



Invited review

A review on recent developments of indole-containing antiviral agents

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ABSTRACT

Indole represents one of the most important privileged scaffolds in drug discovery. Indole derivatives have the unique property of mimicking the structure of peptides and to bind reversibly to enzymes, which provide tremendous opportunities to discover novel drugs with different modes of action. There are seven indole-containing commercial drugs in the Top-200 Best Selling Drugs by US Retail Sales in 2012. There are also an amazing number of approved indole-containing drugs in the market as well as compounds currently going through different clinical phases or registration statuses. This review focused on the recent development of indole derivatives as antiviral agents with the following objectives: 1) To present one of the most comprehensive listings of indole antiviral agents, drugs on market or compounds in clinical trials; 2) To focus on recent developments of indole compounds (including natural products) and their antiviral activities, summarize the structure property, hoping to inspire new and even more creative approaches; 3) To offer perspectives on how indole scaffolds as a privileged structure might be exploited in the future.

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1. Introduction

Indole derivatives occur widely in natural products, existing in different kinds of plants, animals and marine organisms [1]. The indole core is a near-ubiquitous component of biologically active natural products. For example, indole-3-acetic acid (IAA) **1** (Fig. 1), one of the most common naturally-occurring, is a plant hormone of the auxin class [2]; tryptophan **2**, an essential amino acid, participates in many essential biological processes [3]; serotonin or 5-hydroxytryptamine (5-HT) **3**, biochemically derived from tryptophan, is a neurotransmitter and is found in all bilateral animals [4]; melatonin **4**, is a hormone found in animals, plants, and microbes, in which animals use the variation in duration of melatonin production each day as a seasonal clock [5]. The indole core is also well known as one of the most important scaffolds for drug discovery, and it has been a major focus of research for generations [6]. Biological studies of indole-3-carbinol (I3C) **5**, and 3,3'-diindolylmethane (DIM) **6**, also a natural product derived from the digestion of I3C which is found at relatively high levels in cruciferous

vegetables such as broccoli, Brussels sprouts, cabbage and kale, have been the subjects of on-going research due to their interesting anticarcinogenic, antioxidant, and antiatherogenic effects [7–10]; Ajmalicine **7** (also known as δ -yohimbine or raubasine), an indole alkaloid found naturally in various plants, is an antihypertensive drug used in the treatment of high blood pressure [11]. It acts as a α_1 -adrenergic receptor antagonist with preferential actions over α_2 -adrenergic receptors, underlying its hypotensive rather than hypertensive effects [12]. Reserpine **8**, an indole alkaloid, is used to treat high blood pressure and severe agitation in patients with mental disorders [13]. Vinblastine **9**, is used to treat several types of cancer, including Hodgkin's disease, Kaposi's sarcoma, non-Hodgkin's lymphoma, and cancer of the breast or testicles [14].

Indole represents one of the most important structural motifs in drug discovery, and it is described as one of the "privileged scaffolds", a term first introduced by Evans and co-workers to define scaffolds which are capable of serving as ligand for a diverse array of receptors [15–17]. Indole derivatives have the unique property of mimicking the structure of peptides and to bind reversibly to enzymes [18–21], which provide tremendous opportunities to discover novel drugs with different modes of action. There are seven indole-containing commercial drugs in the Top-200 Best Selling Drugs by US Retail Sales in 2012 [22]. This is highlighted by Cialis, an approved drug for the treatment of men's erectile dysfunction (ED), the signs and symptoms of benign prostatic

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List of abbreviations

IAA	indole-3-acetic acid	HAART	highly active antiretroviral therapy
5-HT	5-hydroxytryptamine	MERS	middle east respiratory syndrome
I3C	indole-3-carbinol	EVD	ebola virus disease
DIM	3,3'-diindolylmethane	EFVR	efavirenz-resistant
WHO	world health organization	HDAC	histone deacetylase
ED	erectile dysfunction	ADME	absorption, distribution, metabolism, and excretion
OD	once-daily	RBV	ribavirin
BPH	benign prostatic hyperplasia	SVR	sustained viral response
HIV	human immunodeficiency virus	NHR	N-terminal heptad repeat
HCV	hepatitis C virus	DKA	diketo acid
HSV	herpes simplex virus	RT	reverse transcriptase
VSV	vesicular stomatitis virus	RTIs	reverse-transcriptase inhibitors
H1N1	influenza virus A	NNRTIs	non-nucleoside reverse transcriptase inhibitors
CV	cyanoviryl	IAS	indolylarylsulfone
IE	immediate-early	INIs	integrase inhibitors
SARS	severe acute respiratory syndrome	PPIs	protein–protein interactions
RSV	Respiratory Syncytial Virus	BVDV	Bovine viral diarrhea virus
		HRV	Human rhinovirus
		FDV	Fosdevirine

