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Synthesis, Characterization and Anti-inflammatory Activity of Novel Triazolodiazepine Derivatives

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Abstract: *A number of new triazolodiazepine derivatives starting from piperidin-4-ones via diazepam-5-ones were synthesiszed, with a view to test the novel compounds for biological activities. The structure of the synthesized compounds has been established by FT-IR, ^{1}H NMR, ^{13}C NMR, Mass and Elemental Analysis. The newly synthesized compounds were tested for their anti-inflammatory activity by Carrageenan Induced Paw Edema Method.*

Keywords: *Anti-inflammatory, Characterization, Diazepan-5-one, Piperidin-4-one, Synthesis, Triazolodiazepine.*

I. INTRODUCTION

Benzodiazepines enhance the effect of neurotransmitter, gamma-amino butyric acid (GABA) which results in sedative, hypnotic (sleep inducing), anxiolytic (anti-anxiety), anticonvulsant, muscle relaxant, amnesic and antiinflammation action [1,2]. Benzodiazepines have very recently been synthesized and utilized as both β-turn and γ-turn peptidomimetics. For a long time after the discovery of the effects of the 1,4-benzodiazepin-2-ones, there was a search for endogenous ligands to the benzodiazepine receptor subsite of the $GABA_A$ receptor. Better understanding of peptide interactions of the GABA receptor subtypes has lead to recent improved design on benzodiazepine ligands [3].

Triazole derivatives are known to exhibit various pharmacological properties such as, antimicrobial [4], antitubercular [5], anticancer [6], anticonvulsant [7], anti-inflammatory, analgesic [8] and antiviral [9]. Triazoles have also been incorporated in a wide variety of therapeutically interesting drugs including H_1/H_2 histamine receptor blockers, CNS stimulants, antianxiety agents and sedatives [10]. Many commercial antifungal drugs contain triazole functional moiety. The best examples for such antifungal drugs are Fluconazole, Voriconazole, Ravuconazole, Itraconazole and Posaconazole. Triazoles are capable of hydrogen bonding. This property is responsible for binding biomolecular targets as well as the increased solubility of the compounds [11]. Triazoles can function as attractive linker units which could connect two pharmacophores to form an innovative bifunctional drug. Hence, these compounds have become increasingly useful and important in constructing bioactive and functional molecules [12]. It is worthy to note that the bioisosteric replacement between the triazole moiety and its bioisostere triazole has received considerable attention in medicinal chemistry, which represented an efficient concept for the discovery and development of novel triazole drugs.

II. EXPERIMENTAL

2.1 General

Infrared spectra were taken on a Perkin-Elmer FTIR 1600 spectrometer using KBr disks. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded on a Bruker spectrometer. Chemical shifts are given in ppm (δ) relative to tetramethylsilane as internal standard and coupling constants (J) are given in Hz. Signals were characterized as s (singlet), d (doublet), t (triplet), and m (multiplet). Melting points were measured by a digital melting point apparatus and were uncorrected. All reactions were followed by TLC using solvent systems of different polarities. The mass spectra were recorded on JEOL GCmate spectrometer.

2.2 Synthesis and Characterization

3-methyl-2,6-diphenylpiperidin-4-one (**1a-1g**) is used as the starting material for the synthesis of the new triazolodiazepine derivatives. Piperidin-4-one (**1a-1g**) on treatment with sodium azide in presence of concentrated H_2SO_4 yielded diazepan-5-one (**2a-2g**). The diazepams on treatment with Lawessen's reagent corresponding thione derivatives were obtained (**3a-3g**). Thione derivatives on treated with acetylhydrazide the target triazolodiazepine compounds were formed (**4a-4g**). All the compounds were screened for anti-inflammatory activity was carried out by Carrageenan Induced Paw Edema Method. Indomethacin was used as the standard drug for comparison. The newly synthesized compounds were characterized by FTIR, ^{1}H NMR, ^{13}C NMR, Mass and elemental analysis.

