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Research Article

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Synthesis, characterization, anti-angiogenic and anti-oxidant activities of 1,5-benzothiazepin-4-(5*H*)-one derivatives

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ABSTRACT

*New 1,5-benzothiazepin-4-(5H)-one derivatives **(9a-9e)** have been synthesized. The anti-angiogenic and anti-oxidant properties of the new derivatives were then evaluated. All the compounds **(9a-9e)** exhibited very good inhibition of capillary proliferation, thus proving their anti-angiogenic properties. In addition, the in vitro antioxidant activities of these compounds were evaluated using diphenyl picryl hydrazine (DPPH), and NO (nitric oxide) assays, and the results were compared with butylated hydroxytoluene (BHT), a well known anti-oxidant. Compounds **(9a-9e)** showed excellent free-radical scavenging activities in the nitric oxide assay, thus proving to be more potent than BHT.*

Keywords: 1,5-benzothiazepin-4-(5*H*)-one, Anti-Angiogenic, Anti-oxidants**,** Suzuki coupling

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INTRODUCTION

1,5-benzothiazepines have potential chemotherapeutic importance as calcium channel blockers [1] anticancer [2], antihypertensive [3], antibacterial [4] agents, anti-HIV [5] and anti-hypertensive. [6] Some of the wellknown drugs are thiazesim **(fig 1)** [7] is used as an antidepressant, diltiazem and clentiazem **(fig 1)** [8, 9] are a well known angina-relieving calcium channel blocker.

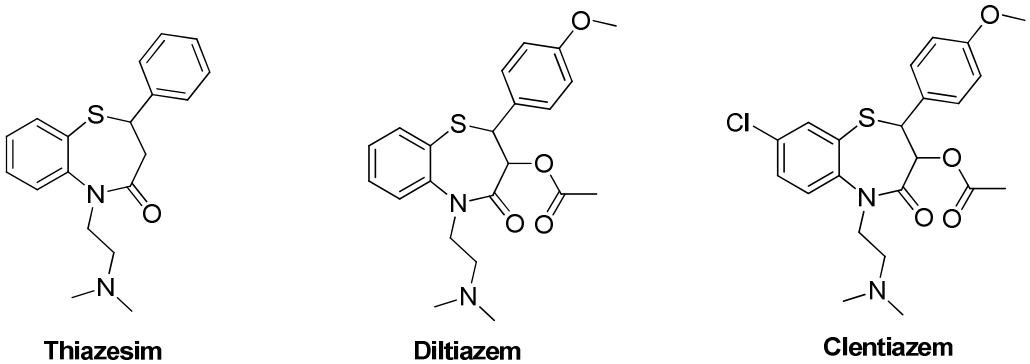


Figure 1: Examples of well known 1,5-benzothiazepines drugs

Angiogenesis is the development of new blood vessels from pre-existing vasculatures and this has been well recognized as an essential hallmark for the growth, invasion and metastasis of tumors. [10] Deregulation of angiogenesis under pathological conditions causes several diseases like diabetic retinopathy, rheumatoid arthritis, and cancer. [11] Thus, the inhibition of tumor angiogenesis provides a therapeutic strategy for treating different types of cancers. In many cases anti-angiogenic agents act as cytostatics and prevent the growth of tumors, though it is thought that they can be made more successful in cancer chemotherapy by combining with cytotoxic agents. [12]

Antioxidants are molecules inhibiting the oxidation of other molecules thereby preventing the cell death that occurs due to the release of free radicals. Reactive oxygen species generated in the cell during anti-oxidation initiate and promote tumor growth as well as other degenerative diseases such as heart attacks, strokes, arthritis and cataracts. [13] Minimizing oxidative damage may be an important approach to the primary treatment of these diseases, since antioxidants prevent the free radical formation, or interrupt an oxidizing chain reaction. Thus, antioxidants can be regarded as important factors for the treatment of cancer. Compounds functioning with groups endowed with potential antioxidant properties are considered as new drugs for chemoprevention and chemotherapy. [14] Therefore, the development of synthetic compounds, capable of scavenging free radicals, has been a great interest.