hyperplasia (BPH), and both ED and the signs and symptoms of BPH [23,24]. There are also an amazing number of approved indole-containing drugs in the market as well as compounds currently going through different clinical phases or registration statuses.

Viral diseases are extremely widespread infections. Some familiar viral diseases include common cold, influenza, chickenpox, herpes, gastroenteritis (stomach flu), human immunodeficiency virus (HIV/AIDS), hepatitis. Viral diseases can lead to serious, and potentially life-threatening complications, it is estimated that viral infections are responsible for more than 60% of the illnesses occurring in developed countries. In 2003, the severe acute respiratory syndrome (SARS) epidemic originated from southern China

took the lives of nearly 800 people worldwide. Middle East Respiratory Syndrome (MERS) is a viral respiratory illness first reported in Saudi Arabia in 2012. It is caused by a corona virus called MERS-CoV. As of June, 2014, the World Health Organization (WHO) reported 699 cases of human infection with MERS, including at least 209 deaths. The most recent outbreak of Ebola virus disease (EVD) in West Africa in 2014 since its first appearance in 1976 has prompted WHO to declare international public health emergency. As of October, 2014, WHO reported that the current outbreak of Ebola has infected more than 7470 people and killed more than 3431 (Updated October 3, 2014). Antiviral drugs play an important role in fast-spreading epidemics; however almost all antivirals are

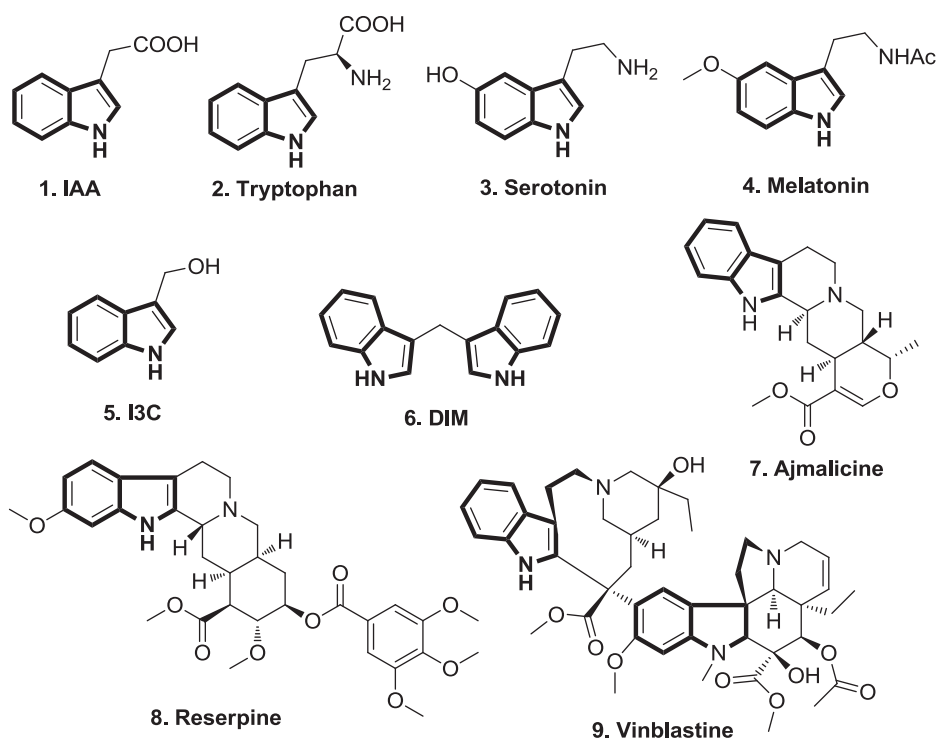


Fig. 1. Structures of indole-containing natural products and drugs.

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