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Synthesis of various 1,5-benzothiazepine derivatives from 1-{4'-[(4''-methyl piperazinyl)diazenyl]phenyl}-3-(substitutedphenyl)prop-2-en-1-one and studies of their antimicrobial activity

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ABSTRACT

2-{4'-[(4''-methylpiperazinyl)diazenyl]phenyl}-4-(substitutedphenyl)-1,5-benzo thiazepine have been synthesized from 1-{4'-[(4''-methylpiperazinyl) diazenyl]phenyl}-3-(substitutedphenyl)prop-2-en-1-one with 2-mercaptoaniline. The compounds have been screened for their antimicrobial activities against different microorganisms at 128 µg/mL, 256 µg/mL and 512 µg/mL. The structures of novel synthesized compounds have been established on the basis of elemental analysis, IR, ^{1}H NMR and mass spectral data.

Key words: 2-mercaptoaniline, antimicrobial activity, spectral data

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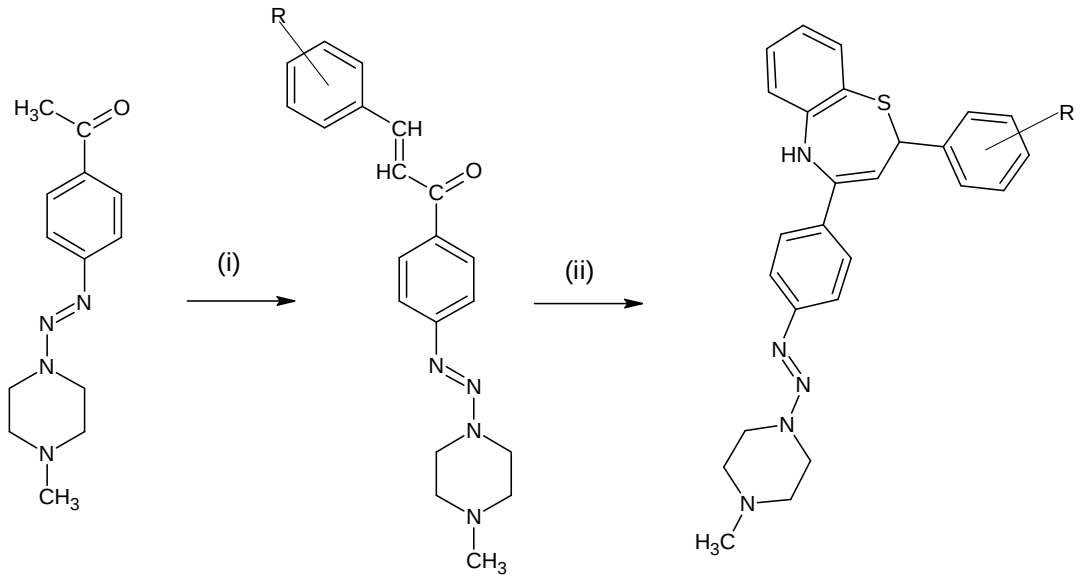
INTRODUCTION

Benzothiazepines have attracted as an important class of heterocyclic compounds in the field of drug and pharmaceutical research. Benzothiazepines are seven member heterocyclic compounds now a day they have received considerable attention and claimed various therapeutic activities and hence, they utilized in drug research [1-8]. Recently, attention is being directed to their synthetic methods, chemical and biological properties. Moreover, 1,5-benzothiazepine moiety is a privileged class of pharmacophore, as compounds bearing this structural unit possess a broad spectrum of biological activities such as anti-convulsant, Ca+2 channel antagonist, anti-anginal, anti HIV, squalene synthetase inhibitor,V2 arginine vasopressin receptor antagonist, HIV-1 reverse transcriptase inhibitor [9-11], antifungal [12], antimicrobial [13] and anti-HIV [14].

The starting compound 4-aminoacetophenone on a diazotization and coupling with N-methylpiperazine yield 1-{4'-[(4"-methylpiperazinyl) diazenyl]phenyl}ethan-1-one [15]. To a solution of 1-{4'-[(4"-methylpiperazinyl) diazenyl]phenyl}ethan-1-one in ethanol, KOH and various substituted aldehyde were added portion-wise with constant stirring to furnish the compound 1-{4'-[(4"-methylpiperazinyl)diazenyl]phenyl}-3-(substituted phenyl)prop-2-en-1-one [16,17] **2a-j**. Compound, upon cyclization with 2-mercaptoaniline yields the title compound in good yield. The structure of **3a-j** was established through IR, ^{1}H NMR and mass spectral data.

