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Review

Synthetic approaches towards the multi target drug spironolactone and its potent analogues/derivatives

Fayaz Ali Larik [a], Aamer Saeed [a,*], Danish Shahzad [a], Muhammad Faisal [a], Hesham El-Seedi [b], Haroon Mehfooz [a], Pervaiz Ali Channar [a]

[a] Department of Chemistry, Quaid-i-Azam University, 45320 Islamabad, Pakistan
[b] Division of Pharmacognosy, Department of Medicinal Chemistry, Uppsala University, Biomedical Centre, Box 574, SE-751 23 Uppsala, Sweden

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ABSTRACT

Spironolactone is a well-known multi-target drug and is specifically used for the treatment of high blood pressure and heart failure. It is also used for the treatment of edema, cirrhosis of the liver, malignant, pediatric, nephrosis and primary hyperaldosteronism. Spironolactone in association with thiazide diuretics treats hypertension and in association with furosemide treats bronchopulmonary dyspepsia. The therapeutic mechanism of action of spironolactone involves binding to intracellular mineralocorticoids receptors (MRs) in kidney epithelial cells, thereby inhibiting the binding of aldosterone. Since its first synthesis in 1957 there are several synthetic approaches have been reported throughout the years, Synthetic community has devoted efforts to improve the synthesis of spironolactone and to synthesize its analogues and derivatives. This review aims to provide comprehensive insight for the synthetic endeavors devoted towards the synthesis of a versatile drug spironolactone and its analogues/derivatives.

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* Corresponding author.
E-mail address: aamersaeed@yahoo.com (A. Saeed).

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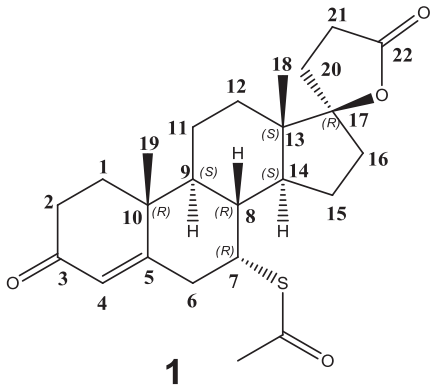

Fig. 1. Structure of Spironolactone **1.**

1. Introduction

Spironolactone **1** (Aldactone), 7α-Acetylthio-3-oxo-17α-pregn-4-ene-21,17-carbolactone (Fig. 1), was first developed in the late 1950s as a potassium-sparing diuretic for the treatment of hypertension and congestive heart failure [1–4]. Presently, this synthetic aldosterone antagonist has achieved unparalleled significance as a therapeutic agent effective against various diseases (Fig. 2) such as pediatric [5], edema [6], cirrhosis of the liver [7], malignant [8], nephrosis [9] and primary hyperaldosteronism [10]. Spironolactone in association with thiazide diuretics is used to treat hypertension [11] and in association with furosemide for the treatment of bronchopulmonary dyspepsia [12]. Spironolactone and eplerenone (Fig. 3) compete with aldosterone for binding to intracellular receptors, causing decreased gene expression and reduced synthesis of protein mediator that activates Na^+ channels in the apical membrane (site 1) and decreased the number of Na^+/K^+ATPase pumps in basolateral membrane (site 2). However, the extensive use of spironolactone may lead to dehydration, hyponatraemia and hyperkalaemia along with the number of endocrinological side effects such as gynecomastia and loss of sexual potency in men and menstrual irregularities, breast enlargement in women [13–15]. Furthermore, this drug is associated with many benefits as compared to its disadvantages for the last five decades. Much work has been published by synthetic chemists describing the synthesis of Spironolactone **1** at length. Moreover, a lot of efforts are being made to synthesize newer mineralocorticoids (spirorenone, drospirenone and related compounds) having better characteristics devoid of side effects than **1**. It is an important versatile drug which may be further structurally modified to produce next-generation therapeutic agents [16]. The aim of the current review is to present a detailed account of the published synthetic protocols of **1**, its analogues and derivatives.

1.1. Part A: synthetic protocols for spironolactone

1.1.1. Industrial synthesis of spironolactone: the highest yielding method

The retrosynthetic analysis of Spironolactone **1** is shown in Fig. 4. The retrosynthetic approach has been shown in order to

Fig. 2. Applications of spironolactone and eplerenone.