2.2.1. 3,5-Dimethyl-6,8-diphenyl-6,7,8,9-tetrahydro-5*H*-[1,2,4]triazolo [4,3-*d*][1,4]diazepine **(4a)**

3-Methyl-2,7-diphenyl-1,4-diazepan-5-thione (0.01 mol) was refluxed with acetyl hydrazide (0.01 ml) in n-butanol in the presence of 0.1 ml of acetic acid for 8-12 hours. The progress of the reaction was monitored by TLC. After the completion of the reaction, n-butanol was distilled out completely and 25 ml acetone was added. Acetone was then distilled out completely. The solid obtained was purified by flash chromatography.

m.p. 140-142 °C, Yield 84 %. FTIR (KBr, cm^{-1}) ν_{max}: 3440 (-NH), 2924 (Ar-CH), 1661 (-C=N), 1450 (-C=C), 1250 (-N-N), 1109 (-C-N-C); ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.32 (d, J = 7 Hz, 3H, CH_3), 2.50 (s, 3H, triazole-CH_3), 3.60 (dd, J = 3.5 Hz, 1H, H6a), 3.43 (dd, J = 8 Hz, 1H, H6b), 4.1 (d, J = 9 Hz, 1H, H2), 4.9 (t, J = 7 Hz, 1H, H3), 4.24 (d, J = 6 Hz, 1H, 7H), 7.25-7.50 (m, 10H, Ar-H); ^{13}C NMR (DMSO-d_6, 125 MHz): 154.19; 144.35; 142.08; 129.87; 129.53; 129.12; 128.95; 128.81; 128.31; 128.00; 127.12; 126.99; 65.74; 63.58; 59.63; 32.56; 18.20; MS: m/z 318 [M+1]. Anal. Calcd for C, 71.91; H, 7.48; N, 16.77. Found: C, 71.89; H, 7.51; N, 16.72.

2.2.2. 3,5-Dimethyl-6,8-bis(3-nitrophenyl)-6,7,8,9-tetrahydro-5*H*-[1,2,4]triazolo[4,3-*d*][1,4]diazepine **(4b)**

m.p. 123-125 °C, Yield 77 %. FTIR (KBr, cm^{-1}) ν_{max}: 3300 (-NH), 3039 (Ar-CH), 1654 (-C=N), 1377 (-C=C), 1283 (-N-N), 1115 (-C-N-C); ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.44 (d, J = 6 Hz, 3H, CH_3), 2.2 (s, 3H, triazole-CH_3), 3.67 (d, J = 5 Hz 1H, H6a), 3.49 (dd, J = 7.5 Hz, 1H, H6b), 4.15 (d, J = 9 Hz, 1H, H2), 4.45 (d, J = 7 Hz, 1H, H3), 4.3(m, 1H, H7), 7.1 – 7.6 (m, 8H, Ar-H); ^{13}C NMR (DMSO-d_6, 125 MHz): 169.57, 169.09, 168.50, 159.74, 150.91, 141.23, 127.51, 55.60, 19.57, 9.69; MS: m/z 408 [M+1]. Anal. Calcd for C, 59.16; H, 5.76; N, 19.32. Found: C, 59.08; H, 5.65; N, 19.28.

2.2.3. 6,8-Bis(3-chlorophenyl)-3,5-dimethyl-6,7,8,9-tetrahydro-5*H*-[1,2,4]triazolo[4,3-*d*][1,4]diazepine **(4c)**

