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Benzimidazole scaffold based hybrid molecules for various inflammatory targets: Synthesis and evaluation

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ABSTRACT

Designing of hybrid drugs with specific multitarget profile is a promising line of attack against inflammation. In light of this, a series of benzimidazole scaffold based hybrid molecules were designed by integrating benzimidazoles (containing pharmacophoric elements for COXs and LOXs inhibitors) with phthalimide subunit of thalidomide (pharmacophore element for TNF-α inhibitor) under one construct via molecular hybridization strategy. The designed molecules were synthesized and evaluated for their inhibitory activity against COXs (COX-1, COX-2), LOXs (5-LOX, 15-LOX) enzymes as well as TNF-α inhibitory effect. The results revealed that, compounds (**3a–l**) obtained showed inhibition in submicromolar range against COXs and LOXs targets whereas milder inhibitory activity was obtained against lipopolysaccharides (LPS)-induced TNF-α secretion by murine macrophage-like cells (RAW264.7). Within this class of compounds, **3j** emerged as having alluring multiple inhibitory effects on set of COX-1/2 and 5-/15-LOX enzymes (COX-1 IC_{50} = 9.85 μM; COX-2 IC_{50} = 1.00 μM; SI = 9.85; 5-LOX IC_{50} = 0.32 μM; 15-LOX IC_{50} = 1.02 μM) in conjunction with a good anti-inflammatory and analgesic activities. Additionally, compound **3j** showed gastrointestinal safety with reduced lipid peroxidation. Docking results of compound **3j** with COX-2 and 5-LOX were also consistent with the *in vivo* anti-inflammatory results.

1. Introduction

Despite years of studies and irrespective of long passage of anti-inflammatory drugs, efficacy and safety of the drugs- a set of extremely important fundamental issues remains unresolved [1]. The growing realization that inflammation is a complex, multifactorial and crucial in many diseases opens up a whole new avenues for treatment [2]. Current research emphasizes designing of hybrid drugs with a specific multi-target profile as the promising line of attack against inflammation [3].

Demand for hybrid drugs has driven the pursuit of structures possessing multitargeted aptitude. It is well documented that designing of novel drugs on “privileged scaffold” is one of the successful directions in drug discovery. “Privileged scaffold” offered an optimal source of core structure and presented remarkable capability of binding across multitudes of therapeutically relevant biological targets [4]. Among the privileged scaffolds engaged in drug designing, focus on benzimidozole nucleus is noteworthy. Above and beyond synthetic versatility, benzimidazole scaffold endows its derivatives with diverse portfolio as of inflammation targeted drugs by virtue of its inherent affinity against various inflammation related targets. This inspiring biological background has raised lots of concerns on their suitability as a viable scaffold for design of multitargeted anti-inflammatories [5]. On the other hand thalidomide is another significant drug molecule noticeable for its well-known inherent TNFα-inhibitor property liable for its distinguishing immunomodulatory and anti-inflammatory properties. Structure activity studies, analogs and metabolites of thalidomide now clearly disclosed that phthalimide subunit (pharmacophore) of thalidomide is essential for its distinctive pharmacological functions whereas its glutarimide portion (toxicophore) facilitates binding to the human cereblon gene (component of an E3 ubiquitin ligase complex), which is a primary target protein responsible for thalidomide-mediated teratogenicity [3,6].

Following the emerging trend of hybrid drugs and encouraged by biological background of benzimidazole and thalidomide, the possibility of designing novel hybrid molecules was therefore explored using privileged benzimidazole as a core scaffold, which combines, under one construct, pharmacophoric elements that characterize well-known classes of inhibitors of cyclooxygenase isoenzymes (COXs), lipoxygenase isoenzymes (LOXs) and tumor necrosis factor-alpha (TNF-α) via molecular hybridization drug design strategy. A preview of the overall design strategy illustrated in Fig. 1. The pharmacophoric element needed for cyclooxygenase and lipoxygenase inhibitors where

