

Improved Method for the Synthesis of New 1,5-Benzothiazepine Derivatives as Analogues of Anticancer Drugs

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Abstract: (\pm)cis-2-(4-Methoxyphenyl)-3-hydroxy/methoxy-2,3-dihydro-1,5-benzothiazepin-4[5H/5-chloroacetyl/5-(4'-methylpiperazino-1')acetyl]-ones have been synthesized by the condensation of 2-aminobenzene thiols with methyl(\pm)trans-3-(4-methoxyphenyl)glycidate in xylene. The synthesized compounds have been characterized by elemental analyses and spectral data and screened for their antimicrobial activity.

Keywords: 1,5-Benzothiazepin derivatives, anticancer drugs.

Introduction

The importance of the 1,5-benzothiazepine nucleus has been well proved as illustrated by a large number of patents, as chemotherapeutic agents, available on it. A number of biological activities have been associated with it, such as antihypertensive [1,2], antiasthmatic [2,3], analgesic [4], cardiovascular [5], platelet aggregation inhibitor and Ca antagonist [2]. Recently Ahmed et al [6,7] patented 1,5-benzothiazepine derivatives as potential anticancer drugs.

With this in mind, some new 1,5-benzothiazepine derivatives have been synthesized in search of better therapeutic agents, by a convenient single pot method.

Results and Discussion

Synthesis

(\pm)cis-2-(4-Methoxyphenyl)-3-hydroxy-2,3-dihydro-1,5-benzothiazepin-4(5H)-ones (**3**) have been synthesized by the condensation of 2-aminobenzenethiols (**1**) with methyl (\pm)trans-3-(4-methoxyphenyl)glycidate (**2**) in xylene at 160°C for 16-20 hrs under a nitrogen atmosphere. Compounds **3** on methylation with dimethyl sulphate and alkali yielded (\pm)cis-2-(4-methoxyphenyl)-3-

methoxy-2,3-dihydro-1,5-benzothiazepin-4(5H)-ones (**4**). Compounds **4** on treatment with chloroacetylchloride gave (\pm)cis-2-(4-methoxyphenyl)-3-methoxy-2,3-dihydro-1,5-benzothiazepin-4-(5-chloroacetyl)-ones (**5**) which in turn afforded (\pm)cis-2,3-dihydro-1,5-benzothiazepin-4-[5-(4'-methylpiperazino-1')acetyl]-ones (**6**), on treatment with N-methylpiperazine. (Scheme 1).

The physical data of compounds **1** to **6** is given in Table-1.

In the IR spectra of compounds **3**, a broad band in the range 3600-3110 cm^{-1} was obtained due to the merged N-H and O-H stretching vibrations. Compounds **4** showed a less broad band, in the region 3180-3140 cm^{-1} due to the presence of only the N-H group. This band was absent in compounds **5** and **6**.

The N-H bending vibrations were observed as a sharp medium to strong band at 1540-1500 cm^{-1} in compounds **3** and **4**. The C-S-C linkage of the seven membered ring caused a weak and sharp absorption band at 800-760 cm^{-1} in all the compounds. The C=O group was observed as a strong and sharp band at 1660-1600 cm^{-1} in these compounds. The C-O-C linkage showed two sharp and strong bands at 1360-1340 cm^{-1} and 1070-1020 cm^{-1} due to asymmetric and symmetric vibrations respectively. The

