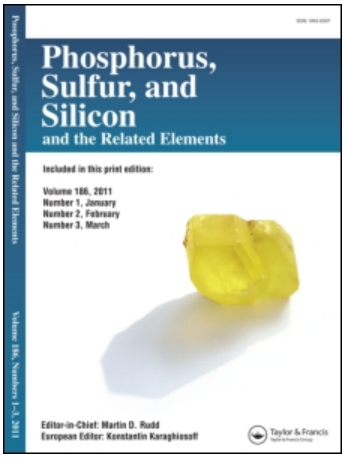

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1,4-Diazepines Bearing Thieno(2,3-*b*)Thiophene and Cyclohexene Carboxylate Moieties

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*Bis[thieno(3,2-b)-1,4-diazepine] (**4**) and bis[imidazo(1′,2′)thieno(3,2-b)-1,4-diazepine (**7**) derivatives were prepared starting with thieno(2,3-b)thiophenes (**1**) and (**2**), respectively. Also, benzodiazepine derivatives (**11a–f**) were prepared via a reaction of cyclohexenone carboxylates (**8a–f**) with cyclohexylamine and chloroacetyl chloride followed by cyclization. Also, dibenzoazepines (**13**) and (**14a,b**) were prepared via a reaction of (**8a**) with o-phenylenediamine and o-aminophenol or o-aminothiophenol.*

Keywords 1,4-Diazepine; imidazothieno-1,4-diazepines; thienodiazepine; thienothiophene

Benzodiazepines have been widely employed in clinical practice as anxiolytics, sedative-hypnotics, anticonvulsants, vasopressin antagonists, and HIV reverse transcriptase inhibitors.[1–3] There have been several reports concerning the pharmacological activity of benzodiazepines with chloro-substituents in the C-7 position of the benzene ring of benzodiazepine dereivatives.[4–7] On the other hand, the synthesis of tricyclic 1,4-benzodiazepines as well as their 1,5-isomers[8,9] has attracted attention recently.[10–16] The reason to study thieno[2,3-b]diazepine derivatives was their structural relationship with tranquilizer Clobazam.[17] Because of the bioisosterity of the two rings, replacement of the benzene nucleus by a thiophene ring may provide pharmacologically active compounds.

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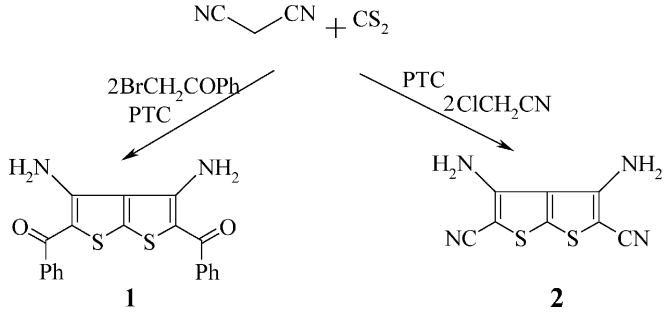
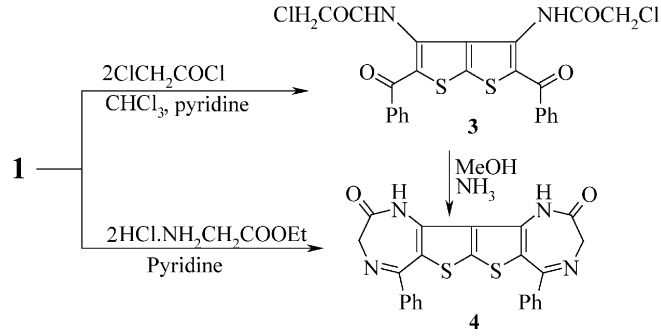
RESULT AND DISCUSSION

In an extension of our work of benzodiazepines,[18] 3,4-diamino-2,5-dibenzoylthieno[2,3-*b*]-thiophene (**1**) and 3,4-diaminothieno[2,3-*b*]thiophene-2,5-dicarbonitrile (**2**) were selected as starting materials for the synthesis of thienodiazepins and were prepared by a reaction of malononitrile, CS_2, and phenacyl bromide or chloroacetonitrile in 1:1:2 molar ratios under phase-transfer catalysis conditions, respectively (Scheme 1).[19]



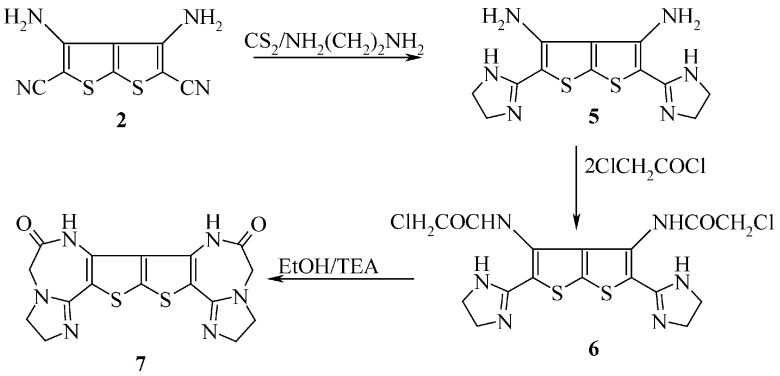
SCHEME 1

Thus, the reaction of compound (**1**) with two moles of chloroacetyl chloride in dry chloroform containing a few drops of pyridine gave the corresponding 2,5-dibenzoyl-3,4-bis(chloroacetamido)thieno[2,3-*b*]thiophene (**3**). On treating compound (**3**) with methanol saturated with ammonia gas in a closed system, it underwent intramolecular cyclization to furnish the promising bis(2,3-dihydro-5-phenyl-1*H*-thieno[3,2-*b*]-1,4-diazepin-2-one) (**4**). However, the latter compound was also obtained upon heating compound (**1**) with ethylglycinate hydrochloride in pyridine (Scheme 2).