Preparation of 1-{4'-[(4"-methylpiperazinyl)diazenyl]phenyl}-3-(substitutedphenyl) prop-2-en-1-one **2a-j**.

Reaction Scheme-I



1 2a-j 3a-j

Scheme-I

Reagents and conditions: (i) Diff. aldehydes and 40% KOH (ii) 2-mercaptianiline, Gal.acetic acid

Where R= H, 2-OCH_3, 4-OCH_3, 3-Br, 2-Cl, 4-$N(CH_3)_2$, 3-NO_2, 2-OH, 3-OH-4-OCH_3, 3,4-OCH_3

MATERIALS AND METHODS

The melting points of synthesized compounds were determined in open capillary tubes using melting point apparatus, expressed in °C and are uncorrected. The IR spectra of compounds were recorded on Shimadzu Affinity-1 FTIR in KBr disc and absorption bands are expressed in cm^{-1}. The ^1H NMR spectra in DMSO-d6 or CDCl3 were recorded on Bruker WM 400FT MHz spectrometer and chemical shift were reported as parts per million (ppm) down field using TMS as internal standard. The purity of the compounds was checked by TLC on silica gel G plates using ethyl acetate: hexane (1:1) solvent system.

Experimental

To a solution of 1-{4'-[(4"-methylpiperazinyl) diazenyl]phenyl}ethan-1-one (0.01 mole) in ethanol, KOH and various substituted aldehyde (0.01 mole) were added portion-wise with constant stirring. The mixture was stirred for 2 h and then it was refluxed for 4-6 h. The reaction mixture was then cooled at room temperature and the contents were poured into crushed ice and dil. HCl was added. The separated product was filtered and recrystallized from ethyl acetate.

General Procedure

Preparation of 4-{4'-[(4"-methylpiperazinyl) diazenyl]phenyl}-2-(substituted phenyl)-2,5-dihydro-1,5-benzo thiazepine **3a-j.**

A mixture of 1-{4'-[(4"-methylpiperazinyl)diazenyl]phenyl}-3-(substitutedphenyl)prop-2-en-1-one (0.01 mol), 2-mercaptoaniline (0.01 mole) and glacial acetic acid (5 ml) in DMF was reflux for 8-9 h. The reaction mixture was then cooled and left overnight. The solid thus obtained was filtered and recrystallized from acetone.

*4-{4'-[(4"-methylpiperazinyl)diazenyl]phenyl}-2-(2"'-methoxyphenyl)-2,5-dihydro-1,5-benzothiazepine (**3a**).*
Reddish yellow powder (yield, 61%) mp: 222-224 ºC. IR (KBr): 3109 (N-H), 2920 (-CH_3), 1600 (-N=N-), 1233 (Ar-OCH_3). ^1H-NMR (400 Mhz, DMSO) δ: 2.56 (s, 4H, -$(CH_2)_2$(Piperazine ring)), 2.91 (s, 3H, N-CH_3), 3.04 (s, 4H, -

$(CH_2)_2$(Piperazine ring)) 3.73 (s, 1H, -NH(Benzothiazepine ring)), 3.86 (s, 3H, Ar-OCH_3), 5.61 (d, 1H, -Ha(Benzothiazepine ring)), 6.69 (d, 1H, -Hb(Benzothiazepine ring)), 7.21-8.09 (m, 12H, Ar-H). MS m/z: 471 (M^+). Anal. Calcd. For $C_{27}H_{29}ON_5S$, N, 14.84. Found: N, 14.90.

*4-{4'-[(4''-methylpiperazinyl)diazenyl]phenyl}-2-(4'''-methoxyphenyl)-2,5-dihydro-1,5-benzothiazepine (**3b**).*
Reddish yellow powder (yield, 58%) mp: 218-220 ºC. IR (KBr): 3114 (N-H), 2926 (-CH_3), 1598 (-N=N-), 1239 (Ar-OCH_3). ^{1}H-NMR (400 Mhz, DMSO) δ: 2.56 (s, 4H, -$(CH_2)_2$(Piperazine ring)), 2.90 (s, 3H, N-CH_3), 3.05 (s, 4H, -$(CH_2)_2$(Piperazine ring)) 3.70 (s, 1H, -NH(Benzothiazepine ring)), 3.88 (s, 3H, Ar-OCH_3), 5.63 (d, 1H, -Ha (Benzothiazepine ring)), 6.71 (d, 1H, -Hb(Benzothiazepine ring)), 7.23-8.12 (m, 12H, Ar-H). MS m/z: 471 (M^+). Anal. Calcd. For $C_{27}H_{29}ON_5S$, N, 14.84. Found: N, 14.92.