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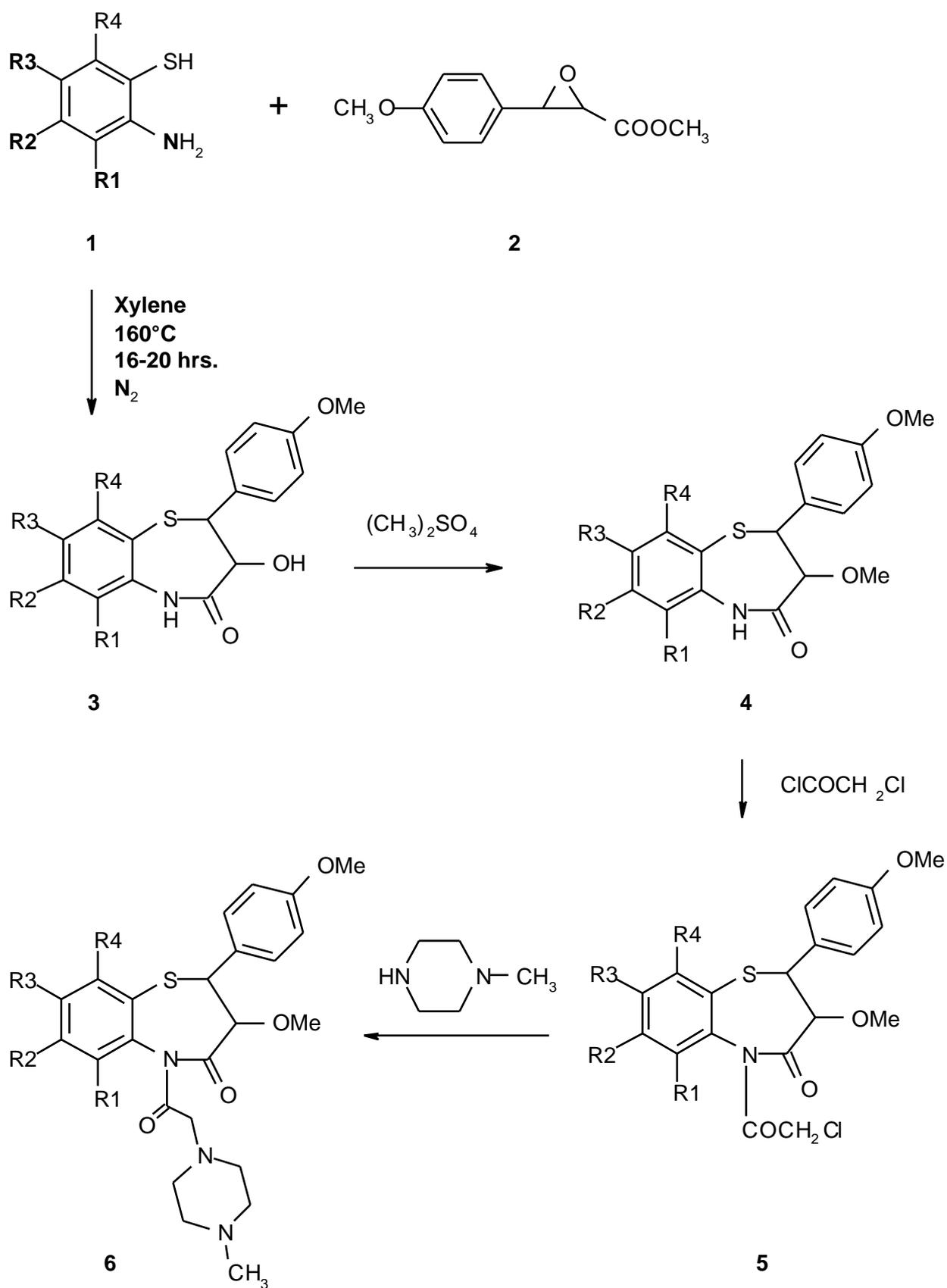
C-H (aliphatic and aromatic), C=C, C-Cl, stretching vibrations were observed at their usual positions. (Table 2).

In the ^1H NMR spectra of compounds **3** the -OH proton was found to be at 8.17-10.00 ppm. The proton of the -NH group was observed at 8.10-8.25 ppm, as a broad singlet. Two characteristic doublets at 2.35-2.92 ppm ($J=8$ Hz) and 3.05-3.44 ppm ($J=8$ Hz) were assigned to

cis-protons at C-2 and C-3. All the compounds showed a complex multiplet of aromatic protons in the range 6.00-7.90 ppm. Protons of the methoxy group were observed at 3.32-3.54 ppm. The piperazine protons were observed at 4.10-4.60 ppm in compounds **6**. The methyl protons, whenever present, were observed at their usual position (1.65-2.30 ppm) as a singlet (Table-3).

Table 1. Characterization data of 1,5-benzothiazepine derivatives.