SCHEME 2

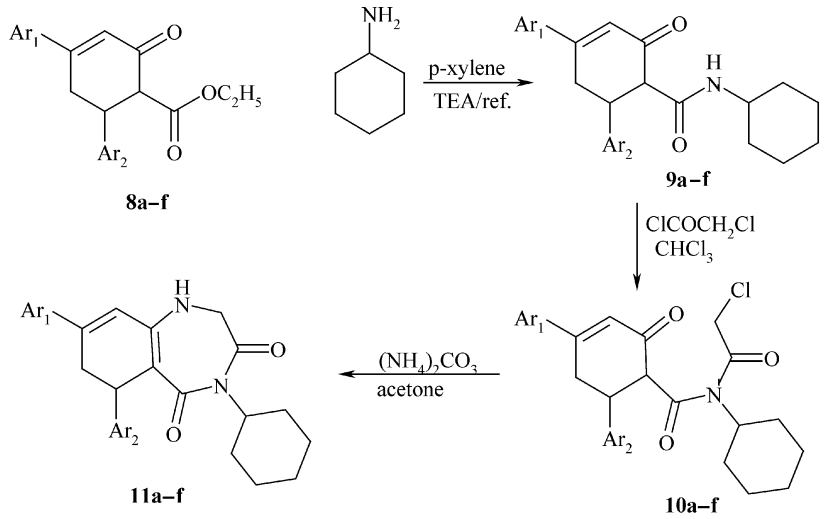
The incorporation of the imidazolyl moiety in imidazothienodiazepine system was achieved by converting the cyano groups of compound (**2**) into a dihydroimidazolyl residue, followed by some substitution reaction . Thus, the interaction of compound (**2**) with ethylenediamine in the presence of carbon disulfide afforded 3,4-diamino-2,5-bis(4,5-dihydro-1*H*-imidazolyl)thieno[2,3-*b*]thiophene (**5**).[20] The treatment of compound (**5**) with chloroacetyl chloride furnished 3,4-chloroacetamido-2,5-bis(4,5-dihydro-1*H*-2-imidazolyl)thieno[2,3-*b*]thiophene (**6**), which underwent further cyclization reaction upon refluxing in ethanol in the presence of triethylamine to afford bis(2,3,5,6-tetrahydro-1*H*,-imidazo[1′,2′-*d*]thieno[3,2-*b*]-1,4-diazepin-2-one) (**7**) (Scheme 3).



SCHEME 3

On the other hand, the synthesis of 2,3,4,5,6,7-hexahydro-6,8-diphenylbenzo-1,4-diazepin-3,5-diones (**11a–f**) were carried out in three steps; the first step included the reaction of cyclohexenone carboxylates (**8a–f**)[21] with cyclohexyl amine by refluxing in p-xylene in the presence of triethylamine as a catalyst to give the corresponding cyclohexylamide derivatives (**9a–f**). These compounds were detected by IR, where the C=O ester disappeared; the NH, C=O of the amide product appeared; the ^{1}H-NMR showed the positions of NH, and cyclohexane and the ethoxy groups disappeared. In the second step, the amide derivatives (**9a–f**) were allowed to react with chloroacetyl chloride to afford the corresponding N-chloroacetamide derivatives (**10a–f**). In the final step, compounds (**10a–f**) heated under reflux with ammonium carbonate to give benzodiazepinone derivatives (**11a–f**) (Scheme 4).

Similarly, the interaction of cyclohexenone ester with *o*-phenylenediamine gave the corresponding amide derivative (**12**),



8a–f **9a–f** **10a–f** **11a–f**

	Ar_1	Ar_2		Ar_1	Ar_2
a	C_6H_5-	C_6H_5-	**d**	C_6H_5-	*p*-Cl- C_6H_4-
b	*p*-Cl- C_6H_4-	C_6H_5-	**e**	*p*-Cl- C_6H_4-	*p*-OCH_3 - C_6H_4-
c	C_6H_5-	*p*-OCH_3 - C_6H_4-	**f**	*p*-OCH_3 - C_6H_4-	C_6H_5-

