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SYNTHESIS AND BIOLOGICAL SCREENING OF NOVEL BENZODIAZEPINE DERIVATIVES

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Abstract:
A new series of 2-((E)-4-(4-(4-fluorophenylthio)phenyl)-2,3-dihydro-1H-benzo[b][1,4]diazepin-2-yl)phenol have been synthesized efficiently. In view of the vital role played by sulfur and fluorine in numerous pharmacological activities, we thought worthwhile to synthesize important benzodiazepines derivatives and investigate the biological activities. All the newly synthesized compounds have been screened for their *in vitro* antimicrobial activity.
Keywords: Benzodiazepine (1,-BZP), Antimicrobial.

Introduction

1,5-Benzodiazepines (1,5-BZP) are the 2 and 3-benzo-fused derivatives of the dihydrodiazepines and are important heterocyclic compounds with a wide range of biological activities [1]. Benzodiazepines, a privileged scaffold received greater attention because of their potential structural diversity. Derivatives of benzodiazepine are widely used as tranquilizing and anticonvulsant agents [2, 3]. Some benzodiazepine derivatives are used in industry [4], in photography [5] and also as anti-inflammatory agents [6]. Benzodiazepines are useful synthons for the synthesis of many significant derivatives with potent biological activities [7-10]. Mainly Benzodiazepines are used as precursor for the synthesis of some fused ring benzodiazepine derivatives, such as oxadiazol [11] and triazol [12]. Benzodiazepines widely used as antianxiety [13] and hypnotic agents [14]. These compounds also used as anti-inflammatory agents [15] and as commercial dyes for acrylic fibers [16]. 1,5-BZP's are widely used as analgesic [17], sedative [18], and anti-depressive agents [19].

Benzodiazepines have been important class of heterocyclic compounds in the field of drugs and pharmaceuticals. A dibenzodiazepine derivative Clozapine is an important antipsychotic drug [20]. In vivo, supported by antagonistic effects on serotonin, muscarine, adrenaline, and histamine receptors, it has been observed that it works on positive and negative psychotic symptoms as well as of treatment-resistant schizophrenia [21]. Clobazam a 1,5BZP derivative is used for epilepsy shows antiepileptic properties and rapidly effective in a matter of hours or within a few days against all varieties of epileptic seizures [22]. Arfendazam has anxiolytic and sedative effects and this compound is a partial agonist at $GABA_A$ receptors [23]

Experimental

Material and Methods

Open capillaries in a paraffin bath have been used to determine the melting points of newly synthesized compounds. The progress of the reaction was monitored by using precoated plates of silica gel G254 supplied by Merck. Infrared (IR) spectra (KBr disc) were recorded on a FTIR-4100 spectrometer and the absorption bands are expressed in cm^{-1}. The ^1H NMR spectra were recorded on a Bruker Advance II 400 MHz spectrometer using TMS as a reference standard. Macro mass spectrometer (Waters) by electro-spray method (ES) was used to record the mass spectra.

General procedure for the synthesis of 2-((*E*)-4-(4-(4-fluorophenylthio)phenyl)-2,3-dihydro-1*H*-benzo[b][1,4]diazepin-2-yl)phenol: chalcone 0.200 g of (**3a-h)** was dissolved in 7 ml of ethanol, to this, 2-3 drops of o-phenyldiamine was added and resulting reaction mixture was

refluxed for three hour. Then the reaction mixture was acidified by using 2-3 drops of acetic acid and the heating was continued for next 3 hr. On the completion of the reaction (checked by TLC), the reaction mixture was poured in a clean and dry beaker. It was filtered and purified by recrystallization from ethanol to afford compound **2(a-h)**.

2-((E)-4-(4-(4-fluorophenylthio)phenyl)-2,3-dihydro-1H-benzo[b][1,4]diazepin-2-yl)-4-chloro-5-methylphenol.10a

^{1}H NMR (400 MHz, DMSO-d6, δppm): 1.74 (s,3H,CH_3),3.04(s,2H, N=C-CH_2), 3.15(s,1H,CH), 5.19 (s,1H,NH), 6.52-7.25 (m, 14 H, Ar-H), 13.2 (s, 1H, -OH).;IR (KBr, cm-1):3312 (NH), 2923 (OH), 1590 (C=N), 1565 (C=C); ES-MS: m/z: 489.

2-((E)-4-(4-(4-fluorophenylthio)phenyl)-2,3-dihydro-1H-benzo[b][1,4]diazepin-2-yl)-4-methylphenol.10b

^{1}H NMR (400 MHz, DMSO-d6, δppm): 1.84 (s, 3H, CH_3) 3.06 (s,2H, N=C-CH_2), 3.34(s,1H,CH), 5.36 (s,1H,NH), 6.75-7.52 (m, 15H, Ar-H), 14.2 (s, 1H, -OH).;IR (KBr, cm-1):3318 (NH), 2928 (OH), 1592 (C=N), 1568 (C=C);ES-MS: m/z: 454

2-((E)-4-(4-(4-fluorophenylthio)phenyl)-2,3-dihydro-1H-benzo[b][1,4]diazepin-2-yl)phenol.10c

^{1}H NMR (400 MHz, DMSO-d6, δppm): 3.07(s,2H, N=C-CH_2), 3.25(s,1H,CH), 5.21 (s,1H,NH), 6.69-7.35 (m, 16H, Ar-H), 15.2 (s, 1H, -OH).;IR (KBr, cm-1):3317 (NH), 2925 (OH), 1593 (C=N), 1562 (C=C); ES-MS: m/z: 441.1.