m.p. 202 – 204 ºC, Yield 74 %. FTIR (KBr, cm^{-1}) ν_{max}: 3301 (-NH), 3046 (Ar-CH), 1602 (-C=N), 1449 (C=C), 1256 (-N-N), 1144 (-C-N-C); ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.33 (d, J = 6.5 Hz, 3H, CH_3), 2.23 (s, 3H, triazole-CH_3), 3.61(dd, J = 3 Hz 1H, H6a), 3.41 (dd, J = 8 Hz, 1H, H6b), 4.15 (dd, J = 3 Hz, 1H, H2), 4.25 (d, J = 4.5 Hz, 1H, H7), 5.01 (m, 1H, H3), 7.5 (m, 8H, Ar-H); ^{13}C NMR (DMSO-d_6, 125 MHz): 156.35 153.94, 149.38, 146.64, 144.26, 140.11, 133.91, 133.66, 131.20, 131.14, 130.92, 130.65, 128.86, 128.70, 128.63, 128.31, 128.19, 128.14, 128.00, 127.93, 127.69, 126.99, 126.92, 126.59, 125.91, 64.67, 63.33, 58.83, 32.31, 29.46, 18.21, 14.80; MS: m/z 389 [M+2]. Anal. Calcd for C, 61.73; H, 6.01; N, 14.40. Found: C, 61.68; H, 6.14; N, 14.43.

2.2.4. 6,8-Bis(3,4-dimethoxyphenyl)-3,5-dimethyl-6,7,8,9-tetrahydro-5*H*-[1,2,4]triazolo[4,3-*d*][1,4]diazepine **(4d)**

m.p. 133-135 ºC, Yield 70 %. FTIR (KBr, cm^{-1}) ν_{max}: 3445 (-NH), 2957 (Ar-CH), 1636 (-C=N), 1402 (-C=C), 1265 (-N-N), 1141 (-C-N-C); ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.50 (d, J = 6.5 Hz, 3H, CH_3), 1.98 (s, 3H, triazole-CH_3), 3.65 (d, 1H, H6a), 3.48 (d, 1H, H6b), 3.75(d, J = 10 Hz, 1H, H2), 4.76 (s, 1H, H3), 4.02 (d, J = 11.5 Hz, 1H, H7), 6.9 (m, 6H, Ar-H); MS: m/z 438 [M+1]. Anal. Calcd for C, 61.73; H, 6.01; N, 14.40. Found: C, 61.68; H, 6.14; N, 14.43.

2.2.5. 6,8-Bis(4-bromophenyl)-3,5-dimethyl-6,7,8,9-tetrahydro-5*H*-[1,2,4]triazolo[4,3-*d*][1,4]diazepine **(4e)**

m.p. 158-160 °C, Yield 77 %. FTIR (KBr, cm^{-1}) ν_{max}: 3420 (-NH), 2924 (Ar-CH), 1640 (-C=N), 1406 (-C=C), 1202 (-N-N), 1100 (-C-N-C); ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.42 (d, J = 7.5 Hz, 3H, CH_3), 2.48 (s, 3H, triazole-CH_3), 3.65 (d, J = 4 Hz 1H, H6a), 3.46 (dd, J = 8 Hz, 1H, H6b), 4.12 (d, J = 9 Hz, 1H, H2), 4.47 (d, J = 7.5 Hz, 1H, H3), 4.32 (m, 1H, H7), 7.1 – 7.6 (m, 8H, Ar-H); ^{13}C NMR (DMSO-d_6, 125 MHz): 143.39, 140.17, 132.64, 131.59, 131.40, 130.00, 129.58, 129.34, 129.24, 121.03, 120.73, 120.35, 63.42, 57.77, 51.98, 23.33, 16.19, 10.82; MS: m/z 478 [M+2]. Anal. Calcd for C, 52.19; H, 5.08; N, 12.17. Found: C, 51.12; H, 5.11; N, 12.12.

