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Research Article

Synthesis and Biological Evaluation of Some Newer 1*H*-Benzo[b][1,5] diazepin-2(3*H*)-one Derivatives as Potential Anticonvulsant Agents

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Abstract

Background: Regardless of the availability of all novel and earlier treatments, seizure control is notoriously complicated. In the hopes of discovering the latest and ultimate therapy, medicinal chemists will keep on to hunt for new antiepileptic compounds with high specificity and low CNS toxicity. The biological effects of benzodiazepine compounds have been examined. Benzene and a diazepine ring are fused together to form the chemical structure. Diverse combinations of moieties attached to the innermost structure in positions 1, 2, 5, and 7 the pharmacological qualities, effect potency, and pharmacokinetic conditions are all influenced by the various side groups.

Methods: This paper describes the synthesis of several 1*H*-benzo[b][1,5]diazepin-2(3*H*)-one derivatives. The substituents at N^1 are benzoyl, 5-substituted-1,3,4-thiadiazoles-2-yl-aminoacetyl. Condensation of orthophenylene diamine with ethyl acetoacetate gave 7-substituted-4-methyl-1*H*-benzo[b][1,5]diazepin-2(3*H*)-ones, which were then linked to benzoyl chloride and chloroacetyl chloride to yield N^1-benzoyl and N^1-chloroacetyl derivatives. N^1-chloroacetyl derivatives were further linked with 5-substituted-1,3,4-thiadiazoles amines using microwave irradiation.

Results: FTIR, 1H-NMR, and mass spectroscopy were used to authenticate the synthesized compounds. The PTZ produced convulsions method was used to test the compounds for anticonvulsant activity. When compared to the control group; Compounds 4a and 4c gave 80% protection at 0.4 mg/kg, whereas Compounds 2a and 2c offered 80% protection at 20 and 30 mg/kg, respectively.

Conclusion: When compared to a control, the experimental synthesis and pharmacological assessment of the 1,5-benzodiazepin-2-one moiety replaced with 1,3,4-thiadiazole yields a potentially active anticonvulsant drug.

Introduction

Epilepsy is a widespread nerve sickness marked by recurrent seizures resulting from uncontrolled electrostatic start in a cluster of brain cells.[1,2] According to the World Health Organization (WHO), about eighty out of every hundred persons living with epilepsy live in developing countries, with the mainstream of them lacking adequate medical care.[3] noteworthy developments in epilepsy medication have been fuelled by the need for an appropriate drug with a low risk of side effects. One of the most regularly prescribed drugs is benzodiazepines (Table 1). Aside from the well-known anxiolytic, sedative, anticonvulsant, myorelaxant, and hypnotic effects, it also has anticonvulsant, anticonvulsant, myorelaxant, and hypnotic properties.[4-7] A large family of chemical compounds with fused heterocycle has received consideration in recent years due to their many biological characteristics.[8-11], antipsychotic,[12] anticonvulsant,[13-15] Antineoplastic.[16-18]

Thiadiazole, in nature, come in four isomeric forms. The ring system's bottomless aromaticity is projected to bestow thiadiazole derivatives' fascinating biological activity, resulting in high in vivo stability and, in all-purpose, be deficient in of toxicity for higher vertebrates, including humans. Compounds with extraordinary qualities are created when this ring is coupled to various useful groups that act together with receptors.[19,20] The synthesis of new derivatives of 1, 5-benzodiazepine-2-one in combination with a benzoyl ring and 1, 3, 4-thiadiazoles in combination with the aforementioned pharmacophores is reported to have enhanced anticonvulsant activity at this time, based on the preceding findings.

The ideal anti-seizure medication, on the other hand,

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Table 1. Classes of benzodiazepines.

