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Exceedingly simplistic one-pot protocol to the synthesis of [1, 5]-benzodiazepine and [1, 5]-benzothiazepine annulated derivatives of carbazolo condensed azepinones

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Abstract

Purpose: A new series of benzodiazepine and benzothiazepine annulated derivatives of carbazolo condensed azepinones were synthesized.

Methodology: Synthesis was done through a one-pot approach. The structure of these compounds was established based on their analytical IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. The antimicrobial activity of the synthesized drugs was evaluated by the disc diffusion method.

Main Findings: The activity index and zone of inhibition were also examined in comparison to standard drugs fluconazole and streptomycin. The synthesized compound has gained much importance due to its diverse biological activities.

Implications: One-pot method is a highly innovative strategy, which has been easy to operate, requires inexpensive material and in applying to a wide range of functionalized substrates.

INTRODUCTION

The heterocyclic ring bearing seven atoms is considered remarkable chemical properties which are easily obtained from five and six-membered systems and these seven-membered compounds no longer belong to esoteric species. The literature on the epidemiology of benzodiazepine use is broad and is distinguished by a very substantial agreement among diverse sources of information about how these drugs are used. The benzodiazepine is a privileged nucleus whose derivatives showed significant therapeutic and biological activities. This nucleus is widely used as antianxiety (Randall et al. 1974), sedative (Fryer et al. 1991), antidepressive (Devi et al. 1988), anticonvulsant (Narayana et al. 2006), neuroleptic and hypnotic agents (Hussenether et al. 2004) Over the year, the heterocycles containing benzodiazepines system has emerged as a significant pharmacophore accomplished with such properties which have found application as an anti-inflammatory (Roma et al. 1991), antiviral (Kavali et al. 2000), anti-HIV-1 (Di Braccio et al. 2001), antimicrobial (Kumar et al. 2007), and antitumor (Kamal et al. 2008), activities. Benzodiazepine derivative is shown in highly pharmacologically active molecules. Nevirapine **(I)** [fig:1] bearing a 1,5-benzodiazepine nucleus is widely used for treating HIV infection, (Nawrocka et al. 2001 and Braccio et al. 2001) clobazam possesses an antiepileptic agent (Kuch et al. 1979) and clozapine act as antipsychotic agents (Beasley et al. 1996).

The significant importance of 1, 5-benzothiazepine moiety has been well well-known as exemplified by a large number of therapeutic compounds which have been patented, as a medicinal utility (Grandolini et al. 1999). A various member of this nucleus has been extensively used as an antihypertensive, antiasthmatic, analgesic, cardiovascular modulator (Kamble et al. 2008 and Inagaki et al. 2000), a vasodilator (Nagao et al. 1973), platelet aggregation inhibitor and Ca antagonist, antiulcer (Yamamoto et al. 1986), anti amnesia, antidementia (Raval et al, 2008), antibacterial, antifungal (Mane et al. 1983) and insecticidal activity (Cherkupally et al. 2008) Diltiazem **(II)** [fig:1] is used in the treatment of angina pectoris, hypertension, arrhythmias and other related cardiac disorders. It also helps to increase the supply of oxygen and blood to the heart (Narta et al. 1990 and Ganjali et al. 2008) Thaizesim have a psycho toxic effect (Opera et al. 2001) Clentiazem act as an antiatherogenic agent (Hagiwara et al. 1997) Clothiapine is very active on 5-HT_2 receptors, is an antimuscarinic potential.

