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Synthesis and pharmacological screening of some novel anti-hypertensive agents possessing 5-Benzylidene-2-(phenylimino)-thiazolidin-4-one ring

Chetan M. Bhalgat [a], Pooja V. Darda [b,*], Kailash G. Bothara [c], Shashikant V. Bhandari [c], Jotsna Gandhi [d], B. Ramesh [a]

[a] Department of Pharmaceutical Chemistry, Sri Adichunchanagiri College of Pharmacy, B.G. Nagara 571448, Nagamangala (tq), Mandya (dist), Karnataka, India
[b] Department of Pharmaceutical Chemistry, SCSSS'S Sitabai Thite College of Pharmacy, Shirur, 412210 Pune, Maharashtra, India
[c] Department of Pharmaceutical Chemistry, (PG Wing), A.I.S.S.M.S. College of Pharmacy, Pune 411 001, Maharashtra, India
[d] Department of Pharmacognosy, Ashokrao Mane College of Pharmacy, Peth Vadgaon 416 112, Maharashtra, India

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ABSTRACT

In the present study, fourteen derivatives comprising of 5-benzylidene-2-(phenylimino)-thiazolidin-4-one moiety were synthesized. The structures of synthesized compounds were established by elemental analysis, IR, ^{1}H NMR, ^{13}C NMR and mass spectral data and tested for electrocardiographic, antiarrhythmic and antihypertensive activities. Compound **11** was found to be most potent in this series. The pharmacological results suggested that, the antiarrhythmic effects of these compounds were related to their Ca^{++} ion channel antagonistic properties, which are believed to be due to the presence of 5-benzilidine-2-(phenylimino)-thiazolidin-4-one moiety. The antihypertensive effect of β-blocker side chain is enhanced by the presence of less bulky aliphatic and heterocyclic tertiary amines.

1. Introduction

In past twenty years, cardiovascular diseases have become the world's leading cause of death. Most of the currently used antihypertensive agents could not be used in single drug therapy due to their toxicity and side effects. Multiple drug therapy makes the regime complicated and less successful. One of the most important goals of organic and medicinal chemistry is to design and synthesize the molecules having therapeutic value. In this regard, heterocyclic compounds have proven to be versatile support structures that offer a high degree of structural diversity [1].

Combination drug therapy is used now a day, to limit the side effects of the therapeutic agents, used alone in the treatment of certain diseases, with complex and heterogenous pathogenesis. This can be achieved by concomitant administration of two or more single active drugs or by designing hybrid molecules. These hybrid molecules often consist of different pharmacophores, which are linked to each other via spacers [2].

In the long-term treatment of hypertension, there is no single antihypertensive drug which can normalize the elevated blood pressure in all patients. β-Adrenoceptors are known to play an important role in the regulation of the autonomic nervous system and β-blockers have proven to be useful in the pharmacotherapy of serious and widespread cardiovascular diseases [3,4].

A research group in the People's Republic of China noted that a compound, changrolin, was effective as an antiarrhythmic agent during the clinical trials for examining the antimalarial properties of Febrifugine derivatives. Stout and his research group studied the structure of changrolin for its dissimilarity with currently marketed antiarrhythmics [5–9]. Other studies were also carried out with regard to the biological structure activity relationships [5,10,11].

Considering the above mentioned facts, we took 2-arylimino-5-arylidene-4-thiazolidinones rings as a structural requirement to show cardiovascular effects. We changed the pyrrolidin-one [12] ring to substituted thiazolidinone ring and synthesized some 5-benzilidine-2-(phenylimino)-thiazolidin-4-one derivatives (**5**–**18**) as pharmacodynamic hybrids. These novel hybrids were

* Corresponding author.
E-mail addresses: chetanbhalgat2004@gmail.com (C.M. Bhalgat), darda.pooja@gmail.com (P.V. Darda).