No.	Name / Class	Example
1	2-keto compounds	Chlordiazepoxide, Clorazepate, Diazepam, flurazepam, halazepam, prazepam, and others
2	3-hydroxy compounds	Lorazepam, Lormetazepam, Oxazepam
3	7-nitro compounds	Clonazepam, Flunitrazepam, Nimetazepam
4	Triazolo compounds	Adinazolam, Alprazolam, Estazolam, Triazolam
5	Imidazo compounds	Climazolam, Loprazolam

would prevent all seizures while having no negative side effects. Despite this, the current medication not only fails to cease seizure activity in some patients, but it also continues to be useless, causing a variety of side effects such depression, neurotoxicity, sleepiness, ataxia, and hypnosis. There is a strong demand for cutting-edge anticonvulsants because of the unpleasant side effects of currently used anticonvulsants, which make therapy challenging.[21] Only lower ictal epileptiform episodes and not interictal epileptiform episodes are currently treated with antiepileptic drugs. Antiepileptic medicines, on the other hand, have no effect on interictal activity, which entirely prevents seizures, when taken at rest, according to clinical evidence.[22]

Materials and Methods

Chemical

All of the materials used in the experiment were purchased locally and are of laboratory quality. The course of the reaction is monitored using thin layer chromatography (TLC), and the products are purified by recrystallization from ethanol. On a silica gel G covered plate with a thickness of 0.5 mm, the purity of the chemicals was evaluated using TLC. The spectral investigations, IR, and 1H-NMR were determined using standard techniques. Infrared spectra were recorded using a Shimadzu IR Affinity-1 device. Brucker Avance II 400 MHz NMR Spectrometer in DMSO-d6 was used to produce the 1H-NMR spectra. Using a Water Q-TOF MICROMASS, the Mass Spectrum was obtained.

Synthesis of 7-substituted-4-methyl-1H-benzo[b][1,5] diazepin-2(3H)-one derivatives (1a-e)

These derivatives were synthesized as per the reported procedure[23] using an equimolar mixture of ethyl acetoacetate and 4-substituted orthophenylene diamine (OPD) prepared in fresh sodium ethoxide solution and irradiated under microwave (Catalyst; CATA-2R) at 420 watts for 25 minutes; the reaction was checked using TLC. Reaction mixtures were transferred into cold water, filtered, dried, and recrystallized

Synthesis of N^1-benzoyl-7-substituted-4-methyl-1H-benzo[b][1,5]diazepin-2(3H)-one derivatives (2a-e)

In 15 mL of water containing 10% NaOH, an equimolar mixture of 7-sustituted-4-methyl-1*H*-benzo[b] [1, 5] diazepin-2(3*H*)-one and benzoyl chloride was prepared. The benzoyl chloride was added via a dropping funnel. The reaction mixture was treated under microwave (Catalyst; CATA-2R) at 455 Watts for 15-20 minutes; the reaction was checked by TLC. The solid product was filtered, and recrystallized after the reaction mixture was transferred to cold water.

Synthesis of N^1-(α-chloroacetyl)-7-substituted-4-methyl-1H-benzo[b][1,5]diazepin-2(3H)-one derivatives (3a-d)

In 15 mL of 10% NaOH in water, an equimolar mixture of 7-substituted 1, 5-Benzodiazepine-2-one and chloroacetyl chloride was prepared. The addition of chloroacetyl chloride was accomplished using a dropping funnel. The reaction mixture was treated under microwave (Catalyst; CATA-2R) at 455 Watts for 15-20 minutes, the reaction was checked by TLC, the reaction mixture was poured in cold water to obtain the solid.

Synthesis of 2-amino- 5-(4-substituted phenyl) - 1, 3, 4-thiadiazole

A few drops of concentrated sulfuric acid were slowly added in cold to an equimolar mixture of 4-substituted benzoic acid (4-Nitro benzoic acid/ 4-Hydroxy benzoic acid) and thiosemicarbazide. The mixture was refluxed for 4 hours, the reaction was checked by TLC, the reaction mixture was poured in crushed ice and neutralised with concentrated ammonia, and the yellow product was filtered and washed with a saturated solution of sodium bicarbonate and water before being recrystallized.[24,25]

Synthesis of 7-substituted-4-methyl-N^1-α-[5-(4-substituted phenyl) 1,3,4-thiadiazole-2-yl-amino] acetyl-1H-benzo[b][1,5]diazepin-2(3H)-one (4a-d)

An equimolar mixture of N^1- -chloroacetyl-1,5-benzodiazepine-2-one derivative (3a-e), 2-amino-5-(4-substituted phenyl)-1,3,4-thiadiazole, and anhydrous potassium carbonate was prepared in DMF and irradiated under microwave (Catalyst; CATA-2R) at 455 Watts for 15-25 minutes, the product was isolated through extraction in chloroform. (Figure 1).