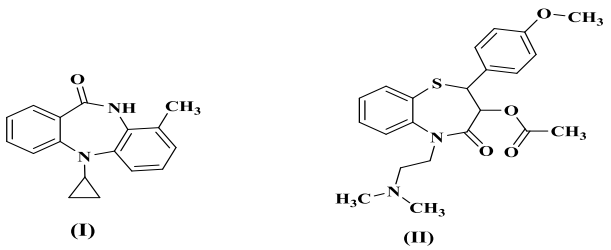
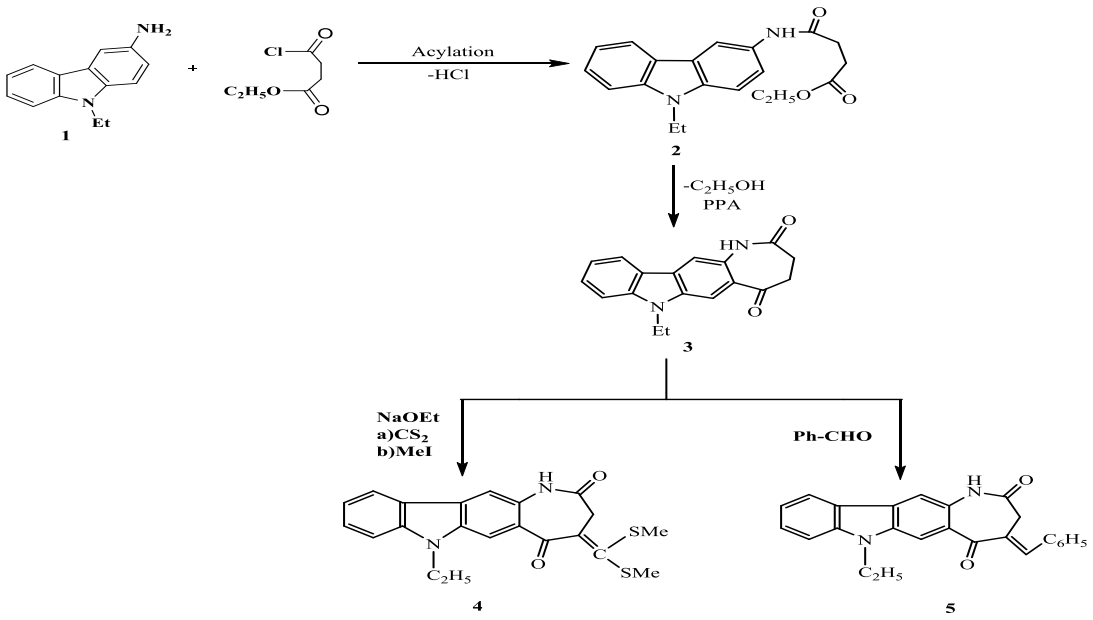
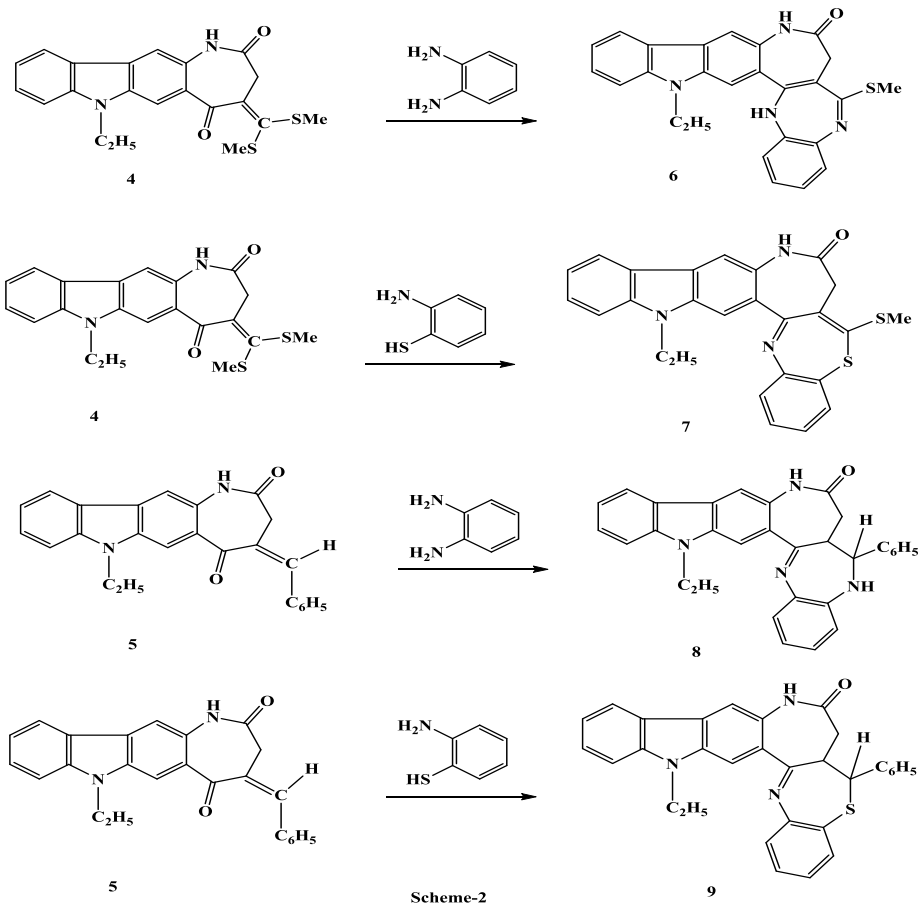