In continuation of our work on development of synthetic methodologies for bioactive molecules, [15,16] our previous work on synthesis and biological activities novel 1,5-benzothiazepin-4(5H)-one derivatives [17] prompted us to extend the work to synthesize and test the antioxidant and antiangiogenic activities of 1,5-benzothiazepin-4(5H)-one analogues.

EXPERIMENTAL SECTION

1.1 Materials and methods

All reagents were purchased from Sigma Aldrich Chemicals. Infrared (IR) spectra were recorded on a JASCO FT/IR-4100 spectrophotometer in KBr disc for solid compounds and nujol for liquids and are reported in reciprocal wave number (cm-1). 1H NMR spectra were recorded in DMSO-d6 at 300 and 400 MHz. The following abbreviations are used for structural assignments of 1H NMR: s, singlet; d, doublet; t, triplet; dd, doublet of doublets; m, multiplet and br, broad. Mass and purity were recorded on a LC–MSD-Trap-XCT. Thin layer chromatography was performed using 600 mesh silica gel plates, and visualization was effected with short wavelength UV light (254 nm). All other commercial reagents were used as received.

1.2 Biological activities

1.2.1 Antioxidant activities

1.2.1.1 DPPH radical scavenging assay

DPPH radical scavenging activity was carried out according to the method of Scherer *et al.* [18] Briefly, DPPH solution (1 mL, 0.1 mM in 95% ethanol) was mixed with different aliquots of **(9a-9e).** After vigorous shaking, the mixture was allowed to stand for 20 min at room temperature. Absorbance of the resulting solution was measured at 517 nm with a UV-VIS spectrophotometer (HITACHI, U-2900). Butylated hydroxyl toluene (BHT) was used as positive control. Radical scavenging potential is expressed as IC50 value, which represents the sample concentration at which 50 % of DPPH radicals are scavenged. Briefly, DPPH solution (1 mL, 0.1 mM in 95% ethanol) was mixed with different aliquots of **(9a-9e)**. After vigorous shaking, the mixture was allowed to stand for 20 min at room temperature. Absorbance of the resulting solution was measured at 517 nm with a UV-VIS spectrophotometer (HITACHI, U-2900). Butylated hydroxyl toluene (BHT) was used as positive control. Radical scavenging potential is expressed as IC50 value, which represents the sample concentration at which 50 % of DPPH radicals are scavenged.

1.2.1.2 Nitric oxide radical scavenging activity

Under physiological conditions, nitric oxide (NO) plays important roles as a neurotransmitter, vasodilator and in the immunological system it fights against tumor cells and infectious agents. During inflammatory reactions, NO is produced by the inducible enzyme NO synthase (iNOS) in cells like macrophages, hepatocytes, and renal cells after stimulation by lipopolysaccharide (LPS), tumor necrosis factor (TNF-α), interleukin (IL-1) or interferon (INF-γ), and acts as a defense and regulatory signal molecule. However, NO is pathogenic when present in excess, as it is a reactive radical itself, and directly damages normal tissues.26 Further, NO can also react with superoxide anion radical to form the even stronger oxidant, peroxynitrite.27 Among the samples studied, **(9a-9e)** showed highly

