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SHORT COMMUNICATION

Synthesis and oral hypoglycemic effect of novel thiazine containing trisubstituted benzenesulfonylurea derivatives

Alok Singh Thakur [a,*], **Ravitas Deshmukh** [a], **Arvind Kumar Jha** [a], **P. Sudhir Kumar** [b]

[a] *Faculty of Pharmaceutical Sciences, SSGI, SSTC, Junwani, Bhilai, C.G., India*
[b] *School of Pharmaceutical Sciences, Siksha O Anusandhan University, Bhubaneswar, Odisha, India*

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Sulfonylcarbamate;
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Abstract A new series of 3-(4-substituted phenyl)-1-(4-(4,6-dimethyl-6H-1,3-thiazin-2-yl)phenylsulfonyl)-1-substituted urea (5a–o) was synthesized by an effectual route via sulfonylcarbamates and explores the novel site for substitution in sulfonylurea as well as the way of thiazine can be prepared. The molecules were established by elemental analysis and spectroscopic *viz*. IR, ^{1}H NMR, ^{13}C NMR and MS techniques. All the fifteen derivatives were shown very prominent oral hypoglycemic effect at the dose of 40 mg/kg body weight (p.o.) in respect of standard drug glibenclamide and control. The hypoglycemic effect was studied using oral glucose tolerance test in normal and NIDDM in STZ-rat model. The compounds **5a**, **5d**, **5f**, **5i**, **5k** and **5n** were dominant out of fifteen derivatives for blood glucose lowering activity (more than 80%) when comparing with NIDDM control. These derivatives were either containing simply phenyl ring (**5a**, **5f** and **5k**) on to the second amine of sulfonylurea (**R′ = H**) or nitro group at the para position in compound **5d**, **5i** and **5n** (**R′ = NO$_2$**) to produce significant oral hypoglycemic effect. Other structural activity relationship is also observed regarding the heteroaromatic and substituted aromatic group at R and R′ position respectively.

1. Introduction

Type 2 diabetes mellitus is the very common metabolic disease, which is illustrated by the blemish of insulin secretion as well as its sensitivity. Generally it is considered as sulfonylureas exert the hypoglycemic effect through promoting the insulin secretion from receptor of pancreatic β-cell (Kecskemeti et al., 2002). However some reports have been published to suggest that the sulfonylureas do not penetrate the β-cell of

* Corresponding author. Mobile: +91 9752097870.
E-mail address: alokthakur1985@yahoo.com (A.S. Thakur).
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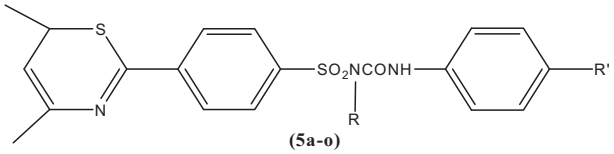
pancreas which results the binding of this pharmacophore in very specific sites of plasma membrane of β-cell (Flatt et al., 1994). It may be due to lower lipophilicity or due to ionized form of sulfonylureas. The second generation sulfonylurea is so potent stimulator of insulin secretion shown a great success for the treatment of type 2 diabetes, but due to exert hyperinsulinemia that causes the weight gain or hypoglycemia bears hindrance on their success (Hamaguchi et al., 2004). Other than hypoglycemic effect sulfonylurea are established for cytotoxicity (Jung et al., 1996), antimicrobial (Krajacić et al., 2005), vasodilator (Khelili et al., 1995) and antitubercular (Pan et al., 2012) all these consideration persuade the researcher to develop an effective oral hypoglycemic sulfonylurea derivative.