2.2.6. 4,4'-(3,5-Dimethyl-6,7,8,9-tetrahydro-5*H*-[1,2,4]triazolo[4,3-*d*][1,4]diazepine-6,8-diyl)diphenol **(4f)**

m.p. 260-262 °C, Yield 66 %. FTIR (KBr, cm^{-1}) ν_{max}: 3424 (-NH), 3090 (Ar-CH), 1606 (-C=N), 1402 (-C=C), 1260 (-N-N), 1118 (-C-N-C); ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.45 (d, J = 7.5 Hz, 3H, CH_3), 2.40(s, 3H, triazole -CH_3), 3.81(s, 1H, H6a), 3.50 (d, J = 9 Hz, 1H, H6b), 4.1(d, J = 8 Hz, 1H, H2), 7.1 (m, 8H, Ar-H); MS: m/z 350 [M+1]. Anal. Calcd for C, 70.17; H, 7.21; N, 10.91. Found: C, 70.57; H, 7.57; N, 11.83.

2.2.7. 3,5-Dimethyl-6,8-distyryl-6,7,8,9-tetrahydro-5*H*-[1,2,4]triazolo[4,3-*d*][1,4]diazepine **(4g)**

m.p. 210-212 °C, Yield 80 %. FTIR (KBr, cm^{-1}) ν_{max}: 3400 (-NH), 2959 (Ar-CH), 1603 (-C=N), 1457 (-C=C), 1256 (-N-N), 1143 (-C-N-C); ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.4 (d, J = 5 Hz, 3H, CH_3), 2.23 (s,

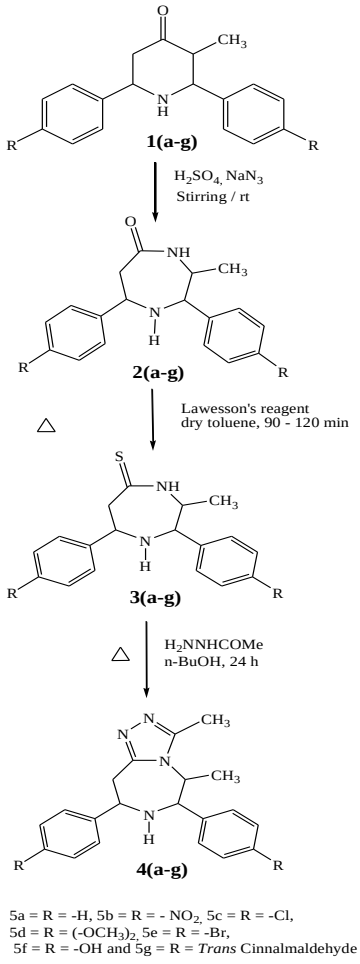
3H, triazole-CH_3), 7.5 (m, 10H, Ar-H); ^{13}C NMR (DMSO-d_6, 125 MHz): 160.90, 132.68, 129.88, 126.88, 113.49, 55.49, 10.21, 9.79; MS: m/z 370 [M+1]. Anal. Calcd for C, 74.17; H, 7.51; N, 14.91. Found: C, 74.57; H, 7.57; N, 14.83.

1.4. Anti-inflammatory Activity

1.4.1. Carrageenan Induced Hind Paw Edema Method [13]

Albino rats of either sex weighing 150-250 gms were divided into six groups of six animals each. Group one served as control which received only saline. Group two animals received the standard drug indomethacin (10 mg/kg po). The remaining groups of animals were administered with test drugs (50 mg/kg po). All the drugs were administered orally. After one hour of the administration of the drugs, 0.1 ml of 1 % w/v carrageenan solution in normal saline was injected into the sub-plantar region of the left hind paw of the rat. The paw volume of the rats were measured in the digital plethysmometer (Ugo basile, Italy) at the end of 0 min and 180 min. The percentage increase in paw edema of the treated group was compared with that of the control and the inhibitory effect of the drugs were studied. The relative potency of the drugs under investigations was calculated based upon the percentage inhibition of inflammation.

Inspired by the biological significance of diazepine and triazole derivatives, we have synthesized some new triazolodiazepine derivatives following the scheme (Scheme **1**).



