Biomedicine & Pharmacotherapy 103 (2018) 923–938

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

DNA gyrase inhibitors: Progress and synthesis of potent compounds as antibacterial agents

Tabassum Khan[a,*], Kaksha Sankhe[b], Vasanti Suvarna[a], Atul Sherje[a], Kavitkumar Patel[a], Bhushan Dravyakar[a]

[a] Dept. of Pharmaceutical Chemistry and QA, SVKM's Dr. Bhanuben Nanavati College of Pharmacy, Mumbai, India
[b] Dept. of Quality Assurance, Ciron Drugs & Pharmaceuticals Pvt. Ltd., Palgarh, India

ARTICLE INFO

Keywords:
DNA gyrase
DNA gyrase inhibitors
Quinolones
Spiropyrimidinetriones
Coumarins
Chebulinic acid

ABSTRACT

DNA gyrase is classified as topoisomerase II, an ATP-dependent enzyme that is vital in the transcription, replication of DNA and chromosome segregation processes. It plays a crucial role in all bacteria except higher eukaryotes and this makes it a desirable and viable therapeutic target for development of new antibacterial agents. Fluoroquinolones are commonly used effective antibacterial agents that target DNA gyrase, however the spectrum of side-effects and emerging bacterial resistance with no new drugs in the antibacterial pipeline has fuelled intensive research in this area. New chemical entities with varied scaffolds possessing DNA gyrase inhibiting properties have been determined by screening chemical libraries that could serve as good leads for antibacterial drug development. A wide range of natural products and protein-based compounds have been identified and studied as DNA gyrase inhibitors and this adds a huge amount of structural diversity that can be exploited and harnessed in the discovery of new antibacterial agents. The development of new chemical compounds with DNA gyrase inhibitory activity (from natural sources, random screens or rational design) will further validate/corroborate the potential of this enzyme as a useful target. This review presents an overview of the DNA gyrase inhibitors obtained from natural and synthetic sources, their syntheses schemes and spectrum of biological activity of a variety of scaffolds and their analogues. The authors hope to provide focused direction for development of new chemical entities, synthetic routes for analogue synthesis, structure activity relationships and biological activity. The most potent ones can be used as templates to design novel compounds targeting DNA gyrase and are effective against resistant bacterial strains and biofilms.

1. Introduction

DNA topoisomerases are enzymes that bring about changes in the topology of DNA i.e. they can interconvert relaxed and supercoiled forms of DNA [1,2]. They play a crucial role in controlling the physiological function of the genome and in DNA processes of replication, transcription recombination repair and chromosome decondensation [3,4]. Hence these enzymes serve as attractive targets for designing new antibacterial drugs. Topoisomerase inhibitors act as an obstacle to the ligation step in the microbial (gram positive and gram negative) cell cycle, generating single and double stranded breaks that damage the integrity of the genome leading to apoptosis (cell death) in the proliferating cell [5]. DNA gyrase is a type IIA topoisomerase belonging to gyrase, heat-shock protein 90 (Hsp 90) histidine kinase MutL (GHKL), protein kinases and the DNA mismatch repair protein MutL (Mismatch from replication recognized by *mutL*)) family of enzymes. These enzymes are associated with many fundamental biological processes that involve DNA- they are involved in segregation of DNA after replication, initiation of DNA replication and gene expression [8]. It is one of the most investigated and validated targets for the development of new antibacterial agents. Its absence in the mammalian organism and its crucial role in the bacterial DNA replication cycle makes this enzyme a suitable target for the development of antibacterial drugs with selective toxicity. It comprises of two subunits-gyrase A and gyrase B that together form the catalytically active heterotetrameric enzyme (i.e. A2B2). The role of the A subunit is breakage and reunion of the double DNA strand, while the B subunit (DNA gyrase B) possesses the ATPase activity, providing a sufficient amount of energy for the DNA supercoiling [6–9].

DNA gyrase being a highly appealing drug target, a large number of inhibitors have been synthesized and characterized with quinolones and aminocoumarins being the most widely studied compounds [10].

* Corresponding author.
E-mail address: tabassum.khan@bncp.ac.in (T. Khan).

https://doi.org/10.1016/j.biopha.2018.04.021
Received 2 January 2018; Received in revised form 24 March 2018; Accepted 3 April 2018

Currently, the 6-fluoroquinolones class of compounds are the only DNA gyrase inhibitors used in clinical practice. The quinolones create restriction in the process of rejoining double-strand breaks in DNA while aminocoumarins and cyclothialidines (cyclic peptides) block the ATPase activity of DNA gyrase [11,12]. In addition to the above compounds, two proteinaceous poisons, microcin B17 and CcdB block *Escherichia coli* gyrase in a manner similar to that of quinolones. Most of these inhibitors fall into two groups based on their site of action and mechanism of inhibition: inhibitors such as fluoroquinolones, CcdB and microcin B17 affect the cleavage–religation step, while coumarins and cyclothialidines prevent ATP hydrolysis [13]. Despite the potency of existing drugs, several bacterial strains resistant to the current therapeutic regimen have emerged. This review aims to classify DNA gyrase inhibitors based on their source into drugs obtained from natural resources and drugs of synthetic origin. DNA gyrase is a validated target for the development of antimicrobial drugs hence synthesis of novel gyrase inhibitors is a highly active research area. This review also summarizes the current strategies utilized for discovery and synthesis of new chemical scaffolds as potential DNA gyrase inhibitors.

