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Review article

Tamoxifen a pioneering drug: An update on the therapeutic potential of tamoxifen derivatives

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ABSTRACT

Tamoxifen (ICI 46 474), *trans*-1-(4-β-dimethylaminoethoxyphenyl)-1,2-diphenylbut-1-ene, is the most commonly used drug for the treatment of estrogen receptor positive breast cancer and has been saving lives worldwide for the past four decades. Tamoxifen is considered a pioneering drug due to its ubiquitous use in both treatment and chemoprevention of breast cancer and also for research addressing novel selective estrogen receptor modulators (SERMs). Tamoxifen is cost effective, lifesaving, and devoid of major side effects in the majority of patients. The discovery of tamoxifen metabolites such as 4-hydroxy tamoxifen, *N*-desmethyl tamoxifen, and endoxifen has facilitated understanding of tamoxifen's and its metabolites' mechanisms of action in breast cancer therapy. Continuous efforts are being made by both industry and academia to synthesize novel tamoxifen derivatives in order to better understand the mechanism of this drug's action and to generate new agents with reduced side effects for many therapeutic targets. This review article comprises the tamoxifen derivatives reported in the literature in the last few years and we anticipate that it will assist medicinal chemists in the synthesis of novel and pharmacologically potent agents for various therapeutic targets.

Contents

1. Introduction

Tamoxifen (**1**) (Fig. 1) is considered a groundbreaking drug in medical oncology that has saved many lives over the past four

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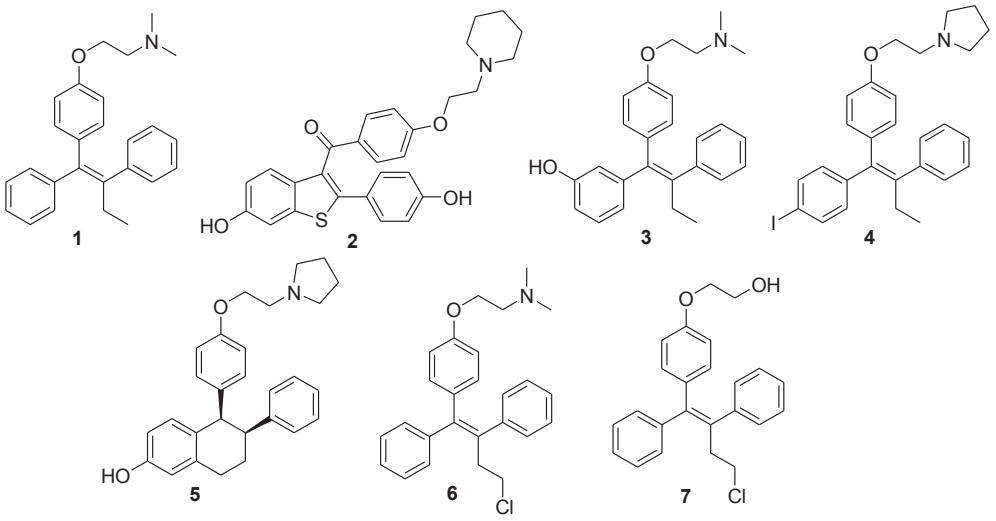

Fig. 1. Chemical structure of drug tamoxifen (**1**), raloxifene (**2**) and important tamoxifen derivatives in clinical development trials; droloxifene (**3**), idoxifene (**4**), lasofoxifene (**5**), toremifene (**6**) and ospemifene (**7**).

decades and progressed to become a significant part of our healthcare [1–4]. The story of the development of tamoxifen as a pioneering medicine for cancer treatment is very fascinating and inspiring for researchers worldwide who are working toward the development of novel medicines for various diseases. In the late 1950s, in the laboratories of Imperial Chemical Industries Ltd. Pharmaceutical division now known as AstraZeneca, a team with Dora Richardson (chemist), Michael J. K. Harper (reproductive endocrinologist), and Arthur L. Walpole (Head of Reproduction Research) was given the task of developing a post-coital contraceptive (the morning-after pill). Eventually, tamoxifen (Imperial Chemical Industries (ICI) 46 474, an antiestrogenic *trans* isomer of a substituted triphenyl ethylene, was invented and received marketing approval as a fertility treatment, but the drug never actually proved useful in human contraception. Walpole was very interested in exploring tamoxifen's application in cancer research and treatment [5]. In 1972, Walpole collaborated with V.C. Jordan to conduct scientific research that led to the reinvention of the failed ICI 46 474 contraceptive to become tamoxifen, the first targeted agent for the treatment and prevention of breast cancer [6–11].