4-{4'-[(4''-methylpiperazinyl)diazenyl]phenyl}-2-(phenyl)-2,5-dihydro-1,5-benzothiaze-pine (**3c**).
Light Red powder (yield, 67%) mp: 189-191 ºC. IR (KBr): 3080 (N-H), 2925 (-CH_3), 1600 (-N=N-). ^{1}H-NMR (400 Mhz, DMSO) δ: 2.57 (s, 4H, -$(CH_2)_2$(Piperazine ring)), 2.92 (s, 3H, N-CH_3), 3.08 (s, 4H, -$(CH_2)_2$(Piperazine ring)), 3.76 (s, 1H, -NH(Benzothiazepine ring)), 5.65 (d, 1H, -Ha(Benzothiazepine ring)), 6.71 (d, 1H, -Hb (Benzothiazepine ring)), 7.26-8.15 (m, 13H, Ar-H). MS m/z: 441 (M^+). Anal. Calcd. For $C_{26}H_{27}N_5S$, N, 15.85. Found: N, 15.91.

*4-{4'-[(4''-methylpiperazinyl)diazenyl]phenyl}-2-(3'''-bromophenyl)-2,5-dihydro-1,5-benzothiazepine (**3d**).*
Reddish powder (yield, 66%) mp: 264-266 ºC. IR (KBr): 3082 (N-H), 2924 (-CH_3), 1600 (-N=N-), 710 (Ar-Br). ^{1}H-NMR (400 Mhz, DMSO) δ: 2.54 (s, 4H, -$(CH_2)_2$(Piperazine ring)), 2.94 (s, 3H, N-CH_3), 3.06 (s, 4H, -$(CH_2)_2$ (Piperazine ring)), 3.73 (s, 1H, -NH(Benzothiazepine ring)), 5.61 (d, 1H, -Ha(Benzothiazepine ring)), 6.66 (d, 1H, -Hb(Benzothiazepine ring)), 7.23-8.10 (m, 12H, Ar-H). MS m/z: 520 (M^+). Anal. Calcd. For $C_{26}H_{26}N_5SBr$, N, 13.45. Found: N, 13.53.

*4-{4'-[(4''-methylpiperazinyl)diazenyl]phenyl}-2-(2'''-chlorophenyl)-2,5-dihydro-1,5-benzothiazepine (**3e**).*
Reddish yellow powder (yield, 61%) mp: 164-166 ºC. IR (KBr): 3092 (N-H), 2933 (-CH_3), 1609 (-N=N-), 698 (Ar-Cl). ^{1}H-NMR (400 Mhz, DMSO) δ: 2.58 (s, 4H, -$(CH_2)_2$(Piperazine ring)), 2.91 (s, 3H, N-CH_3), 3.10 (s, 4H, -$(CH_2)_2$ (Piperazine ring)), 3.77 (s, 1H, -NH(Benzothiazepine ring)), 5.63 (d, 1H, -Ha(Benzothiazepine ring)), 6.73 (d, 1H, -Hb(Benzothiazepine ring)), 7.26-8.07 (m, 12H, Ar-H). MS m/z: 476 (M^+). Anal. Calcd. For $C_{26}H_{26}N_5SCl$, N, 14.71. Found: N, 14.79.

*4-{4'-[(4''-methylpiperazinyl)diazenyl]phenyl}-2-(4'''-dimethylaminophenyl)-2,5-dihydro-1,5-benzothiazepine (**3f**).*
Reddish yellow powder (yield, 58%) mp: 141-143 ºC. IR (KBr): 3090 (N-H), 2931 (-CH_3), 1604 (-N=N-). ^{1}H-NMR (400 Mhz, DMSO) δ: 2.33 (s, 6H, -$N(CH_3)_2$), 2.56 (s, 4H, -$(CH_2)_2$(Piperazine ring)), 2.90 (s, 3H, N-CH_3), 3.12 (s, 4H, -$(CH_2)_2$(Piperazine ring)), 3.77 (s, 1H, -NH(Benzothiazepine ring)), 5.63 (d, 1H, -Ha(Benzothiazepine ring)), 6.71 (d, 1H, -Hb(Benzothiazepine ring)), 7.26-8.09 (m, 12H, Ar-H). MS m/z: 484 (M^+). Anal. Calcd. For $C_{28}H_{32}N_6S$, N, 17.34. Found: N, 17.40.