2. Classification and functions of topoisomerases

Topoisomerases play an essential role in all organisms since they control and maintain the topological state of the DNA in the cell [14]. DNA cleavage in all topoisomerases enzyme is followed by the emergence of a transient phosphodiester bond between tyrosine residues in the protein. Topoisomerase enzymes that cut single strand of the DNA are described as type I which is further classified into type IA subfamily if the protein is attached to a 5′ phosphate of DNA or type IB subfamily if the protein is linked to a 3′ phosphate of DNA. Topoisomerase enzymes that cleave both strands to generate a staggered double-strand break are classified as type II topoisomerases. The classification of topoisomerases is represented in (Fig. 1.) [15].

2.1. Eukaryotic topoisomerase enzymes

Eukaryotic topoisomerases are classified into two categories- type I and type II (Fig. 1). These enzymes are found in eukaryotes, mammalian cells, yeast and drosophila.

2.1.1. Type I topoisomerase

This enzyme (Fig. 2.) is a monomer and causes single strand breaks in double-stranded DNA [15].This is further subdivided (based on structure and mechanism) into topoisomerases IA and IB [16,17]. Type IA topoisomerases comprises of four domains, I-IV. Domain I consists of TOPRIM (Topoisomerase- Primase), whereas domains III and IV form a helix-turn-helix domain containing the catalytic tyrosine residue. Domains III and IV each consist of a flexible bridge of domain II connecting each other [18]. Firstly, single strand of DNA attaches to domain III and I. As a result of catalytic tyrosine residue, the DNA

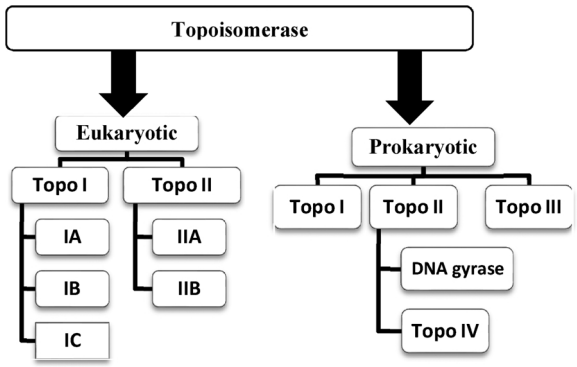

Fig. 1. Classification of topoisomerases.

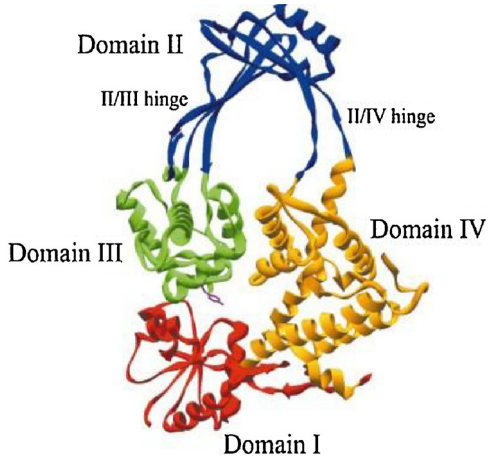

Fig. 2. Type I topoisomerase [15].

backbone breaks leading to formation of transient 5′ phosphotyrosine intermediate followed by separation of the strands using domain II. Topo IB consists of an N-terminal breakage- reunion domain i.e. (NTD), a capping and catalytic lobe and a C-terminal domain. It solves the problem of positively or negatively supercoiled DNA. Currently topoisomerase V is the only member of type IC class of topoisomerases. This was obtained from the *Methanopyrus kandleri* and its mechanism of action is similar to type IB topoisomerase. The function of type 1 topoisomerase in eukaryotic cells is to relax the negatively and positively supercoiled forms of DNA [19].

2.1.2. Type II topoisomerase

This enzyme has two subclasses i.e. type IIA and IIB topoisomerases. Type IIA topoisomerases are able to simplify DNA topology, while type IIB topoisomerases do not. Type IIA topoisomerases create double-stranded breaks with four-base pair overhangs, while type IIB topoisomerases create double-stranded breaks with two base overhangs. They have no supercoiling activity [19].

2.2. Prokaryotic topoisomerase enzymes

2.2.1. Type I topoisomerase

This enzyme is a monomer and most likely a single chain polypeptide. It is encoded by *topA* gene. *E. coli* topoisomerase I was broadcasted in 1971 and named as the omega protein [19].

Prokaryotic topoisomerases

E. coli I	Topoisomerases I	Relaxes only negatively supercoiled DNA
E. coli I	Topoisomerases III	Involved in chromosome stability and plasmid segregations.
E. coli II	DNA gyrase	Introduces negative supercoiling, required for chromosome replication.
E. coli II	Topoisomerases IV	No supercoiling activity.

2.2.2. Type II topoisomerase

This class includes the enzymes- DNA gyrase and Topoisomerase IV. DNA gyrase (Fig. 3.) is made up of two subunits A and B. The active holoenzyme is comprised of two Gyrase A (GyrA) and two Gyrase (GyrB) subunits that form A2B2 heterotetramer. The 97 kDa A subunit is composed of a 59 kDa (GyrA59) N-terminal domain (NTD) and a 38 kDa C-terminal domain (GyrA-CTD) and contains the functional parts that are involved in DNA binding [20]. The C- terminal domain of the GyrA is important for substrate recognition, cellular targeting and