Fig. 1



Scheme-1



Scheme-2

EXPERIMENTAL SECTION

Materials

Melting points were measured on the melting point apparatus BUCHI. The IR spectra were determined on FTIR spectrometer Agilent tech. ^{1}H-NMR and ^{13}C-NMR spectra were recorded in $CDCl_3$ solvent on Bruker DRX-400 MHz spectrometer with TMS as internal reference (value expressed δ in ppm). The purity of all the compounds was checked by thin-layer chromatography in the solvent system (1:9 methanol: benzene). Mass spectra were recorded on waters, QT-OF micromass (LCMS) mass spectrometer.

Synthesis

Synthesis of ethyl 4-(9-ethyl-9H-carbazol-3-ylamino)-4-oxobutanoate (2)

A mixture of 3-Amino-9-ethyl carbazole (**1**) (2.10 g., 0.01 mol) and succinyl chloride derivatives (1.64 g., 0.01 mol) was refluxed in dry pyridine for one hour. The reaction mixture was cooled to room temperature and poured slowly into ice-cold water. The solid mass was filtered washed with cold water and recrystallized with hot water containing a few drops of methanol to give **2** (2.82 g., yield 83%), m.p. 89-90^{o}C.

Synthesis of 7-ethyl-3, 4- dihydroazepino [3, 2-b] carbazol-2, 5 (1H, 7H)-dione (3)

To a suspension of Ethyl 4-(9-ethyl-9H-carbazol-3-ylamino)-4-oxobutanoate **(2)** (2.58g, 0.006 mol), phenylpropanolamine (PPA) (5g.) was heated to reflux for 4h at 150-160^{o}C. The completion reaction was checked by TLC. The reaction mixture was cooled to 20^{o}C and sodium carbonate solution was added to make it alkaline. The crude product was extracted with ethyl acetate (3x10ml). The reaction mass was dried over anhydrous magnesium sulphate and concentrated under reduced pressure. The crude material was purified by column chromatography on silica gel using $CHCl_3$ as an eluent to give **3** (1.32 g., yield 59%), m.p. 158-160^{o}C.

IR (KBr) cm^{-1} 3340[NH str.], 2946[C-H str.ArH], 1712 [C=O], 1704[C=O str.], 1458[C-H str. CH_3], 1072[C-N str.]. **^{1}H-NMR($CDCl_3$) δ,** 8.0(s, 1H), 7.78 (s, 1H,), 7.63(s, 1H,), 7.55(d, 1H,), 7.40(d, 1H) ,7.08(t, 1H), 7.00(t, 1H), 3.89(q, 2H), 2.93(t, 2H), 2.42(t, 2H), 1.51(t, 3H). **^{13}C-NMR (400 MHz, $CDCl_3$)** δ, 171.12, 134.12, 122.21, 120.11, 119.20, 112.18, 110.09, 109.05, 38.23, 34.64, 27.56, 14.45. **MS: [m/z]** 292 (19%, M); Anal. Calc. for $C_{18}H_{16}N_2O_2$: C, 73.95/73.63; H, 5.52/ 5.49; N, 9.58/ 9.67.