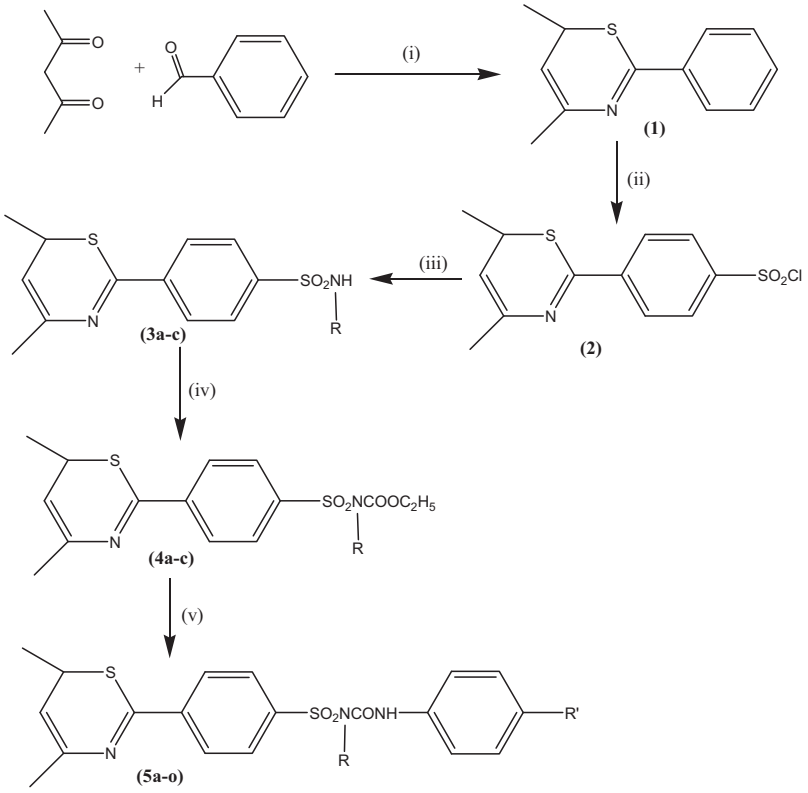
Sulfonylureas are generally undergone the chemical hydrolysis at ionizable hydrogen atom containing nitrogen which is situated between sulfonyl and carbonyl groups. The ionization leads the early cleavage of Sulfonylurea bridge, producing CO_2 and the corresponding sulfonamide and amine (Zheng et al., 2008). Although the second generation sulfonylurea glibenclamide have longer duration of action but accumulates progressively in the β-cell (Kamp et al., 2003). The efficacy and penetration of sulfonylureas can be enhanced by decreasing the rate of ionizable metabolism. This article presents the synthesis of some new trisubstituted sulfonylurea derivatives containing substitution at ionizable nitrogen atom with some aromatic and heteroaromatic groups.

The synthesis of compounds was initiated by the preparation of unsubstituted phenyl ring containing thiazine heterocyclic compound **(1)**. This compound was actually prepared from the condensation of acetylacetone with the ammonium thiocyanate and benzaldehyde under reflux. When it was further reacted with chlorosulfonic acid at the room temperature by using dioxane it results sulfonyl chloride group at the para position of the phenyl ring **(2)**. Which on treatment with the primary amines were produced different sulfonamides **(3)** under mild acidic condition of acetic acid that further converted to sulfonylcarbamates **(4)** after treatment with the ethyl chloroformate in the presence of pyridine base. Finally the hydrolysis of ethyl ester of sulfonylcarbamates with primary amines results the different trisubstituted sulfonylurea derivatives **(5a–o)** (Scheme 1, Table 1).



2. Result and discussion

The targeted trisubstituted sulfonylurea derivatives were prepared and confirmed by various spectroscopic and elemental analyses. Mass spectra and NMR data were helpful to conclude the molecular formula and weight as well as the chemical



Scheme 1 Reagents and reaction conditions: (i) Ammonium thiocyanate, gla. CH_3COOH, reflux 3–4 h, (ii) Chlorosulfonic acid, 1,4 dioxane, stirring at r.t., (iii) Pyridine, aniline (3a), p-nitro aniline (3b), 2-amino pyridine (3c), reflux 3–4 h, (iv) Ethyl chloroformate, anhydrous K_2CO_3, dry acetone, reflux 18–20 h, (v) Substituted primary aromatic amines ($R'NH_2$), toluene, reflux 3–4 h.