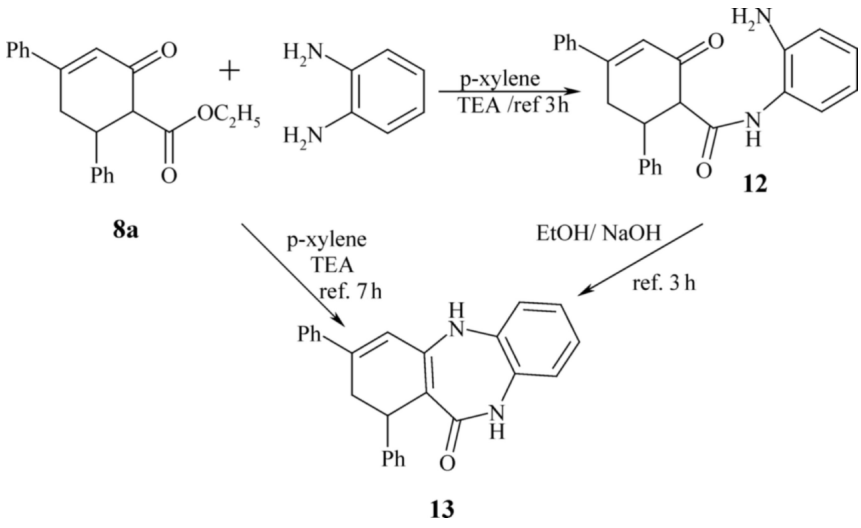
SCHEME 4

which was heated under reflux in ethanol containing aq. NaOH to afford the corresponding dibenzodiazepine derivative (**13**). Also, compound (**13**) was obtained in a one-pot reaction by heating compound (**8a**) with o-phenylene diamine under reflux in *p*-xylene in the presence of TEA as a base (Scheme 5).

In contrast, a dibenzothiazepine and dibenzoxazepine derivative was prepared via heating (**8a**) with *o*-aminothiophenol or o-aminophenol in p-xylene containing TEA as a base (Scheme 6).

EXPERIMENTAL

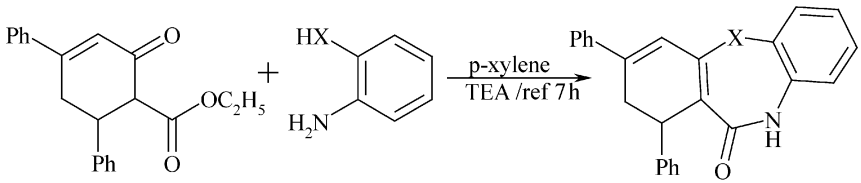
All melting points were determined on a Koffler melting points apparatus and are uncorrected. ^{1}H-NMR spectra were recorded on a Varian 390 at 90 MHz spectrometer using TMS as internal reference (chemical shifts in δ, ppm), and IR in KBr were obtained on a Nicolet 710 FT-IR spectrophotometer (ν_{max} in cm^{-1}). The elemental analysis was carried out on a Perkin Elmer 240°C elemental analyzer.



SCHEME 5

2,5-Dibenzoyl-3,4-bis(chloroactamido)thieno[2,3-*b*] thiophene (3)

A stirred solution of 3,4-diamino-2,5-dibenzoylthieno[2,3-*b*]thiophene (**1**) (1.9 g, 5 mmol) in 20 mL of dry chloroform and 0.5 mL of pyridine was stirred at r.t. Subsequently, (12 mmol) of chloroacetyl chloride was added dropwise, and the reaction mixture was allowed to stand for 2 h. The reaction mixture was washed with water, and the chloroform layer dried, and evaporated. The solid formed was separated as white needles, 2.17g (87%), m.p. 142°C (from ethanol). IR 3250(NH), 1690, 1660(C=O) cm^{-1}. ^1H NMR δ: 9.10(s, 2H, 2NH), 7.20–7.80(m, 10H, arom.), 3.90(s, 4H, $2CH_2$). Anal. calcd for $C_{24}H_{16}N_2O_4S_2Cl_2$: C, 54.42; H, 3.03; N, 5.27; S, 12.07; Cl, 13.34. Found: C, 54.81; H, 3.12; N, 5.39; S, 12.11; Cl, 13.22.



8a

14a, a, X = S
b, X = O

SCHEME 6

Bis[2,5-Dihydro-5-phenyl-1*H*-Thieno[3,2-*b*]-1,4-diazepione] (4)

Method A

Compound (**3**) (0.5 g, 1 mmol) was stirred in 20 mL of methanol saturated with NH_3 in a closed system for 4 h. The solution was evaporated under reduced pressure, and the residual solid was collected by filtration as a white powder, 0.31 g (69%).

Method B

A suspension of compound (**1**) (0.38 g, 1 mmol) in 25 mL of dry pyridine and (0.28 g, 2 mmol) of ethylglycinate hydrochloride. The mixture was refluxed in an air condenser for 4 h (about 5 mL of pyridine was evaporated (lost) during this time). The lost amount of pyridine and another amount (0.28 g, 2 mmol) of ethylglycinate hydrochloride were added to the reaction mixture and completed the reflux for 16 h. The reaction mixture evaporated to its half volume, cooled, and poured into ice-cooled water; the solid formed was separated as white crystals, 0.26 g (56%), m.p. 256°C (from acetone). IR 3441, 3285(NH), 1660(C=O), 1632(C=C) cm^{-1}. ^1H NMR δ: 9.20(s, 2H, 2NH), 7.30–7.90 (m, 10H, arom.), 3.63 (s, 4H, $2CH_2$). Anal. calcd. for $C_{24}H_{16}N_4O_2S_2$: C, 63.14; H, 3.53; N, 12.27; S, 14.04. Found: C, 63.17; H, 3.51; N, 12.32; S, 14.11.