SCHEME

Scheme 1 Synthesis of Triazolodiazepine Derivatives

III. RESULTS AND DISCUSSION

The IR spectra of the compound viz., 3,5-Dimethyl-6,8-diphenyl-6,7,8,9-tetrahydro-5H-[1,2,4]triazolo[4,3-d][1,4]diazepine (**4a**) exhibited characteristic bands at 1109 cm^{-1}, 1250 cm^{-1}, 1450 cm^{-1}, 1661 cm^{-1} and 3440 cm^{-1} indicative of the stretching frequencies of -C-N-C, -N-N, -C=C, -C=N and -N-H groups respectively. The Ar-CH stretching of the compound **4a** is observed at 2924 cm^{-1}. The IR spectra of compound **4b** also showed significant bands at 1283 cm^{-1} (-N-N), 1377 cm^{-1} (-C=C), 1654 cm^{-1} (-C=N), 3039 cm^{-1} (Ar-CH) and 3300 cm^{-1}(-NH). The presence of nitro group in the compound **4b** is evidenced by the appearance of an absorption band at 1350 cm^{-1}. The presence of C-N-C stretching is evidenced by the

appearance of an absorption peak at 1115 cm^{-1}. All the seven triazolodiazepine compounds showed a broad absorption band around 3400 cm^{-1} for the NH linkage. The compound **4c** shows an absorption band at 660 cm^{-1} for C-Cl linkage. A broad band appearing at 3298 cm^{-1} is indicative of the presence of -OH group in the compound **4f**.

The proton NMR spectra of the triazolodiazepine derivatives synthesized in the present research work gave convincing evidence to the assigned structure of the compounds. A critical analysis of the proton NMR spectrum of the compound viz., 3,5-Dimethyl-6,8-diphenyl-6,7,8,9-tetrahydro-5*H*-[1,2,4]triazolo[4,3-*d*][1,4] diazepine (**4a**) shows a doublet at δ 1.32 (J = 7 Hz) indicative of the methyl protons attached to the diazepine ring. A sharp singlet observed at δ 2.5 may be assigned to the methyl protons attached to the triazole ring. The appearance of double doublets at δ 3.60 (J = 3.5 Hz) and δ 3.43 (J = 8 Hz) may be due to the H6a and H6b protons of the diazepine ring. The H2 proton appears as a doublet at δ 4.1 (J = 9 Hz), whereas the H3 proton appears as a triplet at δ 4.9 (J = 7 Hz). The doublet appearing at δ 4.24 (J = 6 Hz) can be assigned to the H7 proton. The aromatic protons appear as a multiplet in the range δ 7.25-7.50. The proton NMR spectrum of the compound **4b** shows a doublet at δ 1.44 (J = 6 Hz) corresponding to the methyl protons attached to the diazepine ring. A singlet observed at δ 2.2 may be assigned to the methyl protons attached to the triazole ring. A doublet observed at δ 3.67 (J = 5 Hz) and a double doublet observed at δ 3.49 (J = 7.5 Hz) are assigned to the H6a and H6b protons respectively. The H2 and H3 protons of the diazepine ring are observed as doublets at δ 4.15 (J = 9 Hz) and 4.45 (J = 7 Hz) respectively. A multiplet centered on δ 4.35 is attributed to the H7 proton. The aromatic protons of the compound appear as a multiplet in the region around δ 7.1-7.6.