N^1-benzoyl-7-chloro-4-methyl-1H-benzo[b][1,5] diazepin-2(3H)-one (2a)

IR Vmax (KBr cm^{-1}): 3000-3100 (C-H, C═C Ar-), 1700(C═O esters), 1600-1475 (C-H aromatic), 1429-1609(N=C Ar-), 1440-1485 (CH_3 alkanes), 1310-1360(C-N aromatic) which is characteristic of the N1-benzoyl-1,5-benzodiazepin-2-one; ^{1}H-NMR (400MHz, δ ppm, DMSO-d6): 1.13 (s, 3H,CH_3), 2.00 (s, 2H, methylene-

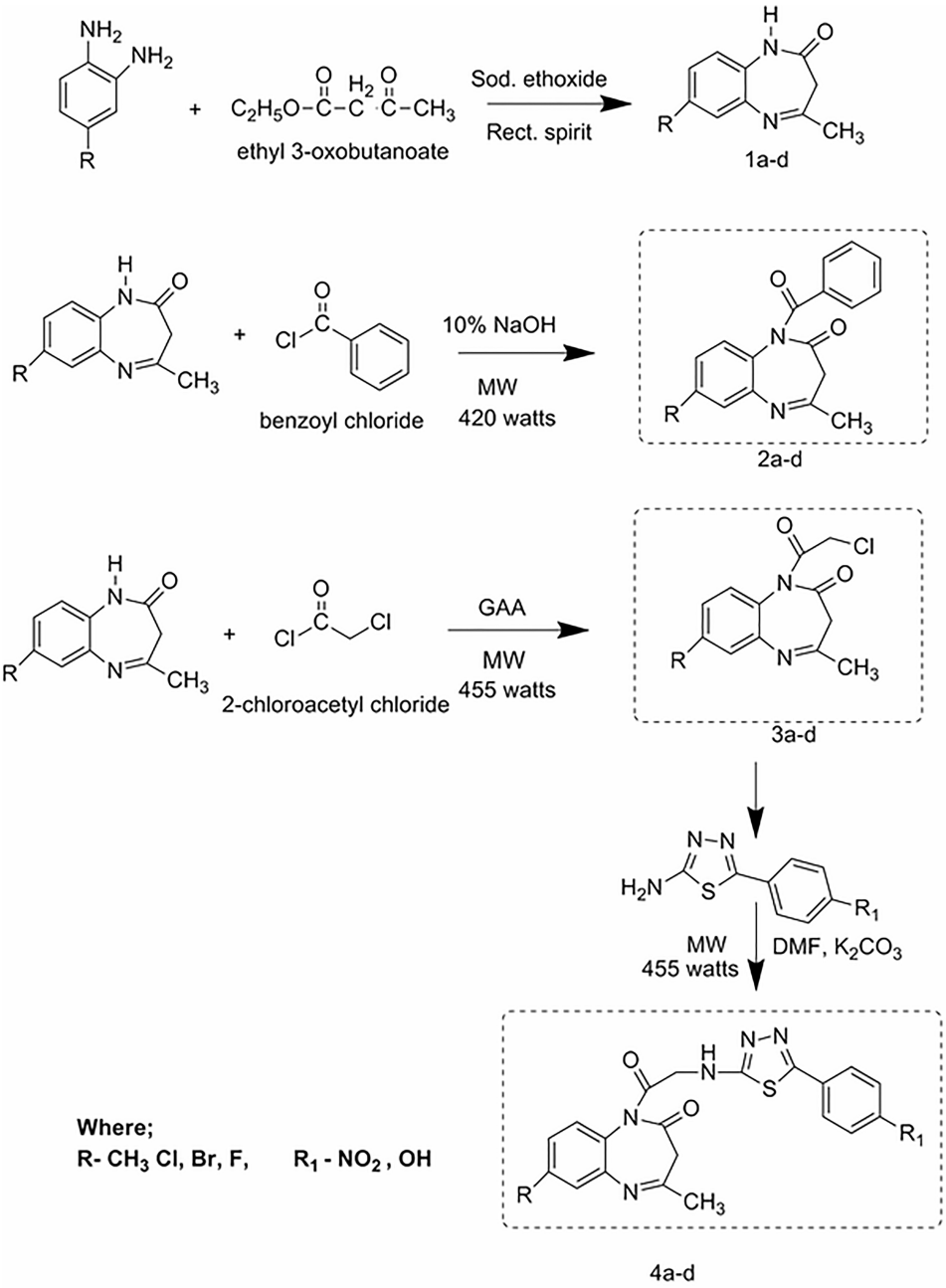

Figure 1. Scheme for synthesis of compound. 1a-d, 3a-d, and 4a-d respectively.