3,4-Diamino-2,5-di[4′,5′-dihydro-1′H-imidazoly]thieno[2,3-*b*]thiophene (5)

To a suspension of (**2**) (0.44 g, 2 mmol), ethylenediamine (3 mL) and carbon disulfide (1 mL) were added dropwise. The reaction mixture was heated on a water bath for 2 h. The precipitated solid was triturated with ethanol (10 mL) and filtered off to give golden yellow crystals, 0.47 g (77%), m.p. 197°C (from ethanol). IR 3420, 3330, 3285, 3120 (NH, NH_2), 1630(C=C) cm^{-1}. ^1H NMR δ : 8.90 (s, 2H, 2NH), 6.20 (s, 2H, NH_2), 4.00–4.30 (d, 4H, $2CH_2$). Anal. calcd. for $C_{12}H_{14}N_6S_2$: C, 47.04; H, 4.61; N, 27.43; S, 20.93. Found: C, 47.21; H, 4.71; N, 27.25; S, 20.90.

3,4-Dichloroacetamido-2,5-di[4′,5′-dihydro-1′H-imidazoly]thieno[2,3-*b*]thiophene (6)

A stirred solution of compound (**5**) (0.31 g, 1 mmol) in 30 mL of chloroform (dry) and (0.2 g, 2 mmol) of triethylamine was stirred at r.t. Subsequently (0.22 g, 2.2 mmol) of chloroacetyl chloride was added dropwise with stirring, and the reaction mixture was allowed to stand at r.t. for 2 h. The reaction mixture was washed with water, and the chloroform layer was dried and evaporate. The solid formed was separated by

filteration 0.3 g (65%), m.p. 201°C (from benzene). IR 3410, 3120(NH), 1660(C=O), 1620(C=C) cm^{-1}. ^1H NMR δ: 9.10 (s, 2H, 2NH), 8.60 (s, 2H, 2NH), 3.10 (s, 4H, $2CH_2$), 3.70(d, 8H, $4CH_2$). Anal. calcd. for $C_{16}H_{16}N_6O_2S_2Cl_2$: C, 41.83; H, 3.51; N, 18.29; S, 13.96; Cl, 15.44. Found: C, 41.96; H, 3.44; N, 18.35; S, 14.01; Cl, 15.39.

Bis[2,3,5,6-Tetrahydro-1*H*-imidazo(1′,2′-d)thieno [3,2-*b*]-1,4-diazepin- 2-one (7)

Compound (**6**) (0.46 g, 1 mmol) in 30 mL of dry dioxane and (0.2 g, 2 mmol) of triethylamine was heated under reflux for 2 h. The precipitate that separated after cooling was washed with water as white crystals, 0.21 g (56%), m.p. 267^{d}°C (from dioxane). IR 3430, 3280(NH), 1670(C=O), 1620(C=C) cm^{-1}. ^1H NMR δ: 9.10 (s, 2H, 2NH), 3.65 (s, 4H, $2CH_2$), 3.40–3.70 (d, 8H, $4CH_2$). Anal. calcd. for $C_{16}H_{14}N_6O_2S_2$: C, 49.73; H, 3.65; N, 21.75; S, 16.59. Found: C, 49.91; H, 3.74; N, 21.68; S, 16.66.

6-(N-Cyclohexylcarboxamido)-3,5-diaryl-2-cyclohexenone derivatives (9a–f)

General Procedure

A mixture of (**8a–f**) (5 mmol) and cyclohexylamine (0.5 g, 5 mmol) in 30 mL of *p*-xylene in the presence of a catalytic amount of triethylamine (few drops) was refluxed for 6 h. The precipitated product was filtered off and recrystallized from the proper solvents.

6-Cyclohexylamido-3,5-diphenylcyclohex-2-enone (9a)

From (**8a**) and cyclohexylamine, a yellow solid 1.4 g (75%), m. p. 135–136°C (from dioxane). IR 3420(NH), 1710, 1668(C=O), 1610(C=N) cm^{-1}. ^1H NMR δ : 8.90 (s, 1H, NH), 7.00–8.01 (m, 10 H, arom.), 5.21 (s, 1H, =CH), 2.80–3.00 (m, 1H, CH–Ph), 2.10–2.30 (dd, 3H, CO-CH-cyclohexanone, CH_2-cyclohexanone), 1.50–2.10 (m, 11H, CH_2-cyclohexane). Anal. calcd. for $C_{25}H_{27}NO_2$: C, 80.40; H, 7.29; N, 3.75. Found: C, 80.33; H, 7.41; N, 3.68.

6-Cyclohexylamido-3-p-chlorophenyl-5-phenylcyclohex-2-enone (9b)

From (**8b**) and cyclohexylamine, a pale yellow solid 1.54 g (77%), m.p. 195°C (from dioxane). IR 3410(NH), 1710, 1668(C=O), 1610(C=C) cm^{-1}. ^1H NMR δ: 8.90 (s, 1H, NH), 7.00–8.01 (m, 9H, arom.),

5.21 (s, 1H, =CH), 2.80–3.00 (m, 1H, CH—Ph), 2.10–2.30 (dd, 3H, —CO—CH-cyclohexanone, CH_2-cyclohexanone), 1.50–2.10 (m, 11H, CH_2-cyclohexane). Anal. calcd. for $C_{25}H_{29}NO_2Cl$: C, 73.61; H, 6.42; N, 3.44; Cl, 8.69. Found: C, 73.73; H, 6.32; N, 3.31; Cl, 8.69.