Synthesis of oxoketenedithioacetals derivatives (4)

To a suspension of 7-ethyl-3, 4 dihydroazepino [3,2-b] carbazol-2,5 (1H,7H)-dione (**3)** (1.75g., 0.006 mol) and CS_2 (1ml, 0.006 mol) in dry benzene (4.0 ml). The reaction mixture was well stirred and a cooled suspension of *t*-BuOK (1.34 g., 0.012 mol) was added after 20 minutes. The completion of the reaction was monitored by TLC. The solution was allowed to stand at room temperature for 4 hours. To this solution, Methyl iodide (2ml, 0.012mol) was slowly added with constant stirring and with external cooling. The reaction mixture was again allowed to stand for 4 h. at room temperature with occasional shaking. The reaction mixture was heated to reflux for 4 hours in a water bath. The reaction mixture was cooled to room temperature and poured onto the crushed ice and the benzene layer was collected. The aqueous portion was extracted with benzene and the combined extracts were washed with water and dried over anhydrous sodium sulphate, the excess solvent was removed under vacuum to give **4** (1.12 g., yield 47%), m.p. 74-75^{o}C.

IR (KBr) cm^{-1} 3230[NH str.], 2949[C-H str.ArH], 1643 [C=O str.], 1731[C=O str.], 1680[C=C unsaturated],1540[C=C str. ArH], 1455[C-H str.-CH_3], 1020[C-N str.], 680[C-S str.] **^{1}H-NMR($CDCl_3$)δ,** 8.0(s, 1H), 7.74(s, 1H), 7.70(s, 1H), 7.55(d, 1H), 7.40(d, 1H), 7.08(t, 1H), 7.00(t, 1H), 3.89 (q, 2H), 2.90(s, 2H), 2.25(s, 6H), 1.51(t, 3H). **^{13}C-NMR (400 MHz, $CDCl_3$)** δ, 187.24, 155.67, 135.20, 121.13, 112.24, 111.10, 109.05, 103.14, 37.14, 21.18, 18.07, 14.61. **MS : [m/z]** 396[25%, M]; Anal. Calc. for $C_{21}H_{20}N_2O_2S_2$: C, 63.61/ 63.36; H, 5.08/ 5.05; N, 7.06/ 7.13; S, 16.17/16.25

Synthesis of *α,β*-unsaturated ketones (chalcones) (5)

A mixture of 7-ethyl-3, 4 dihydroazepino[3,2-b] carbazol-2,5 (1H,7H)-dione **(3)** (2.92g., 0.01mol), benzaldehyde (1.06g., .01mol) and fused sodium acetate (1.8g., 0.015mol) in glacial acetic acid was refluxed for 5 h. The reaction mixture was cooled to room temperature and poured into ice-cooled water. The reaction mass was filtered, washed with water and recrystallized from aqueous ethanol to give **5** (2.30g., yield 60%) m.p. 72-73^{o}C.

IR (KBr) cm^{-1} 3190[NH str.], 2855[C-H str.ArH], 1695 [C=O str.], 1704 [C=O str.], 1610[C=C str.], 1535[C=C str. ArH], 1180[C-N str.], 860[o-monosub] **^{1}H-NMR($CDCl_3$)δ,** 8.0(s, 1H), 7.74(s, 1H), 7.70(s, 1H), 7.55(d, 1H), 7.40(d, 1H), 7.30(s, 2H),7.21(t, 2H), 7.14(t, 1H), 7.08(t, 1H), 7.00(t, 1H), 3.89(q, 2H), 2.90(s, 2H), 1.51(t, 3H) **^{13}C-NMR (400 MHz,$CDCl_3$)δ,** 187.12, 139.23, 138.14, 128.34, 127.01, 125.17, 121.04, 112.09, 108.07, 104.62, 37.86, 28.45, 14.32. **MS : [m/z]** 380 (18%, M^{+}). Anal. Calc. for $C_{25}H_{20}N_2O_2$: C, 78.93/ 78.61; H, 5.30/ 5.28; N, 7.36/ 7.45

