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Antidiabetic Studies of 1-Benzhydryl-Piperazine Sulfonamide and Carboxamide Derivatives

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ABSTRACT

1-benzhydryl-piperazine sulfonamide ***2a-2e*** *and carboxamides* ***3a-3e*** *were evaluated for in vivo antidiabetic activity in streptozotocin induced diabetic rats. The results of the present study clearly indicated that compound* ***2e*** *showed enhanced antidiabetic activity compared to remaining compounds.*

Keywords: 1-benzhydryl-piperazine, Sulfonamides, carboxamides, antidiabetic activity, diabetes mellitus, streptozotocin.

INTRODUCTION

Diabetes mellitus is common metabolic disease worldwide affecting millions of people [1]. The disease is characterized by chronic elevated blood sugar levels for which several reasons like defects of insulin action in tissues or impairment of pancreatic insulin secretion may be responsible. Excessive hepatic glucose production can also significantly contribute to diabetic hyperglycemia.

The non-insulin-dependent diabetes mellitus (NIDDM or type II diabetes) appears in ~75% of the diabetic patients. Hyperglycemia in type II diabetics can be controlled by dietary regulation and exercise, which can be combined with the use of oral hypoglycemic agents. However, this treatment is not entirely satisfactory because blood glucose concentration cannot be regulated as efficiently under normal physiological conditions. This can result in complications occurring in the later life of the diabetic patient

[2]. Therefore, there is an obvious need for novel agents and/or therapeutic strategies that could act more closely to the physiological regulation of blood sugar level.

Current therapies for diabetes mellitus have inherent problems of non-compliances, ineffectiveness and hypoglycemic episodes with insulin and sulfonylurea's [3]. Glitazone type therapeutics is in market but some of them have been reported to have hepatotoxicity [4]. Therefore there is greater need for more effective and better tolerated orally active agents.

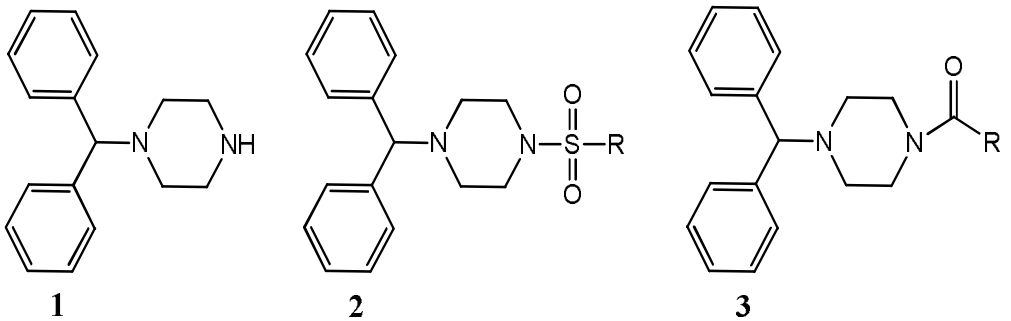
Piperazines have been widely used in biological screening resulting in numerous applications [5] and constitute an attractive pharmacological scaffold present in several drugs. This small and rigid heterocyclic backbone could act on various pharmacological targets. Especially, piperazine nucleus could be found in broad range of biological active compounds displaying antidiabetic results in chronically diabetic rats [6, 7], anticancer [8, 9], antibacterial [10-12], antifungal [13], antimalarial, antipsychotic agents [14], HIV protease inhibitors [15-17], and anti-inflammatory activities [18]. In literature, we also found that diaryl piperazine derivatives were identified as potent and selective dopamine D_4 receptor antagonist [19, 20] enterovirus inhibitors [21] and inhibitors of dopamine uptake in the central nervous system [22]. In continuation of our research [23-32], herein we have evaluated in vivo antidiabetic activity for 1-benzhydryl-piperazine sulfonamides and carboxamides.