6-Cyclohexylamido-3-phenyl-5-*p*-methoxypheny lcyclohex-2-enone (9c)

From (**8c**) and cyclohexylamine, yellow solid 1.4 g (72%), m.p. 290[d]°C (from ethanol). IR 3410(NH), 1715, 1670(C=O), 1610(C=C) cm^{-1}. ^1H NMR δ : 8.90 (s, 1H, NH), 7.00–8.01 (m, 9H, arom.), 5.21 (s, 1H, =CH), 3.70 (s, 3H, CH_3), 2.80–3.00 (m, 1H, CH—Ph), 2.10–2.30 (dd, 3H, CO—CH-cyclohexanone, CH_2-cyclohexanone), 1.50–2.10 (m, 11H, CH_2-cyclohexane). Anal. calcd. for $C_{26}H_{29}NO_3$: C, 77.39; H, 7.24; N, 3.48. Found: C, 77.42; H, 7.11; N, 3.52.

6-Cyclohexylamido-3-phenyl-5-*p*-chlorophenyl-lcyclohex-2-enone (9d)

From (**8d**) and cyclohexylamine, pale yellow solid 1.6 g (81%), m.p. 267°C (from benzene). IR 3410(NH), 1710, 1668(C=O), 1610(C=C) cm^{-1}. ^1H NMR δ : 8.90 (s, 1H, NH), 7.00–8.01(m, 9H, arom.), 5.21(s, 1H, =CH), 2.80–3.00 (m, 1H, CH—Ph), 2.10–2.30 (dd, 3H, CO—CH—cyclohexanone, CH_2-cyclohexanone), 1.50–2.10 (m, 11H, CH_2-cyclohexane). Anal. calcd. for $C_{25}H_{26}NO_2Cl$: C, 73.61; H, 6.42; N, 3.44; Cl, 8.69. Found: C, 73.73; H, 6.22; N, 3.31; Cl, 8.69.

6-Cyclohexylamido-3-p-chlorophenyl-5-*p*-methoxypheny-lcyclohex-2-enone (9e)

From (**8e**) and cyclohexylamine, a white solid 1.8 g (85%), m.p. 202°C (from $CHCl_3$). IR 3410(NH), 1715, 1670(C=O), 1610(C=C) cm^{-1}. ^1H NMR δ : 8.90 (s, 1H, NH), 7.20–7.90 (m, 8H, arom.), 5.21 (s, 1H, =CH), 3.70 (s, 3H, CH_3), 2.80–3.00 (m, 1H, CH—Ph), 2.10–2.30 (dd, 3H, CO—CH-cyclohexanone, CH_2-cyclohexanone), 1.50–2.10 (m, 11H, CH_2-cyclohexane). Anal. calcd. for $C_{26}H_{28}NO_3Cl$: C, 71.63; H, 6.24; N, 3.21; Cl, 8.13. Found: C, 71.73; H, 6.32; N, 3.31; Cl, 8.24.

6-Cyclohexylamido-3-*p*-methoxyphenyl-5-phenylcyclohex-2-enone (9f)

From (**8f**) and cyclohexylamine, white solid 1.5 g (75%), m.p. 177°C (from methanol). IR 3410(NH), 1715, 1670(C=O), 1610(C=C) cm^{-1}.

^{1}H NMR δ : 8.90 (s, 1H, NH), 7.00–8.01 (m, 9H, arom.), 5.21 (s, 1H, =CH), 3.70 (s, 3H, CH_3), 2.80–3.00 (m, 1H, CH—Ph), 2.10–2.30 (dd, 3H, CO—CH-cyclohexanone, CH_2-Cyclohexanone), 1.50–2.10 (m, 11H, CH_2-cyclohexane). Anal. calcd. for $C_{26}H_{29}NO_3$: C, 77.39; H, 7.24; N, 3.48. Found: C, 77.42; H, 7.11; N, 3.52.

6-(N-Chloroacetamido-N-cyclohexylcarboxamido)-3,5-diarylcyclohex-2-enone derivatives (10a–f)

General Procedure

A stirred solution of compounds (**9a–f**) (5 mmol) in 30 mL of chloroform (dry) and (5 mmol) of pyridine was stirred at r.t. Subsequently, (1.16 g, 12 mmol) of chloroacetyl chloride was added dropwise, and the reaction was stirred for 2 h. The reaction mixture was left overnight and then evaporated to its half-volume and was neutralized with sodium bicarbonate solution. The precipitated solid was filtered off and recrystallized from the proper solvents.

6-(N-Chloroacetamido-N-cyclohexylcarboxamido)-3,5-diphernylcyclohex-2-enone (10a)

From (**9a**) and chloroacetyl chloride, a red solid, 1.7 g (75%), m.p. 181°C (from ethanol). IR 1710, 1668, 1660(C=O), 1610(C=C) cm^{-1}. ^{1}H NMR δ: 7.00–8.01 (m, 10 H, arom.), 5.21 (s, 1H, =CH), 3.60 (s, 2H, CH_2) 2.80-3.00 (m, 1H, CH—Ph), 2.10–2.30 (dd, 3H, CO—CH-cyclohexanone, CH_2-Cyclohexanone), 1.50–2.10 (m, 11H, CH_2-cyclohexane). Anal. calcd. for $C_{27}H_{28}NO_3Cl$: C, 72.07; H, 6.27; N, 3.11; Cl, 7.89. Found: C, 72.15; H, 6.21; N, 3.21; Cl, 7.90.