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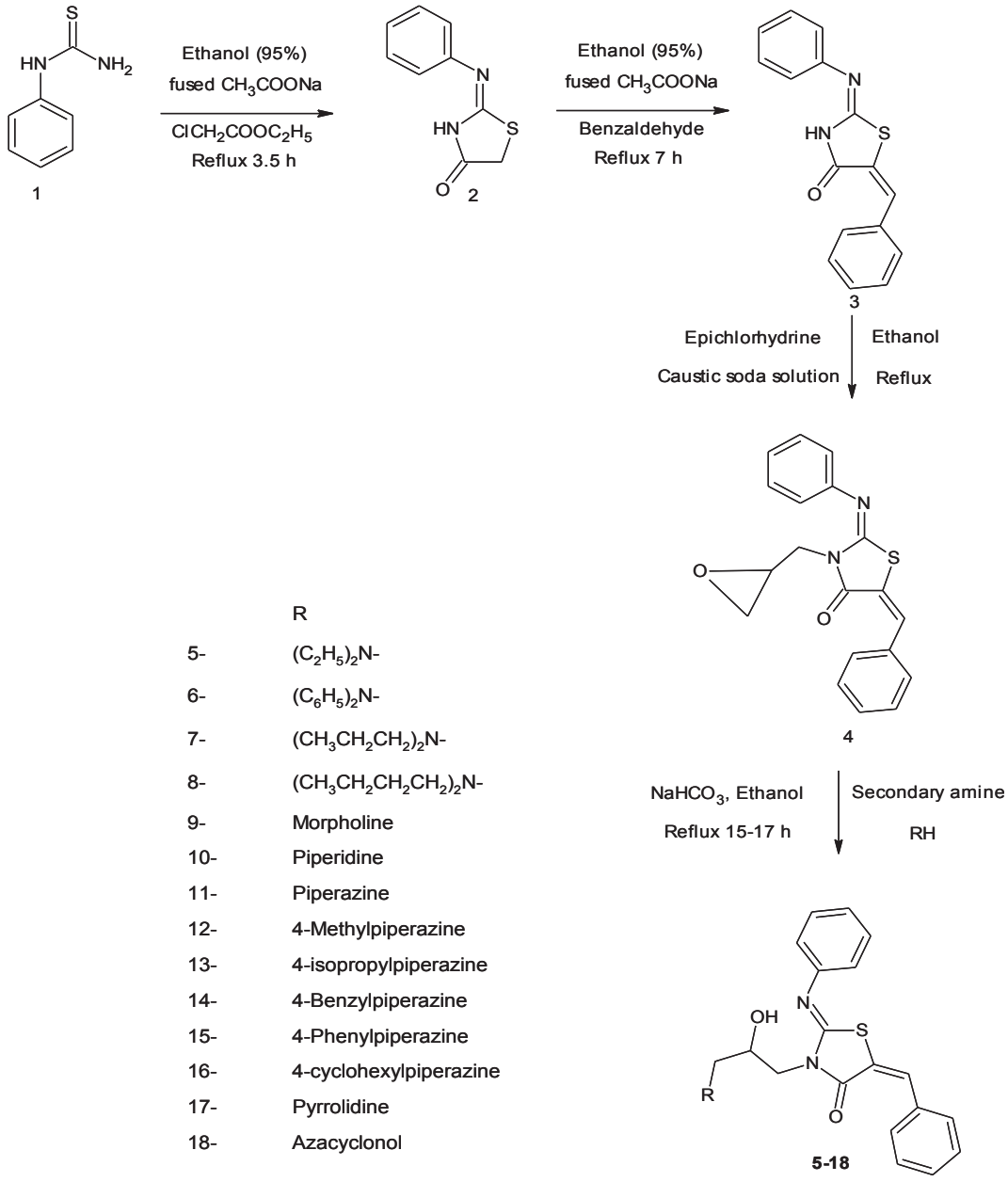
characterized by spectral data and elemental analysis, and then tested for in vivo electrocardiographic, antiarrhythmic and anti-hypertensive activity on normotensive and hypertensive rats.

2. Result and discussions

2.1. Chemistry

In the present work, the title compounds were synthesized by a four step reaction. The starting material i.e. Phenyl thiourea (**1**), was prepared according to the method reported by Malawska et al. [13], using ammonium thiocyanate and benzoyl chloride. This process was optimized in the presence of dry acetone. The acetone was dried for at least 48 h over anhydrous calcium sulfate and distilled just before it was used. 2-Phenyliminothiazolidin-4-one (**2**) was prepared by heating phenyl thiourea and ethylchloroacetate in presence of fused sodium acetate in ethanol (95%) [14]. The reaction of **2** with benzaldehyde in presence of fused sodium acetate in ethanol gave good yield of 5-benzylidene-2-(phenylimino)-thiazolidin-4-one (**3**). The aim of next step was to introduce reactive 2,3-epoxypropyl moiety at the 3rd position of thiazolidin-4-one. Compound **3** was reacted with epichlorhydrine to give 5-benzylidene-2-(phenylimino)-3-(oxiran-2-ylmethyl)-thiazolidin-4-one (**4**) [15–17]. The syrupy residue and the hydrochloric salt of the compound **4** were used immediately in the next step. In the following step, the epoxy bridge was cleaved with secondary amines (diethyl amine, diphenyl amine, di-n-propyl amine, di-n-butyl amine, morpholine, piperidine, piperazine, 4-methyl piperazine, 4-isopropylpiperazine, 4-benzylpiperazine, 4-phenyl piperazine, 4-cyclohexylpiperazine, pyrrolidine, azacyclonol) to obtain 5-benzylidene-3-(2-hydroxy-3-(substituted)propyl)-2-(phenylimino)-thiazolidin-4-ones (**5**–**18**) (Scheme 1).



	R
5-	$(C_2H_5)_2N$-
6-	$(C_6H_5)_2N$-
7-	$(CH_3CH_2CH_2)_2N$-
8-	$(CH_3CH_2CH_2CH_2)_2N$-
9-	Morpholine
10-	Piperidine
11-	Piperazine
12-	4-Methylpiperazine
13-	4-isopropylpiperazine
14-	4-Benzylpiperazine
15-	4-Phenylpiperazine
16-	4-cyclohexylpiperazine
17-	Pyrrolidine
18-	Azacyclonol

Scheme 1. Schematic representation of synthesis of compounds, **5**–**18**.