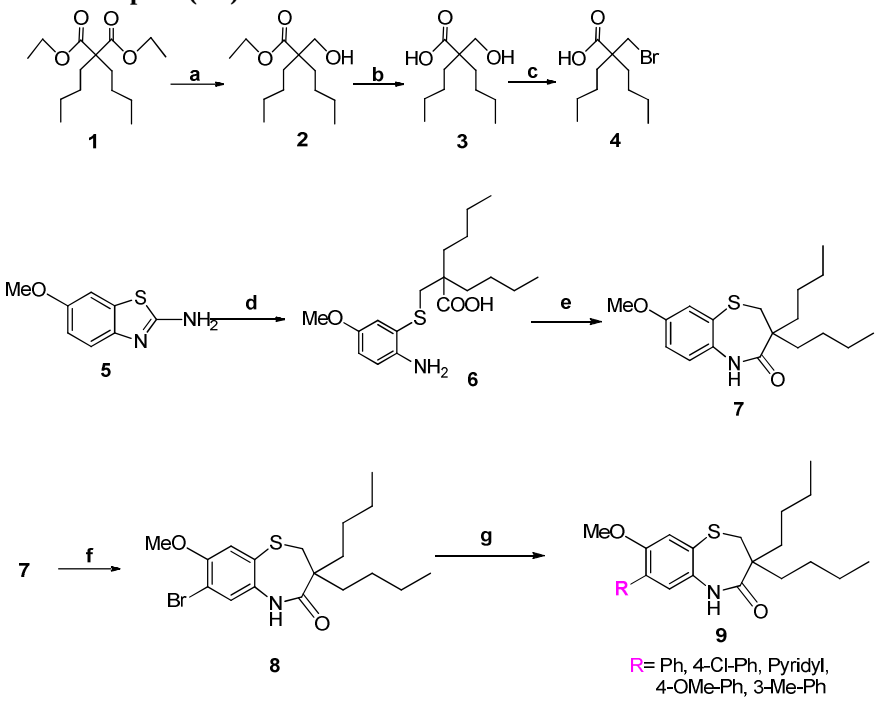
significant (P < 0.01) activity in scavenging NO radical with IC50 values of 83.4 and 106.4 µg/mL, respectively, when compared to 51.79 µg/mL recorded for BHT **(Table 1).**

1.2.2 Antiangiogenic activity

Fertilized eggs were obtained from IVRI, Bangalore, India. All chemicals were purchased from Sisco Research Laboratories, Mumbai, India and they were of analytical grade. Antiangiogenic effects of **(9a-9e)** compounds was studied according to the method of Auerbach *et a*,[19] Briefly, fertilized hens eggs were surface sterilized using 70% alcohol. The eggs were incubated in fan assisted humidified incubator at 37 ºC. On the 4th day, the eggs were cracked out into thin films of the hammock within a laminar flow cabinet and were further incubated. On day 5th when blood vessels were seen proliferating from the center of the eggs within the hammock, filter paper discs loaded with 100 µg of the compounds **(9a-9e)** were placed over the proliferating blood vessels and the eggs were returned to the incubator. Results of antiangiogenic effects of the compounds were noted after 24 h.

1.3 Synthetic method

Scheme 1: 1,5-benzothiazepin-4(5*H*)-one derivatives



***Reagents**: (a) DIBAL-H, $NaBH_4$; (b) NaOH, MeOH; (c) HBr, con. H_2SO_4; (d) aq.KOH, **4**, THF; (e) T_3P, Et_3N; (f) NBS, AIBN 60 °C, 6h; (g) Na_2CO_3 (aq), tetrakis, Pd(dppf), 120 °C, 12h.*

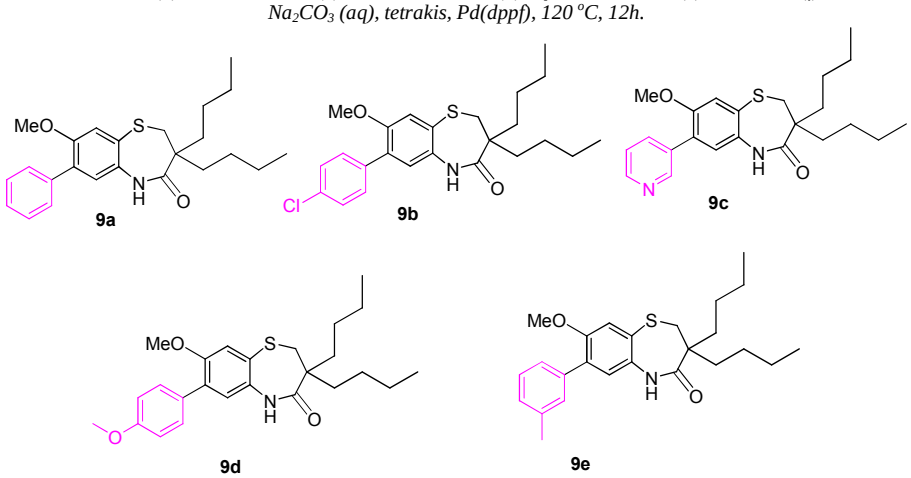


Figure 2: Structures of synthesized 1,5-benzothiazepin-4(5*H*)-one derivatives

1.3.1 Synthetic procedure

In these synthetic protocol compounds 1-7 were synthesized by using standard procedure of our research work [20].