*4-{4'-[(4''-methylpiperazinyl)diazenyl]phenyl}-2-(3'''-nitrophenyl)-2,5-dihydro-1,5-benzothiazepine (**3g**).*
Reddish powder (yield, 65%) mp: 126-129 ºC. IR (KBr): 3096 (N-H), 2937 (-CH_3), 1606 (-N=N-), 1350 (Ar-NO_2). ^{1}H-NMR (400 Mhz, DMSO) δ: 2.56 (s, 4H, -$(CH_2)_2$(Piperazine ring)), 2.88 (s, 3H, N-CH_3), 3.10 (s, 4H, -$(CH_2)_2$ (Piperazine ring)), 3.77 (s, 1H, -NH(Benzothiazepine ring)), 5.60 (d, 1H, -Ha(Benzothiazepine ring)), 6.73 (d, 1H, -Hb(Benzothiazepine ring)), 7.21-8.12 (m, 12H, Ar-H). MS m/z: 486 (M^+). Anal. Calcd. For $C_{26}H_{26}O_2N_6S$, N, 17.27. Found: N, 17.33.

*4-{4'-[(4''-methylpiperazinyl)diazenyl]phenyl}-2-(2'''-hydroxyphenyl)-2,5-dihydro-1,5-benzothiazepine (**3h**).*
Reddish yellow powder (yield, 66%) mp: 193-195 ºC. IR (KBr): 3521 (Ar-OH), 3098 (N-H), 2937 (-CH_3), 1600 (-N=N-). ^{1}H-NMR (400 Mhz, DMSO) δ: 2.57 (s, 4H, -$(CH_2)_2$(Piperazine ring)), 2.93 (s, 3H, N-CH_3), 3.15 (s, 4H, -$(CH_2)_2$(Piperazine ring)), 3.76 (s, 1H, -NH(Benzothiazepine ring)), 5.60 (d, 1H, -Ha(Benzothiazepine ring)), 6.71 (d, 1H, -Hb(Benzothiazepine ring)), 7.18-8.07 (m, 12H, Ar-H), 9.14 (s, 1H, Ar-OH). MS m/z: 457 (M^+). Anal. Calcd. For $C_{26}H_{27}ON_5S$, N, 15.30. Found: N, 15.36.

*4-{4'-[(4''-methylpiperazinyl)diazenyl]phenyl}-2-(3'''-hydroxy-4'''-methoxyphenyl)-2,5-dihydro-1,5-benzothiazepine (**3i**).*
Reddish powder (yield, 63%) mp: 148-150 ºC. IR (KBr): 3511 (Ar-OH), 3092 (N-H), 2933 (-CH_3), 1604 (-N=N-), 1223 (Ar-OCH_3). ^{1}H-NMR (400 Mhz, DMSO) δ: 2.55 (s, 4H, -$(CH_2)_2$(Piperazine ring)), 2.91 (s, 3H, N-CH_3), 3.11 (s, 4H, -$(CH_2)_2$(Piperazine ring)), 3.78 (s, 1H, -NH(Benzothiazepine ring)), 3.68 (s, 3H, Ar-OCH_3), 5.60 (d, 1H, -Ha(Benzothiazepine ring)), 6.70 (d, 1H, -Hb(Benzothiazepine ring)), 7.18-8.10 (m, 10H, Ar-H), 8.89 (s, 1H, Ar-OH). MS m/z: 487 (M^+). Anal. Calcd. For $C_{27}H_{29}O_2N_5S$, N, 14.36. Found: N, 14.42.

*4-{4'-[(4''-methylpiperazinyl)diazenyl]phenyl}-2-(3''',4'''-dimethoxyphenyl)-2,5-dihydro-1,5-benzothiazepine (**3j**).*
Reddish powder (yield, 69%) mp: 170-173 ºC. IR (KBr): 3092 (N-H), 2933(-CH_3), 1604 (-N=N-), 1255 (Ar-OCH_3). ^{1}H-NMR (400 Mhz, DMSO) δ: 2.53 (s, 4H, -$(CH_2)_2$(Piperazine ring)), 2.88 (s, 3H, N-CH_3), 3.09 (s, 4H, -$(CH_2)_2$ (Piperazine ring)), 3.72 (s, 1H, -NH(Benzothiazepine ring)), 3.61 (s, 3H, Ar-OCH_3), 5.68 (d, 1H, -Ha (Benzothiazepine ring)), 6.69 (d, 1H, -Hb(Benzothiazepine ring)), 7.16-8.14 (m, 10H, Ar-H). MS m/z: 501 (M^+). Anal. Calcd. For $C_{28}H_{31}O_2N_5S$, N, 13.96. Found: N, 14.03.