6-(N-Chloroacetamido-N-cyclohexylcarboxamido)-3-*p*-chlorophenyl-5-phernylcyclohex-2-enone (10b)

From (**9b**) and chloroacetyl chloride, a brown solid, 1.7 g (70%), m.p. 173°C (from ethanol). IR 1710, 1668, 1660 (C=O), 1610 (C=C) cm^{-1}. ^{1}H NMR δ: 7.00–8.01 (m, 9H, arom.), 5.21 (s, 1H, =CH), 3.60 (s, 2H, CH_2), 2.80–3.00 (m, 1H, CH—Ph), 2.10–2.30 (dd, 3H, CO—CH-cyclohexanone, CH_2-cyclohexanone), 1.50–2.10 (m, 11H, CH_2-cyclohexane). Anal. calcd. for $C_{27}H_{27}NO_3Cl_2$: C, 66.94; H, 5.62; N, 2.90; Cl, 14.64. Found: C, 67.15; H, 5.52; N, 2.83; Cl, 14.62.

6-(N-Chloroacetamido-N-cyclohexylcarboxamido)-3-phenyl-5-*p*-methoxyphernyl-cyclohex-2-enone (10c)

From (**9c**) and chloroacetyl chloride, a gray solid, 1.58 g (66%), m.p. 156°C (from ethanol). IR 1715, 1670, 1660 (C=O), 1610 (C=C) cm^{-1}. ^1H NMR δ: 7.00–8.01 (m, 9H, arom.), 5.21(s, 1H, =CH), 3.60(s, 2H, CH_2), 3.70(s, 3H, CH_3), 2.80–3.00(m, 1H, CH—Ph), 2.10–2.30(dd, 3H, CO—CH-cyclohexanone, CH_2-cyclohexanone), 1.50–2.10(m, 11H, CH_2-cyclohexane). Anal. calcd. for $C_{28}H_{30}NO_4Cl$: C, 70.06; H, 6.30; N, 2.92; Cl, 7.40. Found: C, 70.15; H, 6.17; N, 2.99; Cl, 7.51.

6-(N-Chloroacetamido-N-cyclohexylcarboxamido)-3-phenyl-5-*p*-chlorophernylcyclohex-2-enone (10d)

From (**9d**) and chloroacetyl chloride, a deep yellow solid, 1.71 g (71%), m.p. 216°C (from ethanol). IR 1710, 1668, 1660(C=O), 1610(C=C) cm^{-1}. ^1H NMRδ: 7.00–8.01(m, 9H, arom.), 5.21 (s, 1H, =CH), 3.60(s, 2H, CH_2), 2.80–3.00(m, 1H, CH—Ph), 2.10–2.30(dd, 3H, CO-CH-cyclohexanone, CH_2-Cyclohexanone), 1.50–2.10(m, 11H, CH_2-cyclohexane). Anal.calcd. for $C_{27}H_{27}NO_3Cl_2$: C, 66.94; H, 5.62; N, 2.90; Cl, 14.64. Found: C, 66.97; H, 5.41; N, 2.97; Cl, 14.71.

6-(N-Chloroacetamido-N-cyclohexylcarboxamido)-3-*p*-chlorophenyl-5-*P*-methoxy-phernylcyclohex-2-enone (10e)

From (**9e**) and chloroacetyl chloride, a brown solid, 1.51 g (59%), m.p. 179°C (from ethanol). IR 1715, 1670, 1660(C=O), 1610(C=C) cm^{-1}. ^1H NMR δ: 7.20–7.90(m, 8H, arom.), 5.21 (s, 1H, =CH), 3.90 (s, 2H, CH_2), 3.70 (s, 3H, CH_3), 2.80–3.00(m,1H, CH—Ph), 2.10–2.30(dd, 3H, CO-CH-cyclohexanone, CH_2-cyclohexanone), 1.50–2.10 (m, 11H, CH_2-cyclohexane). Anal. calcd. for $C_{28}H_{29}NO_3Cl_2$: C, 67.47; H, 5.86; N, 2.81; Cl, 14.23. Found: C, 67.32; H, 5.78; N, 2.81; Cl, 14.17.

6-(N-Chloroacetamido-N-cyclohexylcarboxamido)-3-*p*-methoxyphenyl-5-phernylcyclo-hex-2-enone (10f)

From (**9f**) and chloroacetyl chloride, a pale brown solid, 1.49 g (62%), m.p. 184°C (from ethanol). IR 1715, 16701660(C=O), 1610(C=C) cm^{-1}. ^1H NMR δ: 7.00–8.01 (m, 9H, arom.), 5.21(s, 1H, =CH), 3.90 (s, 2H, CH_2), 3.70 (s, 3H, CH_3), 2.80-3.00(m, 1H, CH—Ph), 2.10–2.30 (dd, 3H, CO—CH-cyclohexanone, CH_2-cyclohexanone), 1.50–2.10 (m, 11H, CH_2-cyclohexane). Anal. calcd. for $C_{28}H_{30}NO_4Cl$: C, 70.06; H, 6.30; N, 2.92; Cl, 7.40. Found: C, 70.13; H, 6.33; N, 2.99; Cl, 7.55.

