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Review article

Hybrid molecules: The privileged scaffolds for various pharmaceuticals

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ABSTRACT

The practice of polypharmacology is not a new concept but the approaches which are being adopted for administering the two or more drugs together are varied from time to time. Taking two or more drugs simultaneously, co-formulation of two or more active agents in a single tablet and development of hybrid molecular entities capable to modulate multiple targets are the three popular approaches for multidrug therapy. The simultaneous use of more than one drug for the chemotherapy of a single disease demands a lot of patient compliance. Hence the present form of polypharmacology is gaining popularity in the form of hybrid molecules (multiple ligand approach). From the last 1-2 decades, the synthesis of hybrid molecules by the combination of different biologically relevant moieties has been under constant escalation along with their evaluation as diverse range of pharmacological agents and as potent drugs. This review is focused on the biological potential of hybrid molecules with particular mention of those exhibiting anti-fungal, anti-tuberculosis, anti-malarial, anti-inflammatory and anti-cancer activities. A comparison of the drug potency of the hybrid molecules with their individual counterparts is discussed for quantifying the significance of the concept of molecular hybridisation.

Contents

Abbreviations: ACTs, artemesinin based combination therapy; CQ, chloroquine; CC_{50}, concentration required to reduce growth by 50%; EC_{50}, half maximal effective concentration; Fqa, ferroquine; GI_{50}, 50% growth inhibitory concentration; IC_{50}, 50% inhibitory concentration; μg, microgram; MIC, minimum inhibitory concentration; MIC_{50}, minimum concentration for 50% inhibition; mm, millimetre; μM, micromolar; nM, nanomolar; SI, selectivity index; TB, tuberculosis; MTB, mycobacterium tuberculosis; NO, nitric oxide; OA, oleanolic acid; GSTπ, glutathione *S*-transferase π; BPU, benzoylphenyl urea; SAR, structure activity relationship; BCG, Bacillus Calmette-Guerin; WHO, World Health Organisation; LOX, lipoxygenase; COX, cyclooxygenase; ROS, reactive oxygen species; DHFR, dihydrofolate reductase; TOPO, Topoisomerase.

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1. Introduction

The efficacy of a drug is controlled by various physico-chemical parameters including absorption, distribution, mechanism of interaction between the drug and its cellular target, metabolism, excretion and toxicity. For the optimization of these parameters, it is essential to have tailor-made design of the molecules. Since it is always advantageous to modify a known pharmacophore for the development of a new drug; the hybrid molecules, obtained by the combination of structural features of two differently active fragments, are the most popular chemical entities to work upon for developing modified scaffolds with much improved and amazing properties in the area of biology as well as medicinal science. Taken from the naturally available myriad of scaffolds with varied biological profiles, amalgamation of two molecular entities exhibits unusual properties [1].

The synthesis of hybrid molecules and their evaluation as diverse range of pharmacological agents and as potent drugs has been under constant escalation for the last two decades. In the present review, we have focused on the biological potential of hybrid molecules with particular mention of those exhibiting antifungal, anti-tuberculosis, anti-malarial, anti-inflammatory activities, and anti-cancer categories of pharmaceutical compounds. The work of recent years on these classes of hybrid molecules is showcased concisely. Each type of the pharmacological entity is divided into two major subsections including the one covering the hybrids synthesized from natural product pharmacophores and the other incorporating only the synthetically prepared pharmacophoric groups. The aim of this review was to make a succinct compilation of the recent findings in synthesis and evaluation of hybrid molecules for various drug categories and to lend a hand to the entire scientific community (both experts and novice) for designing and developing improved pharmacological entities.

2. Hybrid molecules exhibiting anti-fungal activity

Since humans and fungi undergo similar molecular processes, there is always risk of the toxicity of anti-fungal agents to human system. Moreover, the anti-fungal drugs suffer from a serious and major side-effect of developing resistance in its early stage [2]. The imidazoles and the triazoles in late 1980s and early 1990s, respectively originated as efficient antifungal agents but soon confronted the limitation of resistance development. So, the doors remained wide open for the development of more effective agents capable of countering resistance of the serious fungal infections.

2.1. Hybrid molecules based on natural product pharmacophores

Nikkomycin (**1**) and polyoxin (**2**) based hybrid molecules have recently been reviewed by Chaudhary et al. [3]. Nikkomycin and polyoxin (Chart 1) were for the first time isolated from culture of *Streptomyces* sp and were found active as chitin synthase inhibitors. Till now, Nikkomycin Z is used as a potent drug for treating coccidiomycosis, also known as valley fever.

Based on the various options of modification, a lot of work on derivatization of **1** and **2** by incorporating other active drugs like fluconazole, itraconazole for procuring hybrid molecules is reported. These molecules were found to exhibit additive efficacy. Peptide-polyoxin/nikkomycin hybrids are reported as effective antifungal agents (Chart 1, Table 1).

Carvacrol (**3**), another naturally occurring monoterpenoid is an effective antifungal and insecticidal agent while BPU is an insect growth regulator, inhibiting chitin synthesis. These two medicinally significant moieties were interestingly worked upon to synthesize their hybrids as reported by Pete et al. [4] (Chart 2). Compounds **4** and **5** exhibited potent antifungal activities against *Candida albicans* (Table 2) along with good insecticidal properties. Also, the synthesized compounds were found to be non-haemolytic as compared to carvacrol and amphotericin-B which otherwise cause haemolysis. Hence, the new molecules were better and safer than carvacrol and BPU's.

Another naturally occurring moiety coumarin has attracted the attention of researchers to exploit its extensive biological properties as a result of which warfarin, acenocoumarol, armillarisin A, hymecromone and carbochromen were approved for therapeutic purposes. In recent years, some reports have manifested that coumarin backbone in combination with nitrogen-containing heterocyclic moieties such as azetidine, thiazolidine, thiazole etc could significantly increase the antimicrobial efficiency of the hybrid molecules. Keeping up the ideology, Zhou et al. [5] have reported two series (**6**, **7**; Chart 3) of hybrids of coumarin and triazoles and as checked against *A. Fumigatus,* they exhibited significantly improved antifungal activities than fluconazole (Chart 3).

Ronad et al. [6] also explored coumarin moiety and synthesized its Schiff bases (**8**, Chart 4) with variedly substituted aromatic aldehydes. The Schiff bases were further converted to their thiazolidinone derivatives **9** and evaluated against various strains of fungi. Preliminary results showed better antifungal activities of thiazolidinone derivatives than that of Schiff bases. Al-Amiery et al. [7] reported hybrids of coumarin-triazole thione/thiadiazole (**10**, **11**; Chart 5). The synthesized compounds were tested for antifungal activities and indicated significant activities as compared to fluconazole. Bis-coumarin hybrids (**12**, **13**; Chart 6) [8] were found to be potent antifungal agents against *C. albicans* (ATCC 10231), *A. fumigatus* (HIC 6094), *T. rubrum* (IFO 9185), and *T. mentagrophytes* (IFO 40996).

There is still scope for exploring the treasures of simple and natural antifungal moieties. Such compounds (Chart 7) can be