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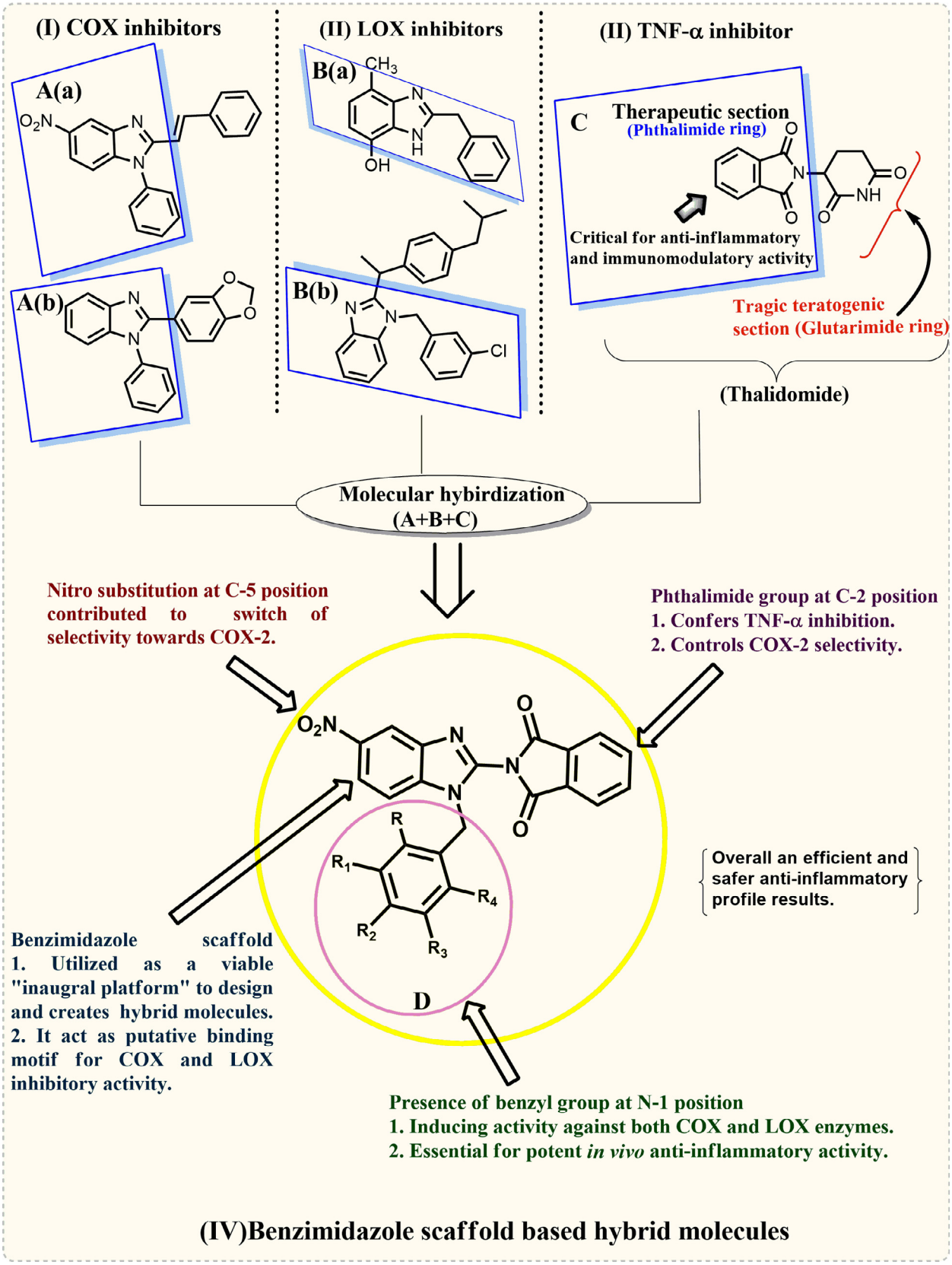

Fig. 1. Design strategy of benzimidazole scaffold based hybrid molecules. Identified pharmacophoric elements for COX inhibitors (IA), LOX inhibitors (IIB) and TNF-α inhibitors (IIIC) highlighted in rectangular framework (blue color). Proposed benzimidazole scaffold based hybridized structure (IV) that, under one construct, combines identified pharmacophoric elements that characterize well known classes of COX, LOX and TNF-α inhibitors via rational molecular hybridization drug design strategy. Further in order to investigate the effect of molecular variation at the D framework of the designed hybridized structure on the *in vivo/in vitro* anti-inflammatory activity, series of 12 compounds generated for SAR studies.