RESULTS AND DISCUSSION

Antibacterial activity

All the compounds **2a-j** was tested for *in vitro* screening against gram-positive *S. aureus* and gram-negative *E. coli* and *P. aeruginosa*. The minimum inhibitory concentration (MIC) was determined using disk diffusion method according to the standard procedure [18] at three-test concentrations 128 µg/mL, 256 µg/mL, 512 µg/mL. Inoculums of standard suspension (0.1 ml of the test organism strain which contains 10^6 bacilli/ml) were added. The tubes were incubated at 37ºC for 48 hr and then examined for the presence or absence of growth of the organism. The lowest concentration, which showed no visible growth, was taken as an end point minimum inhibitory concentration (MIC). The MIC levels of compounds against these organisms are given in **Table I**.

An examination of the data reveals that almost all the compounds showed antimicrobial activity in mild to moderate range.

Table 1 : Antimicrobial activity of the synthesized compounds (3a-j)

Compound	*E. coli*			*P. aeruginosa*			*S. aureus*			*C. albicans*		
	128 µg/mL	256 µg/mL	512 µg/mL	128 µg/mL	256 µg/mL	512 µg/mL	128 µg/mL	256 µg/mL	512 µg/mL	128 µg/mL	256 µg/mL	512 µg/mL
3a	-	-	+	-	-	+	-	-	+	-	-	-
3b	-	-	+	-	-	+	-	-	+	-	-	-
3c	-	+	+	-	+	+	-	+	+	-	-	-
3d	-	+	++	-	+	+	-	+	++	-	-	-
3e	-	+	++	-	-	++	-	+	++	-	-	-
3f	-	+	+	-	+	+	-	-	+	-	-	-
3g	-	-	+	-	-	+	-	-	+	-	-	-
3h	-	+	+	-	+	+	-	+	+	-	-	-
3i	-	-	+	-	+	+	-	-	+	-	-	-
3j	-	-	+	-	-	+	-	-	+	-	-	-

(-)< 6mm, (+) =7 – 10 mm, (++) =11 – 15mm, (+++) = 16 – 21mm, (++++) = 22 – 28mm

Antifungal activity

The antifungal activity of compounds has been assayed *in vitro* at a concentration of 128 µg/mL, 256 µg/mL and 512 µg/mL against *C. albicans*, which were maintained on nutrient agar slants, which were stored at 4ºC. None of the compounds was found to possess better activity than Dithane-M 45 **Table I**.

CONCLUSION

All compounds were found inactive against *E. coli*, *S. aureus*, *P. aeruginosa* and *C. albicans* at 128 µg/mL concentration.

At 256 µg/ml concentration, compounds **3d**, **3e** and **4d** were found to show moderate activity against *E. coli*. While compounds **3d**, **3e**, **4d** and **4e** showed moderate activity against *P. aeruginosa*. Compounds **4d** and **4e** were found

moderate active towards *S. aureus*. While compounds **3b-i**, **4a-c**, **4f**, **4g**, **5b-e**, **5g** and **5i** had showed mild activity towards *S. aureus*. All compounds were found inactive against *C .albicans* at 256 µg/mL concentration.

The screening data indicated that all the compounds were found to show mild to moderate activity against all bacterial species at 512 µg/mL concentration. While compounds **3d**, **3f**, **3g**, **4d**, **4g**, **5g** and **5h** were found to show mild activity towards *C.albicans* at 512 µg/mL concentration.

All compounds were found inactive against *E. coli*, *S. aureus*, *P. aeruginosa* and *C. albicans* at 128 µg/mL concentration.

At 256 µg/ml concentration, compounds **3c-d and 3h** were found to show mild activity against *E. coli*. While compounds **3c**, **3d**, **3f**, **3h** and **3i** showed mild activity against *P. aeruginosa*. Compounds **3c-e** and **3h** were found mild active towards *S. aureus*. All compounds were found inactive against *C .albicans* at 256 µg/mL concentration.
The screening data indicated that all the compounds were found to show mild to moderate activity against all bacterial species at 512 µg/mL concentration. While compounds **3e** was found to show moderate activity towards all bacterial species at 512 µg/mL concentration. Compound **3d** was show moderate activity against both *E. coli*. And *S. aureus* at 512 µg/mL concentration. No compounds were found active against *E. coli*, *S. aureus*, *P. aeruginosa* and *C. albicans* at 512 µg/mL concentration.

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