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Facile Synthesis and Biological Evaluation of Heterocyclic Compounds Containing Diazepam

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Diazepamoxadiazoles **4,5,6,12,14** and **22** were prepared with the binary form system. Diazepamthiadiazoles **15,20** and Diazepamtriazoles **7,8,9,17,18,19** and **21** were also shapely synthesized. Some of these compounds were screened to test their antibacterial activity against *E. coli* and *B. subtilis* compounds 15 and 20 show potent activity against these bacteria.

Key words: Diazepam, Biodynamic heterocyclic systems, Triazoles, Thiadiazoles, Oxadiazoles

INTRODUCTION

Diazepam (7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1, 4-benzodiazepin-2-one) **1** is a therapeutically important drug used as a significant tranquilizer with wide broad spectrum acting on the central nervous system (CNS) (Hoffman, 1980). More recently, derivatives with some heterocyclic systems annulated to the compound **1** have become interest for their physical (Sternbach, 1978; Hara *et al.*, 1978), chemical (Kamiya *et al.*, 1973; Nakajima, 1971) and biological (Miyadera *et al.*, 1977; Stefanovich *et al.*, 1971) properties. On the other hand derivatives of heterocyclic systems binary attached with **1** have not yet recorded in the literature.

1,3,4-Triazoles (Sawhney *et al.*, 1993; Kane *et al.*, 1990; Prasad, 1989), thiadiazoles (Krutovskikh *et al.*, 1977; Skagins *et al.*, 1961; Goeres *et al.*, 1961) and oxadia-zoles (Omodel-Sale *et al.*, 1983; Griffin *et al.*, 1987; Tanaka *et al.*, 1974) have also emerged as potential drugs with antibacterial activity. In continuation of our work on compound **1** (Berghot *et al.*, 1992) and in view of these findings, it was planned to undertake the synthesis of some above bio-dynamic heterocyclic systems binary attached with **1** to secure compounds of enhanced pharmacological activity.

RESULTS AND DISCUSSION

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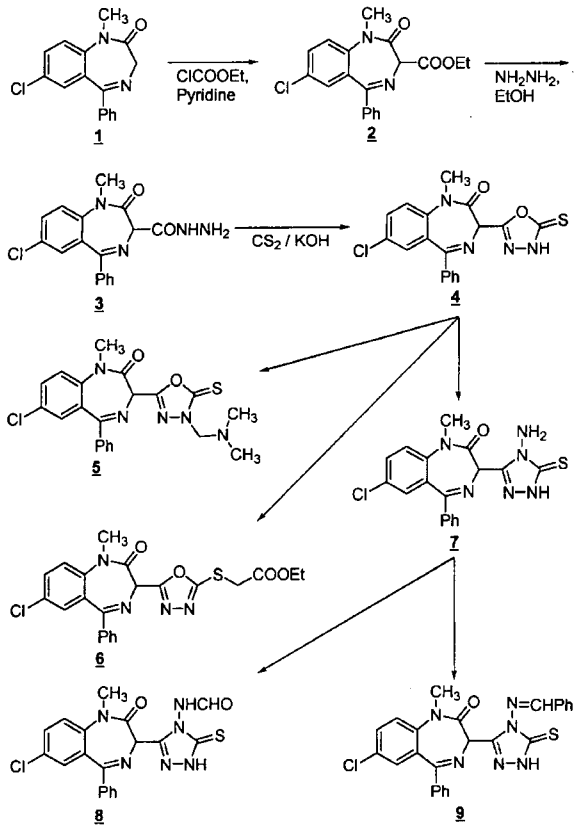
3-Ethyl carboxylate derivative **2** was prepared by the reaction of **1** with ethyl chloroformate in the presence of triethylamine. Firstly, the carboxylate **2** underwent smooth reaction with hydrazine hydrate in ethanol to give 3-carbohydrazide derivative **3** in good yield (75%). The new products **2** and **3** were used as starting materials for synthesis of the desired heterocyclic compounds in this work.