CH_2), 7.29-7.38(m, 3H, Ar-), 7.35-7.88 (m, 4H, Ar-); ^{13}C-NMR (δ_c ppm, DMSO-d6): 27.9,42.0,122.0, 124.3, 127.5, 128.8, 129.0,132.0,134.0,144.1, 161.0, 166.2, 172.3.

N^1-benzoyl-4,7-dimethyl-1H-benzo[b][1,5]diazepin-2(3H)-one (2b)

IR Vmax (KBr cm^{-1}): 2850-2960 (-CH_3 alkanes), 1700(C=O esters), 1600(N=C Ar-), 1410 (C-CH_3 Ar-), 1310-1360(C-N Ar-). ^{1}H-NMR (400MHz, δ ppm, DMSO): 1.06 (s, 3H, CH_3), 2.10 (s, 2H, methylene-CH_2), 2.52 (s, 3H, Ar-CH_3), 7.22-7.25 (m, 3H, Ar-), 7.75-7.92(m, 4H, Ar-); ^{13}C-NMR (δ_c ppm, DMSO-d6): 21.3, 27.9, 42.0,122.0, 127.5, 128.8, 131.3,132.0, 134.2, 142.6, 144.0, 161.0, 166.2, 172.3; MS: ESI; m/z (%); 293.1 M$^+$

N^1-benzoyl-7-bromo-4-methyl-1H-benzo[b][1,5]diazepin-2(3H)-one (2c)

IR Vmax (KBr cm^{-1}): 3010-3100 (Ar- C-H str, C=C str), 1685 (C=O esters), 1615-1482 (C-H Ar-), 1430-1590 (N=C Ar-), 1375-1450 (C-CH_3 Ar-), 1311-1359 (C-N Ar-), 525 (C-Br Ar-); ^{1}H-NMR (400MHz, δ ppm, DMSO): 1.22 (s, 3H, CH_3), 1.81 (s, 2H, methylene-CH_2), 7.02-7.22(m, 3H, Ar-), 7.60-8.02 (m, 4H, Ar-); ^{13}C- NMR (δ_c ppm, DMSO-d6): 28.0, 42.4, 118.0, 125.0, 128.8, 130.3,132.1,133.0, 134.2, 142.6, 144.1, 161.3, 166.2, 172.2.

N^1-benzoyl-7-fluro-4-methyl-1H-benzo[b][1,5]diazepin-2(3H)-one (2d)

IR Vmax (KBr cm^{-1}): 3000-3100 (Ar- C-H), 3025 (C-CH_2

Ar-), 2854-2963 (CH_3 alkanes), 1700 (C=O esters), 1425-1610 (N=C Ar-), 1310-1360 (C-N Ar-), 866 (C-H Ar-); ^{1}H-NMR (400MHz, δ ppm, DMSO): 1.25 (s, 3H,CH_3), 2.09 (s, 2H, methylene-CH_2); 7.14-7.25(m, 3H, Ar-);7.51-7.95 (m, 4H, Ar-); ^{13}C-NMR (δ_c ppm, DMSO-d6): 28.0, 42.4, 109.0, 114.0, 124.8, 127.5, 128.0, 129.9,132.0, 134.2, 144.3, 158.0, 161.1, 166.0, 172.3.

N^1-benzoyl-4-methyl-1H-benzo[b][1,5]diazepin-2(3H)-one (2e)

IR Vmax (KBr cm^{-1}) 3000-3100 (C=C Ar-), 2850-2960 (CH_3 alkanes), 1430-1600 (N=C Ar-), 1375-1450 (C-H Ar-), 1310-1360 (C-N Ar-); ^{1}H-NMR (400MHz, δ ppm, DMSO): 1.20 (s, 3H,CH_3), 2.29 (s, 2H, methylene-CH_2); 7.15-7.29 (m, 4H, Ar-);7.53-7.80 (m, 4H, Ar-); ^{13}C-NMR (δ_c ppm, DMSO-d6): 27.9, 42.4, 122.9, 125.0, 127.5, 128.8, 129.1,132.1, 134.1, 142.0, 161.3, 166.1, 172.1 MS: ESI; m/z (%); 279.1 M$^+$