Step-1: Procedure for the synthesis of Ethyl-[2-n-butyl-2-hydroxy methyl] hexanoate (2)

Diethyl di-n-butyl malonate (25 g, 0.09 mol) was dissolved in toluene (142.8 ml) under N_2 atmosphere and cooled to -60 to -70 ^oC. DIBAL-H (25% in toluene, 31.32 g, 0.22 mol) solution was added at this temperature for 4 h, stirred for 15min. Absolute ethanol (176.76 ml) was added slowly at -40 to -50 ^oC and the temperature was raised to 0 ^oC. $NaBH_4$ (3.49 g, 0.09 mol) was added portion wise below 0 ^oC and the reaction mixture was stirred at room temperature for one hour, cooled to 15 – 20 ^oC and saturated Na_2SO_4 solution was added. The reaction mass was stirred for an hour, filtered through celite bed, extracted with ethyl acetate (25×2), washed with brine, dried over sodium sulfate and concentrated under vacuum at 50-55 ^oC to afford the title compound ***2*** as thick syrup.

Pale yellow liquid, yield 19.0 g, 76%; FT-IR (Paraffin) υ/cm^{-1} : 3617, 2857, 1739; ^1H NMR (400MHz, DMSO-d_6): δ = 4.56(t, 1H, J=4.8), 4.01(q, 2H, J=7.2), 3.42(d, 2H, J=5.2), 1.36-1.49(m, 8H), 1.18(t, 4H, J=7.2), 0.80(t, 6H, J= 8.6); MS (ES) m/z (m+1) : 244.3

Step 2: General procedure for the synthesis of Ethyl-[2-n-butyl-2-hydroxy methyl] hexanoic acid (3)

To a stirred solution of Ethyl-[2-n-butyl-2-hydroxy methyl] hexanoate (15 g, 0.0652 mol) in methanol (67.5 ml), NaOH (5.86 g, 0.146 mol) solution was added and refluxed for 17hrs. Distilled off the methanol at 55-60 ^oC under vacuum, cooled to room temperature and washed with petroleum ether. Aqueous layer was taken back to the reactor, cooled to 10-15 ^oC and acidified with concentrated HCl to get pH 2. Extracted with dichloromethane (25×2) and washed with brine solution. Organic layer was dried over sodium sulfate and concentrated under vacuum at 40 – 45 ^oC to yield thick syrup.

Pale yellow liquid, yield 13.73, 92%; FT-IR(Paraffin) υ/cm^{-1} : 2857, 3359, 2857; ^1H NMR (400MHz, DMSO-d_6): δ = 11.94(s, 1H), 3.40(d, 2H, J=4.8), 1.34-1.46(m, 8H), 1.24(t, 4H, J=7.2), 0.80(t, 6H, J= 8.6); MS (ES) m/z(m+1) : 203.3

Step 3: General procedure for the synthesis of 2-bromomethyl-2-n-butyl hexanoic acid (4)

To a solution of 48% aq. hydrobromic acid con. H_2SO_4 was added slowly at below 25 ^oC over a period of 1h and then added ***2*** (10 g, 0.049 mol). The reaction mixture was heated to 90-95 ^oC and maintained at this temperature for 16 h and cooled to 15-20 ^oC. Extracted the reaction mixture with dichloromethane (25×2). Organic layer was concentrated under vacuum at 40 – 45 ^oC, residue was distilled using high vacuum pump. Product distills at 140-160 ^oC at 1mm pressure.