Synthesis of [1, 5]-benzothiazepino annulated derivatives of carbazolo condensed azepinones (6)

A mixture of *o*-phenylenediamine (0.54g, .005mole) and 4-(bis(methylthio)methylene)-7-ethyl-3,4-dihydroazepino [3,2-b]carbazole-2,5(1H,7H)-dione **(4)** (1.98g, .005mole) was refluxed in DMF for 15 hours at 150^{o}C. The reaction mixture was cooled at room temperature. The resulting solid was filtered and washed thoroughly with water. Recrystallized the desired product **6** from DMF (1.30g, yield 59%), m.p. 210-212^{o}C

IR (KBr) cm^{-1} 3380[NH str.], 2920[C-H str.ArH], 1730[C=O str.], 1580 [C=Nstr.], 1375[C-H str. CH_3], 1030[C-N str.], 680[C-S str.]. **^{1}H-NMR($CDCl_3$)δ,** 8.01(s, 1H), 7.78(s, 2H), 7.54(d, 1H), 7.40(d, 1H), 7.08(t, 1H), 7.00(t, 2H), 7.00(d, 1H), 6.6(t, 1H), 6.5 (d, 1H), 4.0(s, 1H), 3.89(q, 2H), 2.90(t, 2H), 2.25(s, 3H), 1.51(t, 3H).**^{13}C-NMR (400 MHz, $CDCl_3$)δ,** 163.26, 138.01, 137.14, 131.12, 126.20, 125.45, 123.50, 121.34, 119.76, 117.43, 113.40, 109.42, 103.20, 92.67, 37.08, 27.08, 15.06, 14.09. **MS : [m/z]** 439 (18%, M^+). Anal. Calc. for $C_{26}H_{22}N_4OS$: C, 71.21/71.50; H, 5.06/ 5.01; N, 12.78/ 12.34; S, 7.31/ 6.09

Synthesis of [1, 5]-benzothiazepino annulated derivatives of carbazolo condensed azepinones (7)

A mixture of *o*-aminothiophenol (0.62g, .005mole) and 4-(bis(methylthio)methylene)-7-ethyl-3,4-dihydroazepino [3,2-b]carbazole-2,5(1H,7H)-dione **(4)** (1.98g, .005mole) was heated to reflux in DMF for 15 hours. The reaction temperature was raised slowly up to 150^{o}C. The completion of the reaction was monitored by TLC. After cooling to ambient temperature the mixture was poured into ice water. The reaction mass was obtained by filtration, washed thoroughly with double distilled water, dried sodium sulphate and excess solvent was removed under reduced pressure. Further, it was recrystallized from DMF to give **7** (1.45g, yield 63%), m.p. 220-221^{o}C.

IR (KBr) cm^{-1} 3230[NH str.], 2923[C-H str.ArH], 1704[C=O str.], 1596[C=C], 1488[C=N], 1380[C-H str.-CH_3], 1157[C-N str.], 663[C-S str.];