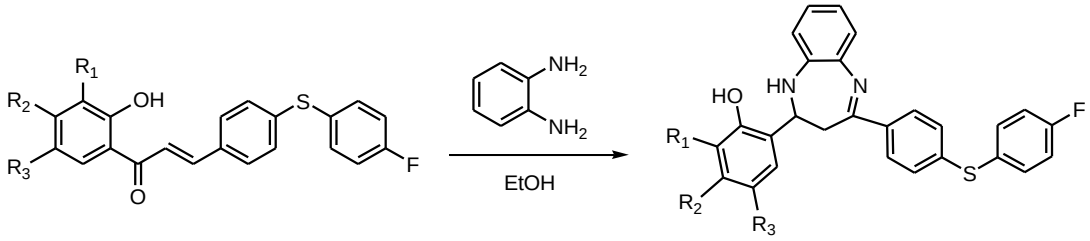
2-((E)-4-(4-(4-fluorophenylthio)phenyl)-2,3-dihydro-1H-benzo[b][1,4]diazepin-2-yl)-4-chlorophenol 10f

^{1}H NMR (400 MHz, DMSO-d6, δppm): 3.1 (s,2H, N=C-CH_2), 3.32 (s,1H,CH), 5.19 (s,1H,NH), 6.50-7.54 (m, 15 H, Ar-H), 14.4 (s, 1H, -OH).;IR (KBr, cm-1):3316 (NH), 2925 (OH), 1594 (C=N), 1564 (C=C); ES-MS: m/z: 475.

Results and discussion

Chemistry

The starting precursor's (E)-1-(2-hydroxyphenyl)-3-(4-(phenylthio) phenyl) prop-2en-1-ones **1a-h was** prepared using o-hydroxyacetophenone and 4-F(phenylthio)benzaldehyde ethanol. The mixture was refluxed for 3hr. The reaction of (E)-1-(2-hydroxyphenyl)-3-(4-(phenylthio)phenyl)prop-2en-1-ones **1a-h** with o-phenyldiamine in ethanol gave the target products **2a-h** (**Scheme 1**, Structural assignments to the newly synthesized compounds were based on their IR, ^{1}H-NMR, Mass spectral data.



1 a-h **2a-h**

Scheme 1. Synthesis of benzodiazepines **2a-h**

Table 1. Physical data of compounds 2a-h.

Comp.	R_1	R_2	R_3	Yield (%)	M. P. (°C)
10a	H	CH_3	Cl	72	135-137
10b	H	H	CH_3	68	87-89
10c	H	H	H	65	95-97
10d	CH_3	H	CH_3	75	119-121
10e	H	H	F	78	125-127
10f	H	H	Cl	64	75-77
10g	Cl	H	Cl	75	70-72
10h	H	H	Br	64	80-82

Antimicrobial activity

Antimicrobial activity of all the synthesized compounds was determined by the well-diffusion method Two Gram-positive bacterial strains *E. coli* and *A. flavus* strains used to study and investigate the antimicrobial activities. The bacterial liquid cultures were prepared in fusion broth. All the newly synthesized compounds were dissolved in DMSO at concentration of 1 mg/mL. The antibacterial activity of DMSO was checked against the test organisms and was found to be nil. In Petri dishes, the molten nutrient agar was poured and allowed to solidify. The holes of 10 mm diameter were punched using a cork borer and completely filled with the test solutions. The culture plates were incubated for 24 hr at 36 °C. The inhibition zone around the holes in each plate was measured after 24 hr. The diameter of inhibition zone and minimal inhibitory concentrations (MICs) showed the antibacterial activity **Table 2**.

Table 2. *In vitro* antibacterial screening of compounds (**2a-h**)

Compound	Inhibition zone (mm) (*Escherichia coli*)	Inhibition zone (mm) (*Aspergillus flavus*)
10a	Nil	Nil
10b	Nil	Nil
10c	Nil	Nil
10d	Nil	24
10e	02	Nil
10f	Nil	Nil
10g	Nil	Nil
10h	Nil	Nil
Control (Solvent)	Nil	Nil

The newly synthesized compounds **2a-h** were evaluated for in-*vitro* antimicrobial activities. The preliminary screening data showed that among active compounds only 10d showed good activity against *Aspergillus flavus*.

Conclusions

In conclusion, synthesis, and antibacterial activities of a novel series of 2-((*E*)-4-(4-(4-fluorophenylthio)phenyl)-2,3-dihydro-1*H*-benzo[b][1,4]diazepin-2-yl)phenol 2a-h, have been presented for the first time *via* synthetic procedure in good yield. In addition, only one derivative showed inhibition zone activity, indicating the future scope for optimization.

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