Pale yellow liquid, yield 4.36 g, 35%; FT-IR(Paraffin) υ/cm^{-1} : 2857, 2923, 512; ^1H NMR (400MHz, DMSO-d_6): δ = 12.62(s, 1H), 3.58(s, 1H), 1.46-1.59(m, 4H), 1.19-1.28(m, 8H), 0.80(t, 6H, J= 8.6); MS (ES) m/z(m+1) : 266.2

Step 5: General procedure for the synthesis of 2-{[(2-amino-5-methoxyphenyl)thio]methyl}-2-n-butyl hexanoic acid (6)

To a stirred solution of amino-6-methoxy benzothiazole (4 g, 0.022 mol) in water (44 ml) was added KOH (12.4 g, 0.22 mol). Refluxed the reaction mixture for 16 h under N_2 atmosphere. Cooled to 15 ^oC and added ***3*** (7.63 g, 0.028 mol) in THF (9.48 ml) slowly over a period of 30 min and then allowed the reaction mass to come to 20-25 ^oC and stirred for 10 h and then refluxed at 60-65 ^oC for 2 h. Cooled to 20-25 ^oC and diluted with water. Adjusted the pH of the reaction to 5 using 1.5N HCl, diluted with water and extracted with DCM (25×2). Organic layer was washed with water and then with brine solution and dried over sodium sulfate and solvent was removed under reduced pressure to yield a thick syrup.

Dark brown liquid, yield 3.6 g, 90%; FT-IR(Paraffin) υ/cm^{-1} : 3363, 3189, 2923, 2857 ^1H NMR (400MHz, DMSO-d_6): δ = 6.83(s, 1H), 6.64(dd, 2H, J=2.8, 0.4), 3.60(s, 3H), 2.95(s, 2H), 1.48-1.56(m, 4H), 1.13(t, 4H, J=6.4), 1.20(t, 4H, J=5.6), 0.80(t, 6H, J= 8.6); MS (ES) m/z(m+1)= 340.3

Step 6: General procedure for the synthesis of 3,3-di-n-butyl-8-methoxy-2,3-dihydro-1,5-benzothiazepin-4(5H)one (7)

To a stirred solution of ***4*** (3 g, 0.0088 mol) in ethyl acetate (27 ml), was added triethyl amine (1.95g, 0.0193 mol). Cooled to 0 ^oC and added T_3P (2.81 g, 0.0088 mol) at 0 ^oC. Stirred at 25 ^oC for 3 h and diluted with ethyl acetate.

Washed the above organic layer with 10% $NaHCO_3$ solution and then washed with water and brine and dried over sodium sulfate and concentrated under vacuum at 50 ^oC to obtain crude product which was purified on silica gel using ethyl acetate and hexane.

Brown solid, yield 3.6 g, 90%; FT-IR(KBr) υ/cm^{-1} : 3092, 2867, 1213, 1644,^{1}H NMR (400MHz, DMSO-d_6): δ =9.48(s, 1H), 7.00(d, 1H, J=8.4), 6.93(d, 1H, J=2.8), 6.82(q, 1H, J=2.8), 3.69(s, 3H), 2.94(s, 2H), 1.39-1.46(m, 4H), 1.14-1.39(m, 8H), 0.80(t, 6H, J= 8.6); MS (ES) m/z(m+1)= 322.0

Step 7: Synthesis of bromo derivative of 1,5-benzothiazepin-4(5H)-one (8)
To stirred solution of ***7***,(2g, 6.22 mmol) in DCM/acetonitrile (10 vol 1:1 ratio), was cooled to 5 ^oC and added *N*-bromosuccinimide (1.32g, 7.42 mmol) over a period of 15 mins. Brought the reaction mixture temperature to 25 ^oC, stirred for 2 hours and cooled to -5 ^oC for 1 hour, filtered, washed with cold acetonitrile and then dried under vacuum to yield an off white solid.