^{1}H-NMR($CDCl_3$)δ, 8.0(s, 1H), 7.79(s, 2H), 7.55(d, 1H), 7.40(d, 1H), 7.2(d, 1H), 7.1(d, 1H),7.1(t, 1H), 7.08(t, 1H), 7.00(t, 2H), 3.89(q, 2H), 2.90(s, 2H), 2.25(t, 3H), 1.51(t, 3H); **^{13}C-NMR (400 MHz, $CDCl_3$)δ,** 168.24, 162.54, 138.21, 130.32, 126.22, 125.92, 123.42, 121.16, 119.20, 114.10, 110.26, 103.12, 98.15, 29.21, 37.05, 18.31, 14.68. **MS : [m/z]** 456 (21%, M^+). Anal. Calc. for $C_{26}H_{21}N_3OS_2$: C, 68.54/68.27; H, 4.65/ 4.69; N, 9.22/ 9.58; S, 14.08/ 14.42

Synthesis of [1, 5]-benzodiazepino annulated derivatives of carbazolo condensed azepinones (8)

A mixture of *o*-phenylenediamine (0.54g, .005mole) and *α,β*-unsaturated ketones (chalcones) **(5)** (1.90g, .005mole) in DMF was heated to reflux for 15 hours. The reaction temperature was raised slowly up to 150^{o}C. The completion of the reaction was checked by TLC. The reaction mixture was cooled to room temperature, solid was collected by filtration and washed thoroughly with distilled water. The solid mass was recrystallised with DMF to give **8** (1.45g, yield 61%), m.p. 180-182^{o}C.

IR (KBr) cm^{-1} 3230[NH str.], 2925[C-H str.ArH], 1704[C=O str.], 1600[C=N], 1540[C=C str.], 1285 [C-H str.], 1050[C-N str.]. **^{1}H-NMR($CDCl_3$)δ,** 8.0(s, 1H), 7.79(s, 2H), 7.55(d, 1H), 7.40(d, 1H), 7.30(d, 2H), 7.21(t, 2H), 7.14(t, 1H), 7.08(t, 1H), 7.00(t, 2H), 7.00(d, 1H), 6.6(t, 1H), 6.5 (d, 1H), 4.0(s, 1H), 3.89(q, 2H), 2.90 (s, 2H), 1.51 (t, 3H). **^{13}C-NMR (400 MHz, $CDCl_3$)δ,** 145.23, 139.24, 128.26, 126.01 121.12, 119.27, 114.02, 109.25, 103.06, 54.41, 37.81, 29.51, 14.09. **MS : [m/z]** 470 (17%, M). Anal. Calc. for $C_{31}H_{26}N_4O$: C, 79.12/ 78.08; H, 5.57/ 5.53; N, 11.91/ 11.50

Synthesis of [1, 5]-benzodiazepino annulated derivatives of carbazolo condensed azepinones (9)

To a mixture of *o*-aminothiophenol (0.62g, .005mole) and *α,β*-unsaturated ketones (chalcones) **(5)** (1.90g, .005mole) in DMF was refluxed for 15 hours at 150^{o}C. After completion of the reaction, the reaction mixture was cooled to room temperature. The crystalline solid was filtered, washed with distilled water and dried under a vacuum. The recrystallization of solid mass from DMF to give **9** (1.35g, yield 55%), m.p. 160-161^{o}C.

IR (KBr) cm^{-1} 3475[NH str.], 2965[C-H str.ArH], 1703[C=O str.], 1580[C=C str. ArH], 1545[C=N str.], 700 [C-S str.]. **^{1}H-NMR($CDCl_3$)δ,** 8.0(s, 1H), 7.79(s, 2H), 5.55(d, 1H), 7.40(d, 1H), 7.30(d, 2H), 7.21(t, 2H), 7.2(d, 1H), 7.14(t, 1H), 7.1(d, 1H), 7.1(t, 1H), 7.08(t, 1H), 7.00(t, 2H), 3.89(q, 2H), 2.90(s, 2H), 1.51(t, 3H). **^{13}C-NMR (400 MHz, $CDCl_3$)δ**, 163.12, 155.12, 153.21, 133.24, 128.21, 126.21, 121.20, 119.20, 111.22, 110.12, 103.37, 52.08, 37.06, 31.19, 14.23. **MS : [m/z]** 489 (12%, M^{++}). Anal. Calc. for $C_{31}H_{25}N_3OS$: C, 76.36/ 76.61; H, 5.17/ 5.22; N, 8.62/ 8.29