7-Chloro-4-methyl-N^1-α-[(4-nitrophenyl)-1,3,4-thiadiazole-2-yl-amino]acetyl-1H-benzo- [b][1,5] diazepin-2(3H)-one . (4a)

IR Vmax (KBr cm^{-1}): 3225 (N-H amine), 3000-3100 (C-H, C=C Ar-), 1700(C=O esters), 1600-1475 (C-H Ar-), 1429-1609(N=C Ar-), 1430-1600 (N=C Ar-), 1440-1485 (CH_3 alkanes), 1310-1360 (C-N Ar-) 1027-1039 (N-N Ar-), 800-1000 (C-S Ar-); ^{1}H-NMR (400MHz, δ, DMSO): 1.21(s, 3H, CH_3), 2.13(s, 2H, methylene CH_2), 4.01(d, 2H, acetyl CH_2),4.10(t, 1H,NH), 7.39-7.60 (m, 3H, Ar-); 7.92-8.25 (m, 4H, Ar-); ^{13}C-NMR (δ_c ppm, DMSO-d6): 28.0, 42.2, 52.2, 122.5, 124.4, 127.5, 128.2, 129.6,132.4, 139.0, 144.0, 147.9, 161.0, 164.2, 166.0, 174.0; Anal. ($C_{20}H_{15}ClN_6O_4S$), Calcd. (Found) %: C, 51.06 (51.05), H, 3.19 (3.18), N, 17.87(17.85), O, 13.61(13.59), S, 6.80 (6.78).

4,7-dimethyl-N^1-α-[(4-hydroxyphenyl)-1,3,4-thiadiazole-2-yl-amino]-acetyl-1H-benzo- [b][1,5] diazepin-2(3H)-one(4b)

IR Vmax (KBr cm^{-1}): 3292(N-H amine), 3090-3100 (C-H, C=C Ar-), 1690(C=O esters), 1475-1605 (C-H Ar-), 1430-1600 (N=C Ar-), 1425-1610 (N=C Ar-), 1435-1490 (CH_3 alkanes), 1305-1365 (C-N Ar-) 1020-1037 (N-N Ar-), 790-1010 (C-S Ar-); ^{1}H-NMR (400MHz, δ, DMSO): 1.35 (s, 3H, CH_3), 2.40 (s, 3H, Ar-CH_3); 2.15 (s, 2H,methylene CH_2), 4.10 (d, 2H,acetyl CH_2), 4.05 (t, 1H, NH), 7.38-7.54 (m, 3H, Ar-), 7.90-8.12 (m, 4H, Ar-); ^{13}C-NMR (δ_c ppm, DMSO-d6): 21.2, 28.0, 42.4, 52.0, 116.4, 122.8, 126.1, 127.7, 128.9, 131.3, 132.0, 158.5, 161.3, 164.1, 166.2, 174.2; Anal. ($C_{21}H_{19}N_5O_3S$), Calcd. (Found) %: C, 59.85 (59.81), H,4.51 (4.47), N, 16.82(16.81), O, 11.40(11.36), S, 7.60 (7.55).

7-Fluro-4-methyl-N^1-α-[(4-nitrophenyl)-1,3,4-thiadiazole-2-yl-amino]-acetyl-1H-benzo-[b][1,5] diazepin-2(3H)-one(4c)

IR Vmax (KBr cm^{-1}): 3336 (N-H amine), 3090-3100 (C-H, C=C Ar-), 3090-3100 (C-H Ar-), 1620-1690 (C=O esters), 1500-1570 (C-NO_2 Ar-), 1400-1600 (N=C Ar-), 1400-1000 (C-F-Ar-), 1310-1360(C—N Ar-). ^{1}H-NMR (400MHz, δ, DMSO): 1.44 (s, 3H, CH_3), 2.1 (s, 2H, methylene CH_2), 3.95 (d, 2H, acetyl CH_2), 4.21 (t, 1H, NH), 7.17-7.62 (m, 3H, Ar-); 7.99-8.32 (m, 4H, Ar-); ^{13}C-NMR (δ_c ppm, DMSO-d6): 27.8, 42.4, 52.0, 109.8, 114.1, 124.4, 128.4, 129.3 134.6, 144.0, 147.9, 158.7, 161.1, 164.2, 166.2, 174.1; Anal. ($C_{20}H_{15}FN_6O_4S$), Calcd. (Found) %: C, 52.86 (52.77), H, 3.56 (3.51), N, 18.50 (18.47), O, 14.09 (14.06), S, 7.04 (7.07); MS: ESI; m/z (%) ;454.0 M$^+$