2,3,6,7-Tetrahydro-1*H*-4-cyclohexyl-6,8-diaryl-1,4-benzodiazepin-3,5-dione (11a–f)

General Procedure

A solution of (**10a–f**) (5 mmol) in acetonitrile (20 mL) containing sodium iodide (0.75 g, 5 mmol) and ammonium carbonate (2 g) was stirred at r.t. for 24 h. The precipitate was filtered off and washed with dichloromethane. The combined filterate was washed with water, dried, and evaporated, and the solid that formed filtered off and recrystallized from the proper solvents.

2,3,6,7-Tetrahydro-1*H*-4-cyclohexyl-6,8-diphenyl-1,4-benzodiazepin-3,5-dione (11a)

From (**10a**), a white solid, 1.56 g (76%), m.p. 198°C (from ethanol). IR 3420(NH), 1670,1668(C=O), 1610(C=C) cm^{-1}. ^1H NMR δ : 8.90(s, 1H, NH), 7.00–8.01(m, 10H, arom.), 5.21(s, 1H, =CH), 4.10(s, 2H, CH_2), 2.80–3.00(m, 1H, CH—Ph), 2.10–2.30 (d, 2H, CH_2-cyclohexanone), 1.50–2.10(m, 11H, CH_2-cyclohexane). Anal. calcd. for $C_{27}H_{28}N_2O_2$: C, 78.61; H, 6.84; N, 6.79. Found: C, 78.69; H, 6.71; N, 6.92.

2,3,6,7-Tetrahydro-1*H*-4-cyclohexyl-6-phenyl-8-*P*-chlorophenyl-1,4-benzodiazepin-3,5-dione (11b)

From (**10b**), a white solid, 1.45 g (65%), m.p. 210°C (from ethanol). IR 3410(NH), 1670, 1668(C=O), 1610(C=C) cm^{-1}. ^1H NMR δ : 8.90(s, 1H, NH), 7.00–8.01(m, 9H, arom.), 5.21(s, 1H, =CH), 4.10(s, 2H, CH_2), 2.80–3.00(m, 1H, CH—Ph), 2.10–2.30(d, 2H, CH_2-cyclohexanone), 1.50–2.10(m, 11H, CH_2-cyclohexane). Anal. calcd. for $C_{27}H_{27}N_2O_2Cl$: C, 72.55; H, 6.09; N, 6.28; Cl, 7.95. Found: C, 72.68; H, 5.91; N, 6.91; Cl, 7.89.

2,3,6,7-Tetrahydro-1*H*-4-cyclohexyl-6-*p*-methoxyphenyl-8-phenyl-1,4-benzodiazepin-3,5-dione (11c)

From **10c**, a white solid, 1.56g (71%), m.p. 226°C (from ethanol). IR 3410(NH), 1670,1660(C=O), 1610(C=C) cm^{-1}. ^1H NMR δ : 8.90(s, 1H, NH), 7.00–8.01(m, 9H, arom.), 5.21(s, 1H, =CH), 4.10(s, 2H, CH_2), 3.70(s, 3H, CH_3), 2.80–3.00(m, 1H, CH—Ph), 2.10–2.30(d, 2H, CH_2-cyclohexanone), 1.50–2.10(m, 11H, CH_2-cyclohexane). Anal. calcd. for $C_{28}H_{30}N_2O_3$: C, 75.99; H, 6.83; N, 6.33. Found: C, 76.09; H, 6.71; N, 6.49.

2,3,6,7-Tetrahydro-1*H*-4-cyclohexyl-6-*p*-chlorophenyl-8-phenyl-1,4 -benzodiazepin-3,5-dione (11d)

From (**10d**), a white solid, 1.78 g (80%), m.p. 256°C (from ethanol). IR 3410(NH), 1680, 1668(C=O), 1610(C=C) cm^{-1}. ^1H NMR δ : 8.90(s, 1H, NH), 7.00–8.01(m, 9H, arom.), 5.21(s, 1H, =CH), 4.10(s, 2H, CH_2), 2.80–3.00(m, 1H, CH—Ph), 2.10–2.30(d, 2H, CH_2-cyclohexanone), 1.50–2.10(m, 11H, CH_2-cyclohexane). Anal. calcd. for $C_{27}H_{27}N_2O_2Cl$: C, 72.55; H, 6.09; N, 6.28; Cl, 7.95. Found: C, 72.71; H, 5.92; N, 6.15; Cl, 7.89.

2,3,6,7-Tetrahydro-1*H*-4-cyclohexyl-6-*p*-methoxyphenyl-8-*p*-chlorophenyl-1,4-benzodiazepin-3,5-dione (11e)

From (**10e**), a white solid, 1.5 g (63%), m.p. 283°C (from ethanol). IR 3410(NH), 1670, 1660(C=O), 1610(C=C) cm^{-1}. ^1H NMR δ : 8.90(s, 1H, NH), 7.20–7.90(m, 8H, arom.), 5.21(s, 1H, =CH), 4.10(s, 2H, CH_2), 3.70(s, 3H, CH_3), 2.80–3.00(m, 1H, CH—Ph), 2.10–2.30(d, 2H, CH_2-cyclohexanone), 1.50–2.10(m, 11H, CH_2-cyclohexane). Anal. calcd. for $C_{28}H_{29}N_2O_3Cl$: C, 70.50; H, 6,13; N, 5.87; Cl, 7.43. Found: C, 70.67; H, 5.99; N, 5.90; Cl, 7.53.