MATERIALS AND METHODS

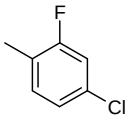
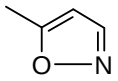
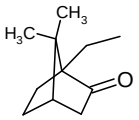
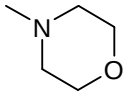
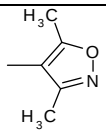
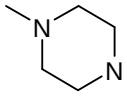
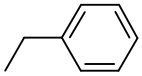
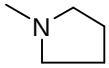
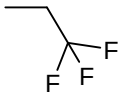
Chemical and instrumentation: Melting points were determined by SELACO-650 hot stage melting point apparatus and were uncorrected. Infra red (IR) spectra were recorded using Jasco FTIR-4100 series. Nuclear magnetic resonance (^{1}HNMR) spectra were recorded on Shimadzu AMX 400-Bruker, 400MHz spectrometer using DMSO as a solvent and TMS as an internal standard (chemical shift in ppm). Spin multiplets are given as a (singlet), d (doublet), t (triplet) and m (multiplet). Mass and purity were recorded on a LC-MSD-Trap-XCT. Silica gel column chromatography was performed by using Merck 7734 silica gel (60-120 mesh) and Merck made TLC plates. The crystallographic measurements were made on a DIP Lab using imaging plate system with graphite monochromatic radiation (Mo Kα). Streptozotocin HCl (STZ) were purchased from sigma chemical Co (St. Louis, MO, USA). Metformin was procured as a gift sample from Dr. Reddy`s labs Hyderabad. Plasma glucose was measured by using commercially available diagnostic kits (Drasania biomedicals Limited, Daman).

Synthesis: The nucleophilic substitution reaction of 1-benzhydryl-piperazine with different sulfonyl chlorides and acid chlorides were carried out in the presence of triethylamine and dichloromethane as a solvent in good yield with good purity. Molecules **2d** and **3d** were characterized by ^{1}H NMR, LC/MS, IR and X-ray crystallographic analysis. The chemical structures of all the compounds are given in table 1.

Table 1. Chemical structure of compounds 2a-2e, and 3a-3e



1 **2** **3**

Compound	R	Compound	R
2a		**3a**	
2b		**3b**	
2c		**3c**	
2d		**3d**	
2e		**3e**	

General Procedure for the Synthesis of Compounds 2d and 3d: A solution of 1-benzhydryl-piperazine **1** (1.0 eq) in dry dichloromethane was taken and cooled to 0-5^{o}C in an ice bath. Triethylamine (3.0 eq) was added to the cold reaction mixture and stirred for 10 min, and then sulfonyl chloride (1.0 eq) / acid chloride (1.0 eq) were added, the reaction mixture was allowed to stir at room temperature for 5-6 h. The progress of the reaction was monitored by TLC. Upon completion, the solvent was removed under reduced pressure and residue was taken in water and extracted with ethyl acetate. The organic layer was washed with 10% ammonium chloride solution finally water wash was given to the organic layer and dried with anhydrous sodium sulphate. The solvent was evaporated to get crude product which was purified by column chromatography over silica gel using hexane: ethyl acetate (8:2) as an eluent.

Synthesis of 1-benzhydryl-4-phenylmethanesulfonyl-piperazine (2d): This was obtained from 1-benzhydryl-piperazine **1** (0.5 g, 1.98 mmol), phenylmethanesulfonyl chloride (0.377 g, 1.98 mmol) and triethylamine (0.601 g, 5.94 mmol). The product obtained was white crystalline solid (0.643 g). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.45-7.50 (b, 5H, Ar-H), 7.35 (d, 4H, Ar-H), 7.24 (t, 4H, Ar-H), 7.15 (t, 2H, Ar-H), 4.4 (s, 1H, -CH-), 4.24 (t, 2H, -CH_2-), 2.9 (t, 4H, -CH_2-), 2.35 (t, 4H, -CH_2-). MS (ESI + ion): m/z = 407.58. IR (KBr, cm^{-1}): 3065, 3025, 2949, 1158, 1323. M.P (^{o}C): 169-171, Purity: 98.6%