The methyl protons of the compound (**4c**) attached to the triazole ring and diazepine ring are observed as a singlet and a doublet at δ 2.23 and δ1.33 (J = 6.5 Hz) respectively. As expected, the H6a and H6b protons appeared as double doublets centered on δ 3.61 (J = 3 Hz) and δ 3.41 (J = 8 Hz) respectively. The double doublet centered on δ 4.15 (J = 3 Hz) is attributed to the H2 proton. The H7 proton appeared as a doublet at δ 4.25 (J = 4.5 Hz). The multiplet centered on δ 5.01 may be assigned to the H3 proton. The aromatic protons appear as a multiplet centered on δ 7.5. In the proton NMR spectrum of the compound, viz., 6,8-Bis(3,4-dimethoxyphenyl)-3,5-dimethyl-6,7,8,9-tetrahydro-5*H*-[1,2,4]triazolo[4,3-*d*] [1,4] diazepine (**4d**), the appearance of an intense peak at δ 3.9 is assigned to the $–OCH_3$ protons. The methyl protons attached to the diazepine ring show a doublet at δ 1.50 (J = 6.5 Hz). A broad singlet appearing at δ 1.98 may be assigned to the methyl protons attached to the triazole ring. As discussed earlier, the H6a and H6b protons appear as doublets at δ 3.65 and δ 3.48 respectively. A doublet appearing at δ 3.75 (J = 10 Hz) is attributed to the H2 proton. A broad singlet appearing at δ 4.76 may be assigned to the H3 proton. The H7 proton exhibits a doublet at δ 4.02 (J = 11.5 Hz). The aromatic protons of the compound appear as a multiplet centered on δ 6.9.

The presence of a methyl group attached to the triazole ring in the compound (**4e**) is evidenced by the appearance of a sharp singlet at δ 2.48. The doublet appearing at δ 1.42 (J = 7.5 Hz) may be attributed to the methyl protons attached to the diazepine ring. As stated elsewhere, the H6a and H6b protons of the diazepine ring show doublets and double doublets at δ 3.65 (J = 4 Hz) and δ 3.46 (J = 8 Hz) respectively. The H2 and H3 protons appear as doublets at δ 4.12 (J = 9 Hz) and δ 4.47 (J = 7.5 Hz) respectively. The multiplet centered on δ 4.32 is assigned to the H7 proton of the diazepine ring. The aromatic protons of the compound appear as a cluster of signals between δ 7.1-7.6.

The ^{13}C NMR spectrum of the compound, viz., 6,8-Bis(3-chlorophenyl)-3,5-dimethyl-6,7,8,9-tetrahydro-5*H*-[1,2,4]triazolo[4,3-*d*][1,4]diazepine **(4c)** exhibited expected signals. The triazole C3 and triazole C5 signals of the compound were recorded at δ 146.64 ppm (C3) and δ 153.94 ppm (C5) respectively. The carbon signals at 14.80 ppm and 18.21 ppm are attributed to the methyl carbons attached to the triazole ring and the diazepine ring respectively. The CH_2 carbon atom of the diazepine resonates at 32.31 ppm. The C2, C7 and C3 carbon absorptions are observed at 58.83, 63.33 and 64.67 ppm respectively. The ipso carbon atoms to which the electronegative chlorine atoms attached, show signals at 133.66 and 133.91 ppm. The carbon atoms of the phenyl ring which is attached to the diazepine ring show carbon signals at 140.11 and 144.26 ppm. The different aromatic carbon atoms of the phenyl ring are observed around 125.91-131.20 ppm.

The expected carbon signals appear in the ^{13}C NMR spectrum of the compound **4e**. The carbon signals at 10.82 and 16.19 ppm can be assigned to the methyl carbon atoms attached to the triazole and the diazepine ring respectively. The carbon peak at 23.33 ppm is attributed to the CH_2 carbon atom of the diazepine ring. The carbon signals appearing at 51.98, 57.77, and 63.42 ppm are due to the C2, C7 and C3 carbon atoms of the diazepine ring respectively. The ipso carbon atoms to which bromine is attached, show carbon signals at 120.74 and 120.35 ppm. The other carbon atoms of the phenyl ring are observed in the range 121.03-132.64 ppm. The C3 and C5 carbon atoms of the triazole ring show carbon signals at 140.17 and 143.39 respectively. The molecular ion peaks observed at the corresponding molecular weight in the mass spectra of the compounds confirm the structure assigned to the compounds.