Biological studies

All the synthesized compounds were evaluated for their antimicrobial activity by the disc diffusion method at 100µg/ml concentration in DMF. Antifungal activity of the synthesized compound was evaluated against *Macrophomina phaseolina* (**MTCC 166**) and *Fusarium solani* (**MTCC 350**) and antibacterial activity against *Pseudomonas aeruginosa* (**MTCC 1688**) and *Bacillus cerus* (**MTCC 1305**). The zone of inhibition and activity index were compared to the standard drugs fluconazol' and 'streptomycin' respectively. The outcome of this study is presented in Table 1. All the synthesized compounds showed superior activity against the fungal and bacterial strains.

RESULTS AND DISCUSSIONS

Progress of strategy to assist the synthesis of numerous compounds based on the privileged pharmacophore is an intense area of research in organic and medicinal chemistry. The synthetic strategy shown in schemes **1** and **2** for the synthesis of **4**–**9** from the commercially available amino-substituted carbazole (**1**) and ethyl substituted succinyl chloride derivatives.

The oxoketenedithioacetals derivatives **(4)** were synthesized by the base-catalyzed condensation with carbon disulfide and methyl iodide. In likewise manner, the synthesis of *α,β*-unsaturated ketones (chalcones) **(5)** from the reaction of Diazepinone carbazoledione **(3)** with benzaldehyde. The intermediate **(4)** and **(5)** were obtained in average to good yield was confirmed by their IR, ^{1}H NMR spectra, which showed downfield multiplet at δ 7.64-7.24 for benzene ring proton

of *α, β*-unsaturated ketone structure **(5).** The adaptability of these novel compounds **4-5** in heteroannulations was evaluated by allowing these to react with *o*-phenylenediamine and *o*-aminothiophenol, which resulted in the corresponding [1,5]-benzodiazepine, [1,5]-benzodiazepine annulated derivatives of carbazole condensed azepinones **(6–9)** in desired yields.

Table 1: Antifungal and antibacterial activity of compounds **6-9**

Comp. no.	*M. phaseolina*		*F. solani*		*P. aeruginosa*		*B. cerus*	
	Zone of inhibition	% activity compared to the standard	Zone of inhibition	% activity compared to the standard	Zone of inhibition	% activity compared to the standard	Zone of inhibition	% activity compared to the standard
6	21	95.4	12.5	56.8	18	90	11	61.1
7	19.9	90.4	11.4	51.8	11	55	14	77.7
8	17	77.2	12.3	55.9	12	60	11	61.1
9	21	95.4	15.4	70.0	12.5	60.5	16	88.8

A key precursor diazepinone carbazoledione **(3)** was prepared from the commercially available amino-substituted carbazole **(1)** with the reaction of ethyl substituted succinyl chloride derivatives followed by Friedel-Crafts acylation, which underwent intramolecular cyclocondensation of the resulting intermediate with PPA. All the synthesized compounds gave desired results on elemental analysis as well as provided a clean and practical route to the incorporation of the bioactive pharmacophores of medicinal utility. All the synthesized compound was confirmed by IR, ^{1}H NMR, and Mass spectral data.

CONCLUSION

In conclusion, two noteworthy features of synthesis and biological studies of [1, 5]-benzodiazepino and [1,5]-benzothiazepino annulated derivatives of carbazole condensed azepinones have been apparent in our study. In this framework, on one side the planned strategy has provided an expedient single-step protocol for the synthesis of heterocycles such as [1,5]-benzodiazepino and [1,5]-benzothiazepino annulated derivatives of carbazole condensed azepinones nucleus from the corresponding oxoketene di thioacetal and chalcone derivatives as well as on the other side, has provided a simple, clean and sensible protocol to the integration of the biological active pharmacophores of therapeutic potential.

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