Synthesis of (4-benzhydrylpiperazin-1-yl)(piperazin-1-yl)methanone (3d): This was obtained from 1-benzhydryl-piperazine **1** (0.5 g, 1.98 mmol), piperazine-1-carbonyl chloride (0.294 g, 1.98 mmol) and triethylamine (0.601 g, 5.94 mmol). The product obtained was brown crystalline solid (0.569 g). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.40 (d, 4H, Ar-H), 7.27 (t, 4H, Ar-H), 7.18 (t, 2H, Ar-H), 4.35 (s, 1H, -CH-), 3.35-3.25 (br s, 8H, -CH_2-), 2.6-2.48 (br s, 4H, -CH_2-). MS (ESI + ion): m/z = 365.3. IR (KBr, cm^{-1}): 2970, 2869, 1652. M.P (^{o}C): 177-179, Purity: 97.65%.

RESULTS AND DISCUSSION

Synthesis and *in vitro* antiproliferative activity of novel 1-benzhydrylpiperazine derivatives **2a, 2b, 2e, 3a-3b, 3d-3e** against human cancer cell lines has been reported [26]. The compound **2c** has synthesized and evaluated as inhibitors of MDA-MB-231human breast cancer cell proliferation [27]. The compounds **2a** [33] and **2d** [34] was structurally characterized by X-ray crystallographic studies.

The compounds **2a-2e** and **3a-3e,** were evaluated for antidiabetic activity in streptozotocin induced diabetic rats (**Table 2)**. The standard drug Metformin was used as a reference to assess the diabetic potency of the proposed drugs. Compounds **2e, 2c, 2d, 3a, 3b, 3c** and **3e** showed promising antidiabetic activity. But out of these, compound **2e** shows highly significant antidiabetic activity from 1st hr onwards and this effect was continued till the end of the experimental period. Whereas compounds **2c, 2d** and compounds **3a**, **3b**, **3c** and **3e** were shows moderate and mild effect respectively.

The significant antidiabetic activity of the compound **2e** probably may be due to the presence of electron withdrawing trifluoro ethyl sulfonyl moiety. Compound **2e** shows 175.3±1.74 mg dl^{-1} activity at 1st h, 155.9±1.16 mg dl^{-1} activity at 2nd h and 129.6.3±2.31 mg dl^{-1} activity at 3rd h. The moderate antidiabetic activity of the compounds may be due to the presence of rigid isoxazole ring in **2c** and benzyl ring in **2d**. The activity of the compound **2c** increases after 1st h and shows 302.7±0.80 mg dl^{-1}, 296.3±1.17 mg dl^{-1}, 151.5±0.67 mg dl^{-1}. Similarly compound **2d** exhibit 302.7±0.61 mg dl^{-1},295.3±1.11 mg dl^{-1}, and 189.2±2.90 mg dl^{-1} activity. Compounds **3a-3e** having amide functional group does not shows activity. It reveals that the presence of sulfonyl functional group play an important role in the antidiabetic activity.
From the results obtained, structure activity relationship can be drawn for **2a-2e,** and **3a-3e** series. In this connection, different electron donating or electron withdrawing groups attached to phenyl ring with sulfonyl and amide functional group are studied for antidiabetic efficacy. We have briefly investigated different SAR for functionalized derivatives. These modifications result in changes the antidiabetic activity profile of the synthesized compounds. In this contrast, first changing the substituent on the substituted phenyl ring **2a**, **2e** and **2d** reveals that electron withdrawing fluoro functionalized derivatives show relatively significant antidiabetic activity. Secondly, heterocyclic substituted derivative **2c** showed relatively less activity compared to that of the aromatic substituted derivatives **2a** and **2d**. In third SAR study, compare the aromatic/heterocyclic substituted sulfonamides **2c, 2a, 2d** and aliphatic substituted sulfonamide **2e**, the aliphatic sulfonyl functionalized derivatives show relatively significant antidiabetic activity. Finally, the sulfonyl functionalized derivatives show relatively significant antidiabetic activity. The above SAR correlation studies reveal that, the nature of the substitution and functional linkage **(-SO_2** or **–CO-)** influences the antidiabetic activity.