4-methyl-N^1-α-[(4-nitrophenyl)-1,3,4-thiadiazole-2-yl-amino]-acetyl-1H-benzo[b][1,5]-diazepin-2(3H)-one (4d)

IR Vmax (KBr cm^{-1}): 3331(N-H amine), 3030 (C-H Ar-), 1375-1450 (C-H Ar-), 1475 (C=C Ar-), 1690 (C=O esters), 1310-1360 (C-N Ar-), 1027-1039 N-N Ar-) 1430-1600 (N=C Ar-), 800-1000 (C-S Ar-); ^{1}H-NMR (400MHz, δ, DMSO) 1.20 (s, 3H, CH_3), 2.11 (s, 2H,methylene CH_2), 4.01 (d, 2H, acetyl CH_2), 3.88 (t, 1H, NH), 7.33-7.65 (m, 4H, Aromatic); 7.91-8.15 (m, 4H, Aromatic); ^{13}C-NMR (δ_c ppm, DMSO-d6): 27.9, 42.0, 52.3, 122.9, 124.4, 125.8, 127.3, 128.1, 129.1, 134.2, 139.5, 142.6, 147.9, 161.2, 164.3, 166.1, 174.3; Anal. ($C_{20}H_{16}N_6O_4S$), Calcd. (Found) %: C, 55.05 (55.04), H,3.67 (3.65), N, 19.27(19.24), O, 14.68(14.65), S, 7.34 (7.32).

Pharmacological activity

Swiss albino mice of either sex weighing 20-22 g were procured from the Haffkin Research Institute in Mumbai, India. The animal's general behavior was normal throughout the experiment to ensure proper testing; mice had free access to food and water for 24 hours prior to testing.[26,27]

Acute oral toxicity (AOT)

Following the OECD 425 guidelines, AOT studies were conducted to determine the LD_{50}. During the acute oral toxicity testing, the test compounds were administered orally. 1mL/100g of animal body weight volume was injected.[28]

Anticonvulsant activity: (ScPTZ-induced seizures test)

The solutions of test compounds were prepared in dimethylsulfoxide and administered intraperitoneally in various doses (Table 2). Pentylenetetrazol (PTZ) in distilled water with a dose of 80 mg/kg (which caused clonic seizures in 100% of the animals) was injected subcutaneously after 30 minutes of administration of the test compound, and observed for 30 minutes. The latency of onset of convulsion, number of episodes of convulsions and percentage protection for control and test were recorded (Figure 2).

Results

Chemistry

TLC was used to monitor the reactions on silica gel G plates, and R_f values were recorded in solvent system

Table 2. Anticonvulsant effect of some synthesized 1H-benzo[b][1,5]diazepin-2(3H)-one derivatives in mice using PTZ induced convulsions method.

Code	Dose (mg/Kg, i.p.)	Latency to Induce convulsions in Min. (Mean ± SEM)	No. of convulsions	% Protection
PTZ (Control)	80	2.02±1.13	5	0
Diazepam	2	-	0	100
4a	0.2	6.55±0.51^{NS}	2	60
	0.4	12.22±2.17**	1	80
4b	0.2	7.88±0.60*	3	40
	0.4	9.14±0.91*	2	60
4c	0.2	7.63±0.68^{NS}	2	60
	0.4	16.54±4.74**	1	80
4d	0.2	4.99±0.71^{NS}	3	40
	0.4	3.47±0.89^{NS}	4	20
2a	20	16.09±6.04**	1	80
	30	18.63±3.18**	1	80
2b	20	2.41±0.34^{NS}	3	40
	30	2.45±0.48^{NS}	3	40
2c	20	6.30±0.16*	2	60
	30	8.22±0.23*	1	80
2d	20	6.16±1.18*	2	60
	30	10.10±2.11*	2	60

N=6, in each group; *: P < 0.05;**: P <0.01; NS: Non significant; One Way ANOVA followed by Dunnett's test.

