in six different attentions (5.0, 2.5, 1.25, 0.625, 0.3125, 0.156 mg/ mL) in DMSO. Mutagenic eventuality was determined in the absence or presence of Aroclor TM- 1254 convinced manly Sprague – Dawley rat liver microsomal enzyme (S9) blend (Xenometrix AG). Positive controls without S9 blend were 2-nitrofluorene(2.0 μ g/ mL) and 4- nitroquinoline N- oxide(0.1 μ g/ mL), whereas 1.0 μ g/ mL and 2.5 μ g/ mL of 2- aminoanthracene results were used as positive controls with S9 against TA98 and TA100, independently. Solvent control was prepared with 4 DMSO. The end of an trial was determined by the change of the index medium colour to unheroic, which was forming from the drop of pH due to revertant bacteria. Numeric wells were counted as positive, and compared with the negative control. Fold induction over the negative control and fold induction over the birth were calculated(Fold induction over the negative control is accepted as the rate of the mean number of positive wells for the cure attention divided by the mean number of positive wells for the zero cure(negative) control.

Methods

The genotoxicity of named composites (2b, 2j, 2m) was determined by Ames assay using Ames MPF98/100 mutagenicity assay sample tackle (Xenometrix AG, Allschwil, Switzerland) as preliminarily described away(63). Salmonella typhimurium strains, TA98 (frameshift mutations) and TA100(base- brace negotiations) were used in the assay. The attention of the composites was between 16 and 5000 μ g/ mL, in agreement with the guideline (64). Composites were prepared in six different attention (5.0, 2.5, 1.25, 0.625, 0.3125, 0.156 mg/ mL) in DMSO. Mutagenic eventuality was determined in the absence or presence of Aroclor TM- 1254 convinced manly Sprague – Dawley rat liver microsomal enzyme (S9) blend (Xenometrix AG). Positive controls without S9 blend were 2-nitrofluorene(2.0 μ g/ mL) and 4- nitroquinoline N- oxide(0.1 μ g/ mL), whereas 1.0 μ g/ mL and 2.5 μ g/ mL of 2- aminoanthracene results were used as positive controls with S9 against TA98 and TA100, independently. Solvent control was prepared with 4 DMSO. The end of a trial was determined by the change of the index medium

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Results

Inhibitory muscle of composites 2a – 2o on COX- 1 and COX- 2 enzymes are given in Supplementary Table S2; ibuprofen and nimesulide were used as non-selective COX and picky COX- 2 impediments in these tests, independently. The composites 2a, 2b, 2f, 2h, 2j and 2m displayed further than 50 inhibitions at the original attention; accordingly, they were assayed at lower attention between 10^{-5} M and 10^{-9} M, and IC₅₀ values were calculated. It has been determined that composites 2b and 2j have promising inhibitory exertion against both COX- 1 and COX- 2 enzymes. IC₅₀ values of the emulsion 2b was 8.096 μ M and 8.369 μ M versus COX- 1 and COX- 2 enzymes, independently; their IC₅₀ values were also similar with those of the reference medicines ibuprofen and nimesulide. Emulsion 2j held 14.18 and 13.09 μ M IC₅₀ values on COX-

1 and COX- 2, independently. Fold induction over the birth is accepted as the rate of the mean number of positive wells for the cure attention divided by zero cure birth. The zero- cure birth is attained by adding one standard deviation to the mean number of positive wells of the zero cure control. However, the value is set to 1 for computation), If the birth is lower than 1. Mutagenicity was determined according to the criteria reported preliminarily. For a birth value of ≤ 3 , significant increases between 2 and 3-fold of the birth were classified as weak mutagen, and increases ≥ 3 -fold of the birth were classified as mutagen. For a birth value of > 3 , significant increases between 1.5 and 2.5-fold of the birth were classified as weak mutagen, and increases ≥ 2.5 -fold of the birth, were classified as mutagen. As a rule, at least two consecutive boluses with significant increases or a significant increase at the loftiest cure position should be observed for a mutagenic emulsion. All of the boluses were compared according to Student's t- test at $p < 0.05$ for statistical significance. Composites that didn't retain any of the characteristics mentioned over were classified as non-mutagenic.

Conclusions

In the present study, conflation and structural verification of some new benzimidazole-morpholine composites were described, and their natural and pharmaceutical value was estimated by applying multiple natural, pharmacological and toxicological tests. Compactly, it can be concluded that the synthesized composites didn't exceptionally inhibit pang, MAO- A and MAO- B enzymes. On the other hand, composites 2b, 2c, 2e and 2m presented respectable antibacterial exertion especially against *Pseudomonas aeruginosa* ATCC 27853. Likewise, a promising exertion was observed for composites 2b and 2j against COX- 1 and COX- 2 enzymes, meanwhile composite 2b was the most active outgrowth in both antimicrobial and COX inhibition assays. It's a common knowledge that microbial infections generally accompanied with fever and inflammation; therefore, among the composites in the series 2-(4- methoxyphenyl)- 1-(2-(morpholin-4-yl) ethyl)- 1H- benzimidazole (2b) seems to be most important seeker for the treatment of a similar complaint, with binary exertion against *Pseudomonas aeruginosa* ATCC and COX enzymes.

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