3.2 Anti-inflammatory Activity

The anti-inflammatory activity of the test compounds by Carrageenan Induced Paw Edema Method is represented in tables (Table **1)** and the corresponding figures are given in the figures (Figure **1)**. Inflammation is considered as a primary physiologic defense mechanism that helps body to protect itself against infection, burn, toxic chemicals, allergents or other noxious stimuli. An uncontrolled and persistent inflammation may act as an etiologic factor for many of this chronic illness. Although it is a defense mechanism, the complex events and mediators involved in the inflammatory reaction can induce, maintain or aggravate many diseases [13]. Edema which develops after carrageenan inflammation is a biphasic event. The initial phase is attributed to the release of histamine and serotonin. The edema maintained between the first and the second phase is due to kinin like substances. The second phase is said to be promoted by prostaglandin like substances. It has been reported that the second phase of edema is sensitive to drugs like hydrocortisone, phenylbutazone and indomethacin [14]. Currently used antiinflammatory drugs are associated with some severe side effects. Therefore, the development of potent antiinflammatory drugs with fewer side effects is necessary.

Among the triazolodiazepine compounds **4a, 4c, 4e and 4g**, the compound **4c** is showing more activity (45 %) when compared to other compounds (**Table 1**). From the values of percentage inhibition, it is evident that the substitution of functional groups, such as -Cl, -Br, -OH, $-NO_2$ and $-OCH_3$ groups has enhanced the antiinflammatory activity of the compounds. It is observed that introducing -Cl group has shown enhanced the antiinflammatory activity of the compound **4c** remarkably.

Table **1,** Anti-inflammatory activity of triazolodiazepine derivatives by carrageenan induced paw edema method

Treatment Group	Paw Thickness at 0 hr (mm)	Paw Thickness at 3 hr (mm)	% Inhibition
Control	0.53 ± 0.01	1.87 ± 0.03	--
Indomethacin	0.66 ± 0.005	0.94 ± 0.01	79
4a	0.63 ± 0.03	1.65 ± 0.01	22
4c	0.68 ± 0.01	1.42 ± 0.05	45
4e	0.58 ± 0.01	1.46 ± 0.01	34
4g	0.64 ± 0.02	1.53 ± 0.01	33

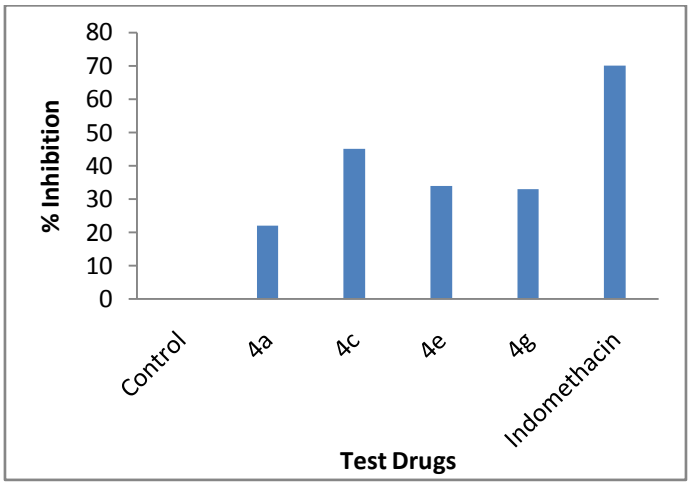


Figure 1 Anti-inflammatory activity of triazolodiazepine derivatives by carrageenan induced paw edema method

IV. CONCLUSION

In the present research work, some novel triazolodiazepine derivatives were synthesized. The compounds were synthesized from piperidones via diazepine derivatives. The structures of the triazolodiazepine compounds were established by FT-IR, ^{1}H NMR, ^{13}C NMR, mass and elemental analysis. The antiinflammatory activity of the representative compounds was tested against Carrageenan Induced Paw Edema Method. Indomethacin was used as the standard drug. The results showed that the synthesized compounds possess fairly good anti-inflammatory activity. However, the activity is less than the standard drug.

Acknowledgements

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