Off white solid, yield 4.5 g, 87%; FT-IR(KBr) υ/cm^{-1} : 3087, 2865, 1221, 1639,^{1}H NMR (400MHz, DMSO-d_6): δ =9.57(s, 1H), 7.29 (d, 1H), 7.07(s, 1H), 3.79(s, 3H), 2.95(s, 2H), 1.42-1.63(m, 4H), 1.14-1.40(m, 8H), 0.81(t, 6H, J= 8.6); MS (ES) m/z(m+2)= 400.0

Step 8: General procedure foe synthesis of 1,5-benzothiazepin-4(5H)-one derivatives (9a-9e)
A solution of bromo indazole 8 (0.4 g, 1 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride [Pd(dppf)Cl2] (10%) in anhydrous DME (10 mL) was stirred under a flow of argon for 1 h. To the solution were added sequentially corresponding boronic (2 mmol) in anhydrous DME (2.6 mL) and potassium carbonate (2 mmol) in water (2.5 mL). The mixture was heated to 80 °C for 2 h and allowed to cool. The reaction mixture was then poured into aqueous saturated $NaHCO_3$ solution and extracted with ethyl acetate. The organic layers were combined, washed with brine and dried over Na_2SO_4. The solution was concentrated in vacuo and the residue was purified by flash column chromatography on silica gel to give the desired product.

9a: White solid, yield 4.5 g, 87%; FT-IR(KBr) υ/cm^{-1} : 3099, 2866, 1218, 1649,^{1}H NMR (400MHz, DMSO-d_6): δ =9.48(s, 1H), 7.52 (d, 2H, J=7.6), 7.50(d, 2H, J=7.6), 7.42(t, 1H, J=7.8), 7.27(s, 1H), 7.09(s, 1H), 3.81(s, 3H), 3.01(s, 2H), 1.44-1.61(m, 4H), 1.15-1.44(m, 8H), 0.80(t, 6H, J= 8.6); MS (ES) m/z(m+1)= 398.34

9b: Off white solid, yield 4.5 g, 87%; FT-IR(KBr) υ/cm^{-1} : 3094, 2872, 1210, 1651,^{1}H NMR (400MHz, DMSO-d_6): δ =9.54(s, 1H), 7.78 (d, 2H, J=7.6), 7.52(d, 2H, J=7.8), 7.30(s, 1H), 7.10(s, 1H), 3.78(s, 3H), 2.98(s, 2H), 1.42-1.63(m, 4H); MS (ES) m/z(m+1)= 433.18
9c: Off white solid, yield 4.5 g, 87%; FT-IR(KBr) υ/cm^{-1} : 3087, 2872, 1217, 1644,^{1}H NMR (400MHz, DMSO-d_6): δ =9.51(s, 1H), 9.18(s, 1H), 8.69 (d, 1H, J=7.8), 7.32(s, 1H), 7.12(s, 1H), 3.83(s, 3H), 2.99(s, 2H); MS (ES) m/z(m+1)= 399.74

9d: Off white solid, yield 4.5 g, 87%; FT-IR(KBr) υ/cm^{-1} : 3096, 2870, 1310, 1216, 1651,^{1}H NMR (400MHz, DMSO-d_6): δ =9.49(s, 1H), 7.62 (d, 2H, J=7.6), 7.30 (s, 1H), 7.12 (s, 1H), 7.06 (d, 2H, J=7.6), 3.89 (s, 1H), 3.84 (s, 1H), 2.98(s, 2H); MS (ES) m/z(m+1)= 428.45

9e: Off white solid, yield 4.5 g, 87%; FT-IR(KBr) υ/cm^{-1} : 3089, 2877, 1218, 1654,^{1}H NMR (400MHz, DMSO-d_6): δ =9.58(s, 1H), 7.69 (s, 1H), 7.39 (t, 1H, J=7.8), 7.30 (d, 1H, J=7.6), 7.25 (s, 1H), 7.18 (d, 1H, J=7.6), 7.11 (s, 1H); MS (ES) m/z(m+1)= 412.34

RESULTS AND DISCUSSION

1.4.1 Antioxidant activities

Antioxidants are characterized by their ability to scavenge free radicals. The antioxidant properties of 1,5-benzothiazepin-4(5*H*)one analogues against various free radicals were investigated and compared with that of BHT at five concentration levels. The values of IC_{50}, and the effective concentration at which 50% of the radicals were scavenged were calculated. Lower IC_{50} value demonstrated greater antioxidant activity. IC_{50} value of BHT was also measured for comparison. The results are tabulated in **Table 1**.

