RESEARCH ARTICLE JPAR 2021

Journal of Pharmaceutical Advanced Research

(An International Multidisciplinary Peer Review Open Access monthly Journal)

Available online at: www.jparonline.com

Synthesis and antibacterial screening of some novel 1,5-benzodiazepine derivatives

Honde Bharat Shivaji*, Kunkulol Rahul Rajendra

Department of Pharmacology, Pravara Institute of Medical Sciences (Deemed University), Loni 413736, Dist. Ahmednagar, (M.S.) India.

Received: 31.08.2020 Revised: 10.09.2021 Accepted: 20.09.2021 Published: 30.09.2021

ABSTRACT: Background: Heterocyclic chemistry is a branch which is inseparable from mankind because humans are totally dependent on the drugs derived from heterocyclic rings. Much attention has been paid to the synthesis of nitrogen containing heterocyclic compounds like benzodiazepines, mainly due to their broad spectrum biological and pharmacological activities. **Aim:** The aim of the present study is to synthesize new derivatives of Benzodiazepine and to evaluate the synthesized derivatives for antibacterial activities. **Method:** A mild, efficient and rapid method was developed for the synthesis of 1,5-benzodiazepine derivatives by the condensation of o-phenylenediamine with substituted ketones by using $FeCl_3$ as a catalyst. The 1,5- benzodiazepine derivatives were determined by Elemental analysis H^1 NMR. The antibacterial activity of 1,5- benzodiazepine derivatives was carried out by spread plate technique by using the microorganisms *Staphylococcus aureus* and *Bacillus subtilis* at a concentration of 100, 200, 400 and 800 µg/ml. The ampicillin was used as the standard drug. **Results**: The antibacterial screening showed that 1,5-benzodiazepine derivatives significantly demonstrated antibacterial activity. **Conclusion:** Present study revealed that among all the synthesized compounds, 2-Methyl 1,5-benzodizapam and 4-diethyl 1,5-benzodizapam were found to be more potent as antibacterial against the microorganisms *S. aureus* and *B. subtilis* agents.

Corresponding author*
Mr. Honde Bharat Shivaji
Department of Pharmacology,
Pravara Institute of Medical Sciences
(Deemed University),
Loni 413736, Dist. Ahmednagar, (M.S.) India.
Tel: +91-9423444609
E-Mail ID: bharat_honde11@rediffmail.com

Keywords: O-phenylenediamine, 1,5-benzodiazepine, Antibacterial, Spread plate technique, *S. aureus*, *B. subtilis*.

INTRODUCTION:

Heterocyclic chemistry is a branch which is inseparable from mankind because humans are totally dependent on the drugs derived from heterocyclic rings. Much attention has been paid to the synthesis of nitrogen containing heterocyclic compounds like benzodiazepines, mainly due to their broad spectrum biological and pharmacological activities. The 1,5-benzodiazepines have recently attracted attention as an important class of heterocyclic compounds in the field of drugs and pharmaceuticals. These compounds are widely used as anticonvulsant, antianxiety, analgesic, sedative, antidepressive, hypnotic agents as well as anti-

inflammatory agents [1]. Other than their biological importance, benzodiazepine derivatives are also commercially used as dyes for acrylic fibres. Moreover, 1,5-benzodiazepine derivatives are valuable synthons that can be used in the preparation of other fused ring compounds such as triazolo, oxadiazolo, oxazino or furanobenzodiazepines. As a result, research in this area is still very active and is directed towards the synthesis of compounds with enhanced pharmacological activity. Generally, benzodiazepines were synthesized by the condensation of o-phenylenediamines with α,β-unsaturated carbonyl compounds, β-haloketones, or ketones. A variety of reagents, such as BF_3 etherate, $NaBH_4$polyphosporic acid, SiO_2, $MgO/POCl_3$, $Yb(OTf)_3$, $Sc(OTf)_3$, Al_2O_3/P_2O_5, or AcOH under microwave irradiation and even in the presence of ionic liquids, are utilized for condensation reactions. Most recently, this condensation has also been reported to proceed in the presence of CAN, (bromodimethyl) sulfonium bromide, organic acids and $AgNO_3$.Recently considerable attention has been devoted to heterogeneous organic transformations utilizing inorganic solid acids.generally, heterogeneous catalyst soffer several advantages such as mild reaction conditions, high selectivity, high throughput and ease of work-up procedures [2].The condensation of *o*-phenylenediamine with ketones under solvent free conditions catalyzed by a $fecl_3$,the reactions were carried out by taking 1:2 ratio mixture of *o*-phenylenediamine and ketone along with a catalytic amount of $fecl_3$ at room temperature giving good to excellent yields of 1,5-benzodiazepines. Cyclic ketones such as cyclohexanone also reacted effectively to produce [3-5].