Compd. No.	R1	R2	R3	R4	Molecular formula	Molecular Wt.	MP °C	Yield %	Elemental Analysis %		
									Calcd. C	(found) H	N
3a	H	H	OC ₆ H ₅	H	C ₂₂ H ₁₉ NO ₄ S	393	268-270	68	67.18 (67.21)	4.83 (4.87)	3.56 (3.51)
3b	H	Cl	CH ₃	H	C ₁₇ H ₁₆ ClNO ₃ S	349.5	242	65	58.37 (58.32)	4.58 (4.54)	4.01 (3.98)
3c	OCH ₃	H	H	Cl	C ₁₇ H ₁₆ ClNO ₄ S	365.5	280	71	55.81 (55.82)	4.38 (4.41)	3.83 (3.79)
4a	H	H	OC ₆ H ₅	H	C ₂₃ H ₂₁ NO ₄ S	407	215-217	62	67.81 (67.76)	5.16 (5.12)	3.44 (3.41)
4b	H	Cl	CH ₃	H	C ₁₈ H ₁₈ ClNO ₃ S	363.5	220	65	59.42 (58.38)	4.95 (4.90)	3.85 (3.81)
4c	OCH ₃	H	H	Cl	C ₁₈ H ₁₈ ClNO ₄ S	379.5	236	63	56.92 (56.89)	4.74 (4.71)	3.69 (3.66)
5a	H	H	OC ₆ H ₅	H	C ₂₅ H ₂₂ ClNO ₅ S	483.5	277-279	65	62.05 (62.01)	4.55 (4.51)	2.90 (2.89)
5b	H	Cl	CH ₃	H	C ₂₀ H ₁₉ Cl ₂ NO ₄ S	440	265-267	66	54.55 (54.59)	4.32 (4.34)	3.18 (3.13)
5c	OCH ₃	H	H	Cl	C ₂₀ H ₁₉ Cl ₂ NO ₅ S	456	253-55	60	52.63 (52.67)	4.17 (4.20)	3.07 (3.02)
6a	H	H	OC ₆ H ₅	H	C ₃₀ H ₃₃ N ₃ O ₅ S	547	291-93	65	65.81 (65.79)	6.03 (6.00)	7.68 (7.64)
6b	H	Cl	CH ₃	H	C ₂₅ H ₃₀ ClN ₃ O ₄ S	503.5	295	62	59.58 (59.52)	5.96 (5.93)	8.34 (8.32)
6c	OCH ₃	H	H	Cl	C ₂₅ H ₃₀ ClN ₃ O ₅ S	519.5	301	71	59.75 (59.71)	5.78 (5.75)	8.08 (8.03)



Scheme 1.

Table 2. The IR spectral data of 1,5-benzothiazepine derivatives.

Comopd. No.	NH/OH	C-H str. (Aliphatic)	C-H str. (Aromatic)	C=C	C=O	C-O-C	C-H (Cyclic)	C-Cl
3a	3600-3150(b)	2880(w)	3090(w)	1580(ms)	1620(s)	1345(s) 1020(m)	1450(m)	-
3b	3580-3110(b)	2850(w)	3100(w)	1600(ms)	1600(s)	1350(s) 1050(m)	1420(m)	780(m)
3c	3550-3200(b)	2900(w)	3050(w)	1560(ms)	1610(s)	1360(s) 1070(m)	1445(m)	740(m)
4a	3150(s)	2920(m)	3000(w)	1580(ms)	1635(s)	1355(s) 1050(m)	1410(m)	-
4b	3180(s)	2850(m)	3080(w)	1560(ms)	1640(s)	1350(s) 1030(m)	1440(m)	780(m)
4c	3140(s)	2885(m)	3010(w)	1600(ms)	1620(s)	1355(s) 1065(m)	1450(m)	760(m)
5a	-	2880(m)	3010(w)	1580(ms)	1650(s)	1360(s) 1060(m)	1420(m)	740(m)
5b	-	2910(m)	3100(w)	1585(ms)	1660(s)	1345(s) 1020(m)	1430(m)	770(m)
5c	-	2875(m)	3080(w)	1600(ms)	1658(s)	1355(s) 1035(m)	1450(m)	780(m)
6a	-	2850(m)	3090(w)	1550(ms)	1650(s)	1340(s) 1045(m)	1440(m)	-
6b	-	2900(m)	3080(w)	1540(ms)	1648(s)	1360(s) 1025(m)	1450(m)	780(m)
6c	-	2845(m)	3010(w)	1510(ms)	1655(s)	1345(s) 1035(m)	1420(m)	750(m)

Table 3. The ¹H NMR spectral data of 1,5-benzothiazepine derivatives in ppm.