All the compounds **(9a-9e)** showed enhanced antioxidant activities compared to BHT with nitric oxide assay at different concentrations (20-100 µg/mL), although these analogues exhibited low interaction with DPPH at 20-100µg/mL concentrations.

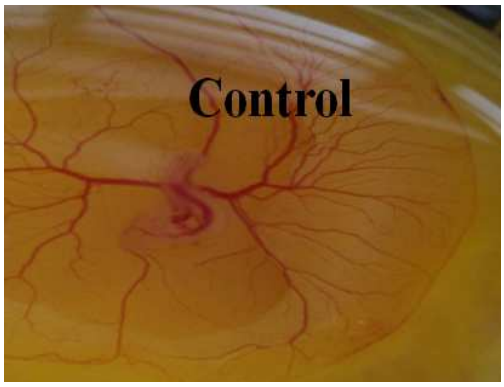
Table 1: Free radical scavenging activity of the compounds (9a-9e)

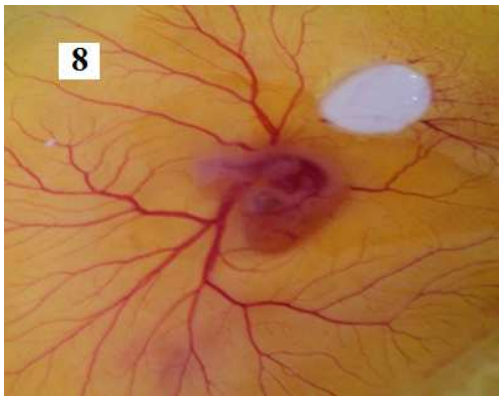
Compounds	IC_{50} values(µg/ml)	
	DPPH	NO
7	145.4	96.2
8	179.9	102.3
9d	162.3	98.76
9b	174.3	106.4
9a	138.4	99.2
9e	168.7	103.2
9c	118.3	83.4
BHT	51.79	121.48

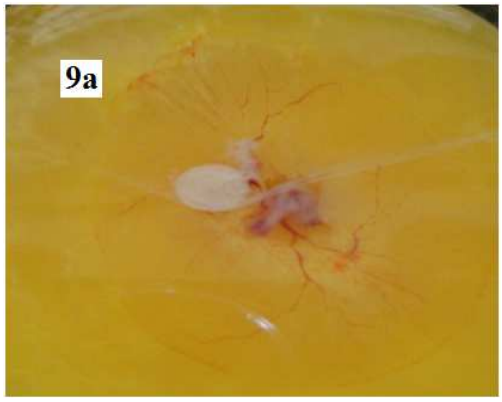
1.4.2 Antiangiogenic activity

Antiangiogenic treatment is one of the main methods of tumor treatment and control of pathological angiogenesis. [20] Pathological angiogenesis is regulated by targeting integrins which are predominantly expressed in most of the tumor cells and endothelial cells of blood vessels. The blocking of the vascular endothelial growth factor (VEGF) and its receptors in a signal transduction pathway also regulates angiogenesis. [21]

In the present investigation, all the compounds **(9a-9e)** showed a reduced proliferation of blood vessels in the shell less CAM assay model of developing embryos. The proliferation of microvessels was regressed in all treated group **(9a-9e) (Figure 1)** supporting their antiangiogenic activity.