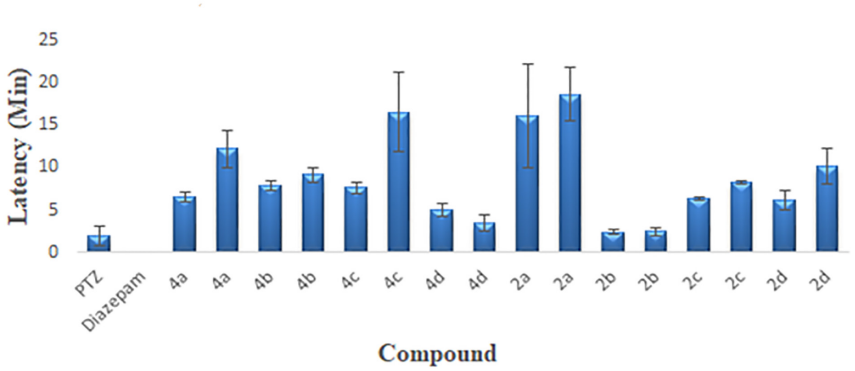

Figure 2. Graphical representation of anticonvulsant effect of some synthesized 1H-benzo [b][1,5] diazepin -2(3H)-one derivatives mice using PTZ induced convulsions method

A (n-hexane: ethyl acetate, 4:1) and solvent system B. (n-hexane: ethyl acetate, 3:2). The final compounds were purified by recrystallization from different solvents, and their melting point ranges were recorded. The compounds were characterized by determination of melting point range, Spectral analysis and elemental analysis.

N^1-benzoyl-7-chloro-4-methyl-1H-benzo[b][1,5]diazepin-2(3H)-one (2a)

White crystalline solid in 78%, 1.21 g; mp: 160-162 ^{0}C; R_f 0.63 (solvent system A); reaction time: 20 min.

N^1-benzoyl-4,7-dimethyl-1H-benzo[b][1,5]diazepin-2(3H)-one (2b)

White crystalline solid in 72% 1.05 g; mp: 164-166 ^{0}C; R_f 0.68 (solvent system A); reaction time: 17 min.

N^1-benzoyl-7-bromo-4-methyl-1H-benzo[b][1,5]diazepin-2(3H)-one (2c)

White crystalline solid in 75% 1.33 g; mp: 128-130 ^{0}C; R_f 0.67 (solvent system A); reaction time: 20 min.

N^1-benzoyl-7-fluro-4-methyl-1H-benzo[b][1,5]diazepin-2(3H)-one (2d)

White crystalline solid in 80% 1.18g; mp: 144-146 ^{0}C; R_f 0.78 (solvent system A); reaction time: 20 min.

N^1-benzoyl-4-methyl-1H-benzo[b][1,5]diazepin-2(3H)-one (2e)

White crystalline solid in 80%, 1.11g; mp: 144-146 ^{0}C; R_f 0.72 (solvent system A); reaction time: 15 min.

7-Chloro-4-methyl-N^1-α-[(4-nitrophenyl)-1,3,4-thiadiazole-2-yl-amino]acetyl-1H-benzo-[b][1,5]diazepin-2(3H)-one. (4a)

White crystalline solid in 58%, 1.36 g; mp: 234-238 ^{0}C; R_f

0.60 (solvent system B); reaction time: 25 min.

4,7-dimethyl-N^1-α-[(4-hydroxyphenyl)-1,3,4-thiadiazole-2-yl-amino]-acetyl-1H-benzo-[b][1,5]diazepin-2(3H)-one(4b)

White crystalline solid in 66%, 1.38 g; mp: 276-278 ^{0}C; R_f 0.64 (solvent system A); reaction time: 20 min.

7-Fluro-4-methyl-N^1-α-[(4-nitrophenyl)-1,3,4-thiadiazole-2-yl-amino]-acetyl-1H-benzo-[b][1,5]diazepin-2(3H)-one(4c)

White crystalline solid in 62%, 1.40 g; mp: 266-270 ^{0}C; R_f 0.61 (solvent system A); reaction time: 25 min.

4-methyl-N^1-α-[(4-nitrophenyl)-1,3,4-thiadiazole-2-yl-amino]-acetyl-1H-benzo-[b][1,5]diazepin-2(3H)-one (4d)

White crystalline solid in 64%, 1.39 g; mp: 220-223 ^{0}C; R_f 0.74 (solvent system B); reaction time: 15 min.