Compound No.	Ar-H	N-H (m)	C ₂ -H (d,J=8Hz,1H)	C ₃ -H (d,J=8Hz,1H)	CH ₂ (s,2H)	OCH ₃ (s,3H)	CH ₃
3a	6.20-7.90	8.10	2.80	3.36	-	3.54 (s,3H)	-
3b	6.10-7.50	8.25	2.92	3.44	-	3.50 (s,3H)	1.96
3c	6.00-7.60	8.15	2.84	3.20	-	3.52 (s,3H)	-
4a	6.10-7.90	8.10	2.82	3.24	-	3.48, 3.32(d,6H)	-
4b	6.20-7.50	8.20	2.74	3.10	-	3.58, 3.45(d,6H)	1.76
4c	6.05-7.85	8.25	2.76	3.05	-	3.44, 3.30(d,9H)	-
5a	6.00-7.45	-	2.66	3.15	4.40	3.50, 3.44(d,6H)	-
5b	6.20-7.90	-	2.78	3.25	4.35	3.48, 3.36(d,6H)	1.65
5c	6.10-7.60	-	2.68	3.30	4.50	3.55, 3.48(d,9H)	-
6a	6.00-7.38	-	2.45	3.18	4.30	3.58, 3.40(d,6H)	2.30
6b	6.05-7.50	-	2.35	3.30	4.25	3.56, 3.46(d,6H)	1.82
6c	6.10-7.40	-	2.45	3.15	4.15	3.54, 3.26(d,9H)	2.10

Antimicrobial activity

All the synthesized compounds were screened for their in vivo antimicrobial activity against the bacteria *S.*

aureus, *E. coli* and fungi *Aspergillus niger*, *Aspergillus flavus*, *Curvularia lunata* and *Fusarium moniliformae* at a concentration of 100 µg/disc in agar media. A single disc method of Bauer et al [8] was employed using

Streptomycin and Mycostatin as the reference compounds in antibacterial and antifungal activity respectively. The

data are given in Table-4.

Table 4. Antimicrobial activity of 1,5-benzothiazepine derivatives: Zone of inhibition (mm) (activity index)*.

Compound No.	<i>E. coli</i>	<i>S. aureus</i>	<i>A. flavus</i>	<i>A. niger</i>	<i>C. lunata</i>	<i>F. moniliformae</i>
3a	10.9 (0.99)	10.1 (1.01)	9.8 (0.96)	10.0 (0.95)	9.3 (1.03)	10.5 (0.94)
3b	10 (0.90)	7.0 (0.70)	8.2 (0.80)	8.9 (0.85)	8.2 (0.91)	10.0 (0.89)
3c	11 (1.00)	8.9 (0.89)	8.9 (0.87)	10.2 (0.97)	9.1 (1.07)	9.8 (0.88)
4a	10.5 (0.95)	10.2 (1.02)	10.1 (0.99)	10.1 (0.96)	8.5 (0.94)	8.8 (0.79)
4b	8.8 (0.80)	7.9 (0.79)	10.0 (0.98)	9.9 (0.94)	7.8 (0.87)	9.2 (0.82)
4c	10.8 (0.98)	9.8 (0.98)	10.1 (0.99)	10.1 (0.96)	7.8 (0.87)	10.0 (0.89)
5a	11.2 (1.02)	10.4 (1.04)	10.2 (1.00)	10.7 (1.02)	9.0 (1.00)	10.5 (0.94)
5b	10.0 (0.91)	10.4 (1.04)	10.2 (1.00)	10.0 (0.95)	8.7 (0.99)	9.8 (0.88)
5c	10.9 (0.99)	10.6 (1.06)	10.4 (1.02)	10.5 (1.00)	9.1 (1.01)	11.0 (0.98)
6a	11.0 (1.00)	10.5 (1.05)	10.9 (1.07)	10.9 (1.04)	9.5 (1.06)	11.0 (0.98)
6b	9.7 (0.88)	7.9 (0.79)	9.8 (0.96)	10.2 (0.97)	8.8 (0.98)	11.2 (1.00)
6c	10.8 (0.98)	10.4 (1.04)	10.2 (1.00)	10.4 (0.99)	9.0 (1.80)	11.8 (1.05)

*Activity index=Inhibition area of the sample/Inhibition area of the standard.