The objective of the present study is to synthesize some benzodiazepine derivatives and to evaluate the synthesized derivatives for antibacterial activity.

MATERIALS AND METHODS:

The o-pydhenylenediamine was procured from HiMedia Lab, Mumbai. All other chemicals and reagents used in this study were of analytical grade and procured from an authorized dealer.

Synthesis of 1,5-Benzodiazepine derivatives:

A mixture of o-pydhenylenediamine (5 mmol) and substituted ketone (10 mmol) was prepared with continuous stirring, to which FeCl3 was added and mixed for 30 to 50 min. After the completion of reaction, the mass was washed with saturated solution of $NaHCO_3$ and NaCl. The reaction was monitored by TLC using ethyl acetate: acetone (2:1) as solvent and iodine vapors as visualising agent. After completion of reaction, warm water (50 ml) was added and the solution was allowed to cool. The precipitated product was filtered off, washed with aqueous methanol (10 ml) and recrystallized from methanol. The scheme for the synthesis of Benzodiazepine derivatives is presented in Fig 1.

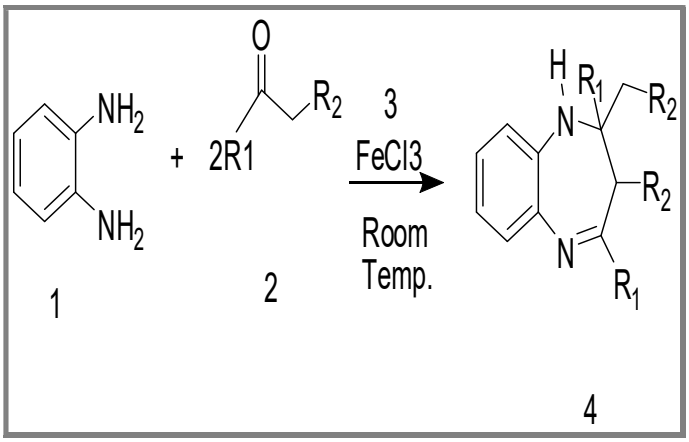

Fig 1. The scheme for the synthesis of Benzodiazepine derivatives.

Identification of synthesized derivatives:

The synthesized derivatives of 1,5-Benzodiazepine were characterized by ^{1}H NMR (Thermo Scientific "Heracell" Vios 160i CR CO2 Incubator, 165 L) [6].

Antibacterial activity:

The plates were inoculated by specific microorganisms by spread plate technique. The bores were made in the solidified agar plate by using a sterile borer. The test solution of specified concentration was added in the bore by using sterile pipette and the plates were kept in freeze for 1 h for diffusion and then incubated at 37 °C for 24 h. After 24 h the plates were examined and zones of inhibition were recorded. All the synthesized compounds were screened for antibacterial activity against both gram positive *S. aureus* and *B. substilis* and gram negative *E. coli* and *Proteus vulgaris* bacteria at a concentration of 100, 200, 400 and 800 µg/ml. Ampicillin was used as a standard for comparison of antibacterial activity. In presence of bases such as NaOH and ethanol is used as a solvent [7,8].