Acute oral toxicity and pharmacological activity

Synthesized compounds of the N^1-benzoyl and N^1-(1,3,4-thiadiazole amino) acetyl series were subjected to acute oral toxicity (AOT) to determine the LD_{50} of compounds based on the OECD 425 guidelines. The doses were calculated by using the AOT425 instate software. Each animal was monitored for signs of toxicity and mortality in the first 30 minutes after dosing, then every 4 hours for the next 14 days. The LD_{50} was 175 mg/Kg (for compound from 2a-2e) and 1.75 mg/Kg (for compounds from 4a-4d). The actual doses used are Dose I as (approx. 1/10th that of LD_{50}) and the Dose II (1.5 times or Two times higher than Dose I). Thus, two doses viz. 20 mg/Kg and 30 mg/Kg for compounds from 2a-2e and 0.2 mg/Kg and 0.4 mg/Kg for compounds from 4a-4d were selected for evaluation. The pharmacological evaluation of the compounds revealed that they delayed the onset of convulsions and reduced the number of episodes of convulsions when compared to a control group. As well as the survival or mortality of the animals was also recorded to calculate percentage protection. When compared to the Control, Compounds 4a and 4c provided 80% protection at 0.4 mg/Kg and Compounds 2a and 2c provided 80% protection at 20 and 30 mg/Kg, respectively.

Discussion

The FTIR spectra of the compounds displayed the presence of typical absorption bands (cm^{-1}) in the region at 3310-3350 (N-H secondary amine), 3000-3100 (C-H Ar-), 2850-2960 (C-H Ar-), 1700 (C═O ester), 1600 and 1475 (C═C Ar-), 1430-1600 (N=C Ar-), 1375-1450 (CH_3 alkanes), 1280-1350 (C-N Ar-), 650-900 (C-H Ar-), The ^{1}H-NMR spectrum of N^1-substituted thiadiazole-1,5-benzodiazepin-2-one showed -CH_3 (3H) as singlet at 2.20-2.44 δ ppm; methylene 2H at 2.10-2.15 δ ppm; acetyl CH_2 singlet near 4 δ ppm.

In this study, the anticonvulsant effect of few of 1,5 benzodiazepines containing 1,3,4- Thiadiazole ring and Benzoyl group was investigated. The rationale for these modifications is to prepare comparable compounds with that of benzodiazepine structure with increased lipophilicity and thus with improved anticonvulsant potential.

The following structure activity relationship was observed among these derivatives:

1. In the benzodiazepine ring the nitrogens should be in the position as 1,5; 1,4
2. Presence of chlorine, fluorine at 7th position of benzodiazepine ring gives more potent compounds as compared to no substitution or methyl substitution
3. Presence of 5'-(p-nitrophenyl)-1,3,4 thiadiazole-2-yl-amino moiety joined through acetyl bridge at N^1 of benzodiazepine ring showed highest protection against the seizures.
4. N^1-benzoyl substituted derivatives are comparatively less potent than those substituted with 5'-(substituted phenyl)-1,3,4 thiadiazole-2-yl-amino acetyl moiety.
5. Among the N^1-benzoyl substituted derivatives, it was found that for 7-chloro or 7-fluoro substituted compounds the latency of onset of convulsions is greater.

Conclusion

Microwaves resulted in faster reaction rates as compared to more cautious heating methods. When compared to the Control group, the compounds delayed the onset of convulsions and reduced the frequency of convulsion episodes. Compounds 4a and 4c provided 80% protection at 0.4 mg/kg and Compounds 2a and 2c provided 80% protection at 20 and 30 mg/kg, respectively. The structural features analysis revealed that substituting a benzoyl group on N^1 of the 1,5-benzodiazepine ring and a substituted 1,3,4-thiazole moiety improved the anticonvulsant potential.

Ethical issues

The animal study protocol was approved by Institutional Animal Ethical Committee.

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Author Contributions

RD had contributed to design of the work, scheme and experimental design, data interpretation, and revising the manuscript critically for important intellectual content. PD contributed in the acquisition of chemicals and the

execution of synthesis experiments, structural analysis of compounds and pharmacological evaluation. CH contributed data analysis and in writing, editing of the manuscript and All authors have read and agreed to the published version of the manuscript.

Conflict of Interest

The authors report no conflicts of interest.

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