The “Father of Tamoxifen”, V. C Jordan, introduced the strategy of targeting estrogen receptor positive tumors with long term adjuvant tamoxifen therapy that increased the survival rate of hundreds of thousands of breast cancer patients around the world [12,13]. Tamoxifen is inexpensive and readily available to underfunded healthcare systems and that feature has caused an increase in its worldwide popularity as a miracle drug for breast cancer. Currently, tamoxifen is used for the treatment of all stages of estrogen receptor (ER) -positive (ER+) breast cancer in pre- and postmenopausal women in addition to hormone treatment for male breast cancer [14,15]. In addition, tamoxifen is used for the treatment of ductal carcinoma *in situ* and for the prevention of breast cancer in women at high risk of developing the disease [16,17]. Initially, tamoxifen was known as an anti-estrogen that reduced estrogen-induced effects by blocking estrogen receptors in breast tissues. Later, rigorous pharmacological investigation of tamoxifen provided evidence that tamoxifen acts as agonist at estrogen receptors in other body tissues such as endometrium, liver, and bone and thus, led to the development of a new drug group, the selective estrogen receptor modulators (SERMs) [18–23]. One of the important examples of a SERM is raloxifene (**2**) (Fig. 1), a failed breast cancer drug that has been successfully used to treat osteoporosis and prevent breast cancer in high risk postmenopausal women [24–27]. Although the benefits of tamoxifen are prominent, the use of tamoxifen is associated with increased risk of side effects such as hot flashes, menstrual abnormalities, uterine cancer and thromboembolic phenomena [28,29]. Since tamoxifen use is associated with an increase in cancer risks and unpleasant side effects, it is generally taken for five years followed by different therapeutics depending on the patient's condition; furthermore, its use is not acceptable for all high-risk women. Further results from the Adjuvant Tamoxifen: Longer against Shorter (ATLAS) trial suggested that ten years of adjuvant tamoxifen therapy can reduce mortality to greater than five years [30].

Tamoxifen is marketed as a single Z (*trans*) isomer of *p*-β-dimethylaminoethoxy-1,2-diphenylbut-1-ene and is considered a lead compound that initiated the SERM development for the treatment of various diseases (such as osteoporosis, rheumatoid arthritis) and also for application of the SERM concept for all the members of the nuclear receptor family [31–38]. Pharmacological studies of tamoxifen in the human body suggested its conversion to three active metabolites: 1.) 4-hydroxy tamoxifen (**8**); 2.) *N*-desmethyltamoxifen (**9**); and 3.) 4-hydroxy-*N*-desmethyltamoxifen, also known as endoxifen (**10**) (Fig. 2) [39–41]. In humans, *N*-desmethyltamoxifen is the primary metabolite followed by endoxifen and then 4-hydroxytamoxifen. These metabolites are potent antiestrogens and are used to understand the tamoxifen's mechanism of action [42,43]. Tamoxifen's pharmacological profile indicates that it is a prodrug, and its anticancer activity occurs via its active metabolite, 4-hydroxy tamoxifen (**8**) and its desmethyl analogue endoxifen (**10**), which are generated by the action of hepatic CYP 2D6 and CYP3A4/3A5 isozymes on tamoxifen after hydroxylation followed by *N*-demethylation [44–45]. It has been established that patients with variant forms of the gene CYP 2D6 do not receive therapeutic benefits from tamoxifen administration or even suffer relapses because of slow tamoxifen prodrug metabolism into its active metabolites [46–48].

Several interesting facts associated with tamoxifen and its metabolites made it a pioneering agent for initiating new therapeutic investigation, and its pharmacogenomics is playing a significant role in redefining health care. In recent years, some of the tamoxifen analogues; for example, droloxifene (**3**), idoxifene (**4**), lasofoxifene (**5**), toremifene (**6**) and ospemifene (**7**) (Fig. 1) have been studied extensively in clinical trials [49]. Literature reports indicate