RESULTS AND DISCUSION:

We have developed a mild, rapid and efficient method for the synthesis of pure 1,5-benzodaipines through the condensation of various ketones with O-phenylenediamines using $FeCl_3$ as the catalyst. The use of commercially available $FeCl_3$ makes this method

Table 1. Physical data of synthesized compounds.

Sl. No.	Compound	R_1	R_2	Mol. Formula	Mol. wt. (g)	% yield	M.P. (°C)	R_f (cm)
1	a	$-CH_3$	$-CH_3$	$C_{14}H_{20}N_2$	216	84	122	0.7
2	b	$-C_6H_5$	$-CH_3$	$C_{24}H_{24}N_2$	340	77	152	0.6
3	c	$-CH_3$	$-C_2H_5$	$C_{16}H_{25}N_2$	245	80	138	0.6
4	d	$-C_6H_5$	$-C_2H_5$	$C_{27}H_{30}N_2$	382	88	144	0.7
5	e	$-C_2H_5$	$-CH_3$	$C_{16}H_{24}N_2$	244	79	123	0.8
6	f	-H	$-CH_3$	$C_{12}H_{16}N_2$	188	91	147	0.8
7	g	-H	$-C_2H_5$	$C_{14}H_{20}N_2$	216	94	158	0.7
8	h	-H	-H	$C_{12}H_{20}N_2$	192	76	158	0.7
9	i	$-CH_3$	-H	$C_{12}H_{16}N_2$	188	88	160	0.8

M.P. – Melting point.

Table 2. Zone of inhibition of synthesized 1,5-benzodaipines derivatives for gram positive bacteria.

Compound	Zone of inhibition (mm)							
	Staphylococcus aureus Dose (µg/ml)				*Bacillus subtilis* Dose (µg/ml)			
	100	200	400	800	100	200	400	800
a	10	12	13	17	12	14	15	17
b	7	8	11	15	8	10	12	15
c	10	12	12	15	12	15	15	17
d	10	12	13	15	09	11	13	16
e	11	13	14	15	11	12	14	15
f	12	14	16	18	12	14	18	20
g	12	13	16	17	10	12	14	17
h	11	12	15	17	10	12	14	16
i	12	13	14	18	10	12	14	16
Ampicillin	13	14	17	19	15	17	18	21

Table 3. Zone of inhibition of synthesized 1,5-benzodaipines derivatives for gram negative bacteria.

Compound	Zone of inhibition (mm)							
	Escherichia coli Dose (µg/ml)				*Proteus vulgaris* Dose (µg/ml)			
	100	200	400	800	100	200	400	800
a	9	11	12	14	9	11	12	14
b	10	12	14	16	10	12	14	16
c	10	11	14	15	10	11	14	15
d	09	11	12	15	08	10	12	12
e	09	11	13	15	11	12	13	14
f	11	12	14	15	09	11	14	15
g	08	10	11	13	08	08	11	12
h	10	11	12	15	09	09	14	15
i	10	12	14	15	09	09	15	15
Ampicillin	14	15	16	18	12	14	16	17

quite simple, more convenient and practical. It is entirely a novel protocol for the preparation of benzodiazepines in a single-step operation. The ^{1}H NMR shows the data that are a: IR (KBr): 3303(N-H), 3060 (unsaturated aromatic C=C), 1687 (C=N); ^{1}H NMR: δ1.7s, 3H, ; 3.0 (d, 1H J=13.2Hz); 3.1 (d, 1H J=13.2Hz):6.8-7.6(m,14H); b:,IR (KBr): 3402(N-H), 3355 (unsaturated aromatic C=C), 1249; c:IR (KBr): 3388(N-H), 3067cm^{-1} (unsaturated aromatic C=C), 1611 (N=C stretching), 1592(C=N); d: IR (KBr): 3054 (unsubstituted aromatic C=C), 1197(C=N); e:IR (KBr): 3381(H-N), 3060 (unsaturated aromatic C=C), 1681 (C=N); f: IR (KBr): 3343 (N-H stretching), 3205(unsaturated aromatic C=C); g: IR (KBr): 3343cm^{-1} (N-H), 2989 (unsaturated aromatic C=C); h: IR (KBr): 3350cm^{-1} (N-H), 3033 (unsaturated aromatic C=C) and i: IR (KBr): 3380cm^{-1} (N-H), 2999 (unsaturated aromatic C=C). The data is given in Table 1.