APPLICATIONS

Antidiabetic activity: All the experimental procedures were carried out in accordance with committee for the purpose of control and supervision of experiments on animals (CPCSEA) guidelines. The study was reviewed (Table 2) and approved by the Institutional Animal Ethics Committee. K.L.E.S's College of Pharmacy, Belagavi, India.

Table 2. Antidiabetic activity of compounds 2a-2e and 3a-3e derivatives

Treatment	**Plasma glucose (mg/dl)**		
	1st hr	2nd hr	3rd hr
Group-1(NC)	91.33±0.71	94.33±0.98	93.17±0.60

Group-2(DC)	303.7±0.88	303.3±0.80	303.3±0.80
Group-3(DS)	151.5±4.83*	94.33±1.20*	91.33±0.91*
Group-4-**2a**	306.0±1.15	304.8±1.13	303.7±0.71
Group-5-**2b**	302.8±0.87	303.2±0.87	302.7±0.91
Group-6-**2c**	302.7±0.80	296.3±1.17*	151.5±0.67*
Group-7-**2d**	302.7±0.61	295.3±1.11*	189.2±2.90*
Group-8-**2e**	175.3±1.74*	155.9±1.16*	129.6.3±2.31*
Group-9-**3a**	302.2±1.19	301.0±1.31	179.2±3.89*
Group-10-**3b**	304.8±0.98	305.0±1.06	277.2±2.54*
Group-11-**3c**	301.0±1.52	305.0±1.03	294.2±2.67*
Group-12-**3d**	307.3±0.76	306.5±0.76	308.8±2.57
Group-13-**3e**	304.2±0.79	301.3±0.80	221.8±3.45*

All data are expressed as mean ±SEM, *P<0.001, when compared to DC group.

Animals: Male wistar rats procured from National institute of Nutrition, Hyderabad (290-300 g) were used in the present study. The animals were kept in individual cages for one week to acclimatize for the laboratory conditions. They were allowed to free access of water and food.

Induction of diabetes: Diabetes was induced by single intraperitoneal injection of 65 mg kg^{-1} STZ (dissolved citrate buffer pH- 4.5). 10% glucose was given in drinking water for 48 h to prevent STZ induced hypoglycemia. After 2 days of STZ injection rats were fasted whole night, plasma glucose was measured by glucose oxidase method. Rats with blood glucose levels of 300 mg dl^{-1} or above were considered to be diabetic.

Experimental Design: The animals were divided into 13 groups 6 animals each and all the test compounds or vehicle were given by oral gavages as follows.
Group -1: Normal Control (NC)- 1.0 mL of 0.5% CMC
Group-2: Diabetic Control (DC) – 1.0 mL of 0.5% CMC
Group-3: Diabetic Standard (DS)-Metformin (30 mg/kg) in 1 mL of 0.5% CMC.
Group-4-13: Diabetic Treated (DT) - test compounds (30 mg/kg) in 1 mL of 0.5% CMC.
After the administration test compounds the blood sample was collected at 1st, 2nd and 3rd h for plasma glucose estimation.

Estimation of plasma glucose: The glucose oxidase method was used for the determination of the plasma glucose.

Statistical Analysis: Results are expressed as mean ± SEM. Statistical Analysis was carried out using One-Way ANOVA followed by Neumann keuls multiple comparison tests. Results were considered significantly different if P<0.001.

CONCLUSIONS

From our experimental results, it could be concluded that the introduction of alkyl trifluoroethyl containing sulfonyl group on the 1-benzhydryl-piperazine system has great potential to get effective antidiabetic compound. The antidiabetic properties induced by the 1-benzhydryl-piperazine framework might involve

distinct mechanisms and from this work we were able to design the best molecules for antidiabetic studies in future research.

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