Experimental

General

All the melting points were determined in open capillary tubes and are uncorrected. The IR spectra were recorded on a Perkin Elmer-833 grating infrared spectrophotometer in KBr pellets.

The ¹H NMR spectra were scanned on a FX 90Q Jeol spectrometer (90 MHz) in CDCl₃/DMSO-d₆ using TMS as the internal standard. The purity of the compounds

synthesized was checked by TLC using silica gel-G as adsorbent.

(±)-cis-2-(4-Methoxyphenyl)-3-hydroxy-8-phenoxy/-7-chloro-8-methyl-9-chloro-6-methoxy-2,3-dihydro-1,5-benzothiazepin-4(5H)-one (3)

Methyl (±)-trans-3-(4-methoxyphenyl)glycidate (2) (0.01 mol) was added slowly to a stirred mixture of substituted-2-aminobenzenethiol (1) (0.01 mol) in xylene at 160°C under a nitrogen atmosphere. The stirring was continued for a further 16-20 hrs, maintaining the temperature and the nitrogen atmosphere. The reaction

mixture was cooled to room temperature and ethanol was added. The product, thus separated from the mother liquor was collected by filtration, washed with ethanol and recrystallized from DMF.

(±)-*cis*-2-(4-Methoxyphenyl)-3-methoxy-8-phenoxy/-7-chloro-8-methyl/-9-chloro-6-methoxy-2,3-dihydro-1,5-benzothiazepin-4(5H)-one (**4**)

(±)-*cis*-2-(4-Methoxyphenyl)-3-hydroxy-8-phenoxy/-7-chloro-8-methyl/-9-chloro-6-methoxy-2,3-dihydro-1,5-benzothiazepin-4(5H)-one (**3**) (0.005 mol), sodium dithionite (0.25 g) and 10% ethanolic potassium hydroxide solution (55 ml) were mixed with dimethyl sulphate (0.014 mol). The reaction mixture was refluxed for 5 hrs and filtered. The filtrate was poured into ice cold water. The precipitate obtained was filtered, dried and recrystallized from benzene.

(±)-*cis*-2-(4-Methoxyphenyl)-3-methoxy-8-phenoxy/-7-chloro-8-methyl/-9-chloro-6-methoxy-2,3-dihydro-1,5-benzothiazepin-4(5-chloroacetyl)-one (**5**)

A solution of (±)-*cis*-2-(4-methoxyphenyl)-3-methoxy-8-phenoxy/-7-chloro-8-methyl/-9-chloro-6-methoxy-2,3-dihydro-1,5-benzothiazepin-4(5H)-one (**4**) (0.005 mol) in dry benzene (100 ml) was added to a solution of chloroacetyl chloride (0.008 mol) in dry benzene (2.5 ml) with stirring. The reaction mixture was refluxed on a water bath for 4 hrs, cooled. Benzene was chilled and then triturated with petroleum ether (60-80°). The product thus obtained was recrystallized from ethanol.

(±)-*cis*-2-(4-Methoxyphenyl)-3-methoxy-8-phenoxy/-7-chloro-8-methyl/-9-chloro-6-methoxy-2,3-dihydro-1,5-benzothiazepin-4[5-(4'-methylpiperazino-1')acetyl]-one (**6**)

A solution of **5** (0.005 mol) in dry benzene (7.5 ml) was treated with N-methylpiperazine (0.013 mol). The resulting solution was subsequently refluxed on a water bath for 5 hrs and cooled. The hydrochloride salt of the

unreacted amine was removed by filtration. The benzene layer was washed well with water to remove traces of the unreacted amine. It was then dried over anhydrous sodium sulphate and filtered. Benzene was removed from the filtrate under reduced pressure and the residual solid was recrystallize from ethanol.

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Samples Availability: Available from the authors.