The antibacterial activity data of the synthesized 1,5-benzodiazepines against gram positive and gram negative bacteria is given in Table 2 and 3. The antibacterial activity shown by synthesized 1,5-Benzodiazepine is well comparable with the standard drug Ampicillin. The antibacterial activity effectiveness of 1,5-Benzodiazepine was found to be more against gram positive bacteria than the gram negative bacteria. Among all the Benzodiazepine derivatives, the compounds f (2-Methyl 1,5-benzodizapam) and i (2-Methyl 1,5-benzodizapam) showed most potent antibacterial activity. It has been observed that as the dose of the drug was increased, the antibacterial activity was also increased.

CONCLUSION:

Synthesis of 1,5-benzodiazepine derivatives by the condensation of o-phenylenediamine with substituted ketones by using $FeCl_3$ as a catalyst. Amongst all synthesized compounds 2-Methyl 1,5-benzodizapam and 4-diethyl 1,5-benzodizapam were found to be more potent as antibacterial activity against the *Staphylococcus aureus* and *Bacillus subtilis*. Whereas compound 2-Methyl 1,5-benzodizapam and C was more active against antibacterial *Escherichia coli* and *Proteus vulgaris*as. The zone of inhibition of synthesized compounds was compared with the standard drug ampicillin at four different concentrations.

ACKNOWLEDGEMENT:

The authors are thankful to the Department of Chemistry, University of Pune, for spectral data study and the Principal of Pravara Institute of Medical Sciences (Deemed University), for providing laboratory facilities.

REFERENCES:

1. Lundquist K. In: Katritzky AR, Rees CW, editors. Comprehensive Heterocyclic Chemistry. Pergamon: Oxford; 1984. pp. 166-175.
2. Hruby VJ, Deb KK, Yammato DM, Hadley ME, Chan WY. [1-Penicillamine,2-leucine]oxytocin. Synthesis and pharmacological and conformational studies of a potent peptide hormone inhibitor. J Med Chem, 1979; 22(1): 7-12.
3. Brown JD. Chemistry of Heterocyclic Compounds: The Pyrimidines. Vol. 16. Singapore: John Wiley & Sons, Inc; 1970.
4. Sakamoto T, Kondo Y, Yamanaka H. A Facile Synthesis of 4-Arylbutyrolactones via the Palladium-catalyzed Arylation of 1,3-Dioxep-5-ene. Heterocycle, 1993; 36(11): 2437-2440.
5. Henke BR, Aquino CJ, Birkemo LS, Croom DK, Dougherty RW, Ervin GN, et al. Optimization of 3-(1H-indazol-3-ylmethyl)-1,5-benzodiazepines as potent, orally active CCK-A agonists. J Med Chem, 1997; 40(17): 2706-2725.
6. Keeler J. Understanding NMR Spectroscopy. 2nd ed. USA: Wiley; 2013.
7. Balouiri M, MoulaySS, Ibnsouda K. Methods for *in vitro* evaluating antimicrobial activity: A review. J Pharm Anal, 2016; 6(2): 71-79.
8. Munuswamy H, Thirunavukkarasu H, Rajamani S, Kuppan E, Ernest ED. A review on antimicrobial efficacy of some traditional medicinal plants in Tamilnadu. J Acute Dis, 2013; 2(2): 99-105.

Conflict of Interest: None
Source of Funding: Nil
Shivaji HB*, Rajendra KR. Synthesis and antibacterial screening of some novel 1,5-benzodiazepine derivatives. J Pharm Adv Res, 2021; 4(9): 1380-1383.