2,3,6,7-Tetrahydro-1*H*-4-cyclohexyl-6-phenyl-8-*p*-methoxyphenyl-1,4-benzodiazepin-3,5-dione (11f)

From (**10f**), a gray solid, 1.87 g (85%), m.p. 198°C (from *p*-xylene). IR 3410(NH), 1670, 1660(C=O), 1610(C=C) cm^{-1}. ^1H NMR δ : 8.90(s, 1H, NH), 7.00–8.01(m, 9H, arom.), 5.21(s, 1H, =CH), 4.10(s, 2H, CH_2), 3.70(s, 3H, CH_3), 2.80–3.00(m, 1H, CH—Ph), 2.10–2.30(d, 2H, CH_2-cyclohexanone), 1.50–2.10(m, 11H, CH_2-cyclohexane). Anal. calcd. for $C_{28}H_{30}N_2O_3$: C, 75.99; H, 6.83; N, 6.33. Found: C, 76.14; H, 6.22; N, 6.29.

6-N-(2-Anilino)carboxamido-4,5,6-trihydro-3,5-diphenyl-2-cyclohexenone (12)

A mixture of (**8a**) (1.6 g , 5 mmol), o-phenylenediamine (0.54 g, 5 mmol), and triethylamine (0.5 g, 5 mmol) in 30 mL of *p*-xylene. The reaction mixture was heated under reflux for 3 h, and the solid formed was separated as pale yellow crystals, 1.28 g (67%), m.p. 205°C (from xylene). IR 3420, 3320, 3285(NH, NH_2), 1710, 1668(C=O) cm^{-1}. ^1H NMR δ : 9.20(s, 1H, NH), 7.00–7.90(m, 14H, arom.), 6.10(s, 2H, NH_2), 5.21(s, 1H, =CH), 2.80–3.00(m, 1H, CH—Ph), 2.10–2.30(dd, 3H, CO—CH-cyclohexanone,

CH_2-cyclohexanone). Anal. calcd. for $C_{25}H_{22}N_2O_2$: C, 78.51; H, 5.80; N, 7.32. Found: C, 78.60; H, 5.73; N, 7.50.

8,9-Dihydro-8,10-diphenyl 1H,6*H*-dibenzo-1,4-diazepines (13)

Compound (**12**) (1.9 g, 5 mmol) in 30 mL of ethanol and 5 mL (10% NaOH) was heated under reflux for 7 h. The separated solids were collected by filteration as a white solid, 0.9 g (50%), m.p. 196°C (from dioxane). IR 3420, 3380(NH), 1680(C=O) cm^{-1}. ^1H NMR δ : 9.10(s, 1H, NH), 8.80(s, 1H, NH) 7.20–8.10(m, 14 H, arom.), 5.21(s, 1H, =CH), 2.80–3.00(m,1H, CH—Ph), 2.10–2.30 (dd, 3H, CO—CH-cyclohexanone, CH_2-Cyclohexanone). Anal. calcd. for $C_{25}H_{20}N_2O$: C, 82.39; H, 5.53; N, 7.69. Found: C, 82.26; H, 5.39; N, 7.71.

8,9-Dihydro-8,10-diphenyl 1H,6*H*-dibenzo-1,4-diazepines (13) and (14 a,b)

General Procedure

A mixture of (**8a**) (1.6 g, 5 mmol) and *o*-phenylenediamine (0.54 g, 5 mmol) or *o*-aminothiophenol (0.6 g, 5 mmol), or o-aminophenol (0.55 g, 5 mmol) in 30 mL of *p*-xylene and triethylamine (5 mmol). The reaction mixture was heated under reflux for 7 h. The separated solids were collected by filteration and recrystallized from the proper solvents.

8,9-dihydro-8,10-diphenyl 1H,6*H*-dibenzo-1,4-thiazepines (14a)

Yellow solid, 1.0 g (56%), m.p. 291°C (from benzene). IR 3420(NH), 1675(C=O) cm^{-1}. ^1H NMR δ : 9.10(s, 1H, NH), 7.100–8.10(m, 14H, arom.), 5.21(s, 1H, =CH), 2.80–3.00(m, 1H, CH—Ph), 2.10–2.20(d, 2H, CH_2-cyclohexanone). Anal. calcd. for $C_{25}H_{19}NSO$: C, 78.71; H, 5.07; N, 3.68. Found: C, 79.07; H, 4.91; N, 3.59.

8,9-Dihydro-8,10-diphenyl-1H,6*H*-dibenzo-1,4-oxazepines 14b

White solid, 1.0 g (56%), m.p. 319°C (from dioxane). IR 3420(NH), 1675(C=O) cm^{-1}. ^1H NMR δ : 9.10(s,1H,NH), 7.100–8.10(m, 14H, arom.), 5.21(s, 1H, =CH), 2.80–3.00(m, 1H, CH—Ph), 2.10–2.20(d, 2H, CH_2-Cyclohexanone). Anal. calcd. for $C_{25}H_{19}NO_2$: C, 82.17; H, 5.24; N, 3.83. Found: C, 82.28; H, 5.08; N, 3.92.

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