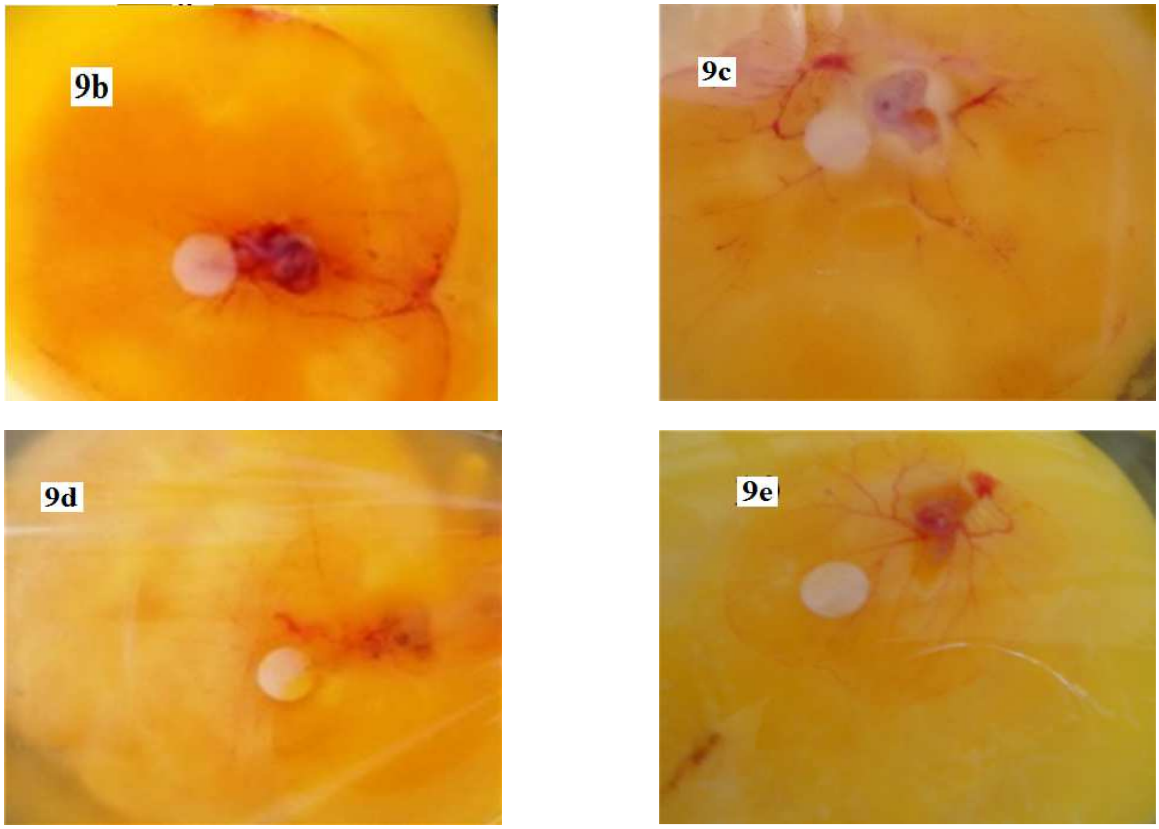


Figure 2: Inhibition of angiogenesis *in vivo* of 1,5-benzothiazepin-4-(5*H*)-ones (9a–9e) in shell- less CAM assay

CONCLUSION

In this research work, new 1,5-benzothiazepin-4(5*H*)-one derivatives have been synthesized and their antioxidant and antiangiogenic activities have been assessed. Oxidative stress and angiogenesis are important biological mechanisms by which tumorgenesis and tumor progression occur. Antiangiogenic determined in the shell-less CAM model revealed that **9a-9e** compounds are endowed with interesting anti-tumor activities. Further, antioxidants have proved to protect against oncogenic transformations resulting from radiation and free-radicals in experimental systems. The significant multiple antioxidant activities of 1,5-benzothiazepin-4(5H)-one derivatives, especially the high nitric oxide radical scavenging activity of **9a-9e**, appear to protect the cells by neutralizing or trapping reactive oxygen species and other free radicals. From this study, this can be concluded that rational design of 1,5-benzothiazepin-4(5H)-one derivatives can be developed to create useful anti-angiogenic and antioxidant agents that could lead further research work on this potent nucleus.

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