Reaction of **3** with carbon disulphide in the presence of ethanolic potassium hydroxide gave the required 1,3,4-oxadiazole derivative **4**. Compound **4** underwent Mannich reaction with dimethylamine in the presence of 40% formaldehyde solution to give the required *N,N*-dimethylaminomethyl derivative **5**. Also, **4** was reacted with ethyl chloroacetate to give ethyl thioacetate derivative **6**. Hydrazinolysis of **4** with hydrazine hydrate yielded the corresponding **7** which on refluxing with formic acid in dry benzene gave *N*-formylamino derivative **8**. Also, compound **7** condensed with benzaldehyde to give *N*-arylidineamino derivative **9** (Scheme 1). The structures of the products **4-9** were supported by physical and spectral data.

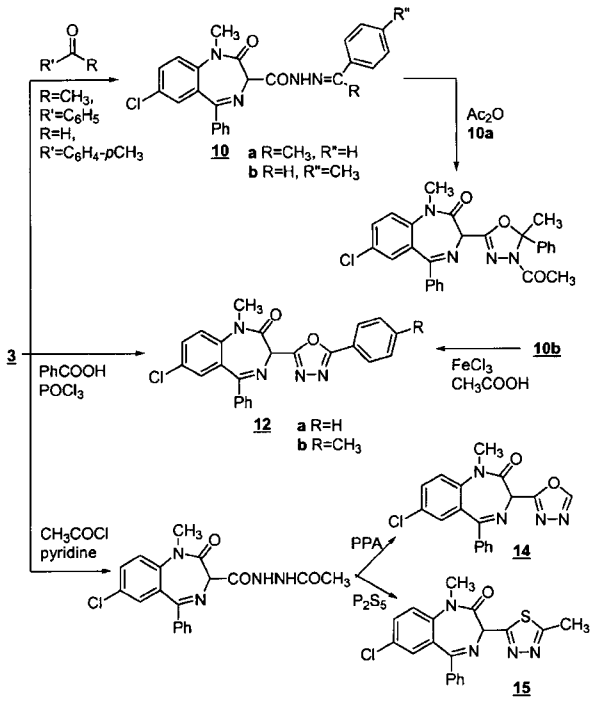
Furthermore, the reaction of **3** with acetophenone in boiling ethanol produced the corresponding hydrazone **10**a, similarly, the hydrazone **10**b was yielded from the reaction of **3** with p-tolualdehyde in the presence of catalytic amount of hydrochloric acid. In the treatment of hydrazone **10**a with excess acetic anhydride, cyclization reaction occurred to give 1,3,4-oxadiazoline derivative **11**, while, 1,3,4-oxadiazole **12**b was afforded by oxidation and cyclization of **10**b with ferric chloride in acetic acid. The formation of **11** and **12**b are analogous to that



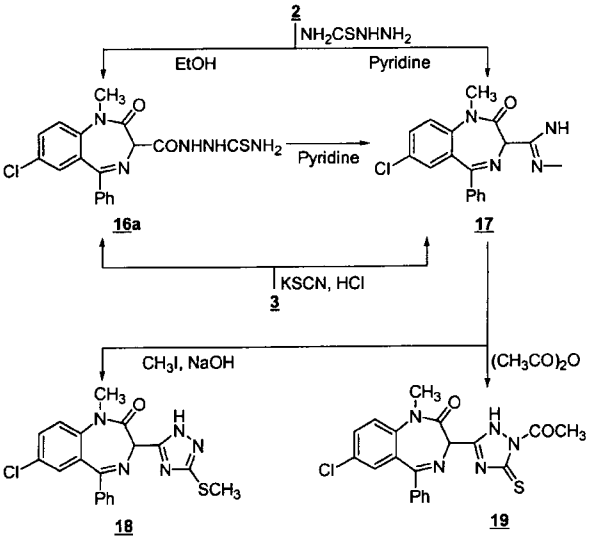
Scheme 1. Synthesis of *N-formylamino* and *N*-arylidine-amino derivatives

reported (Saad *et al.*, 1986; Kudari *et al.*, 1993). 1,3,4-Oxadiazole **12**a was also obtained in one step by reaction of **3** with benzoic acid in the presence of phosphorous oxychloride (Berghot *et al.*, 1993). Diacylhydrazine **13** was prepared by refluxing **3** with acetyl chloride in pyridine, which on cyclization with polyphosphoric acid gave the substituted 1,3,4-oxadiazole derivative **14,** while the reaction of **13** and phos-phorous penta sulphide gave 1,3,4-thiadiazole derivative **15** (Scheme 2). Similar observations has been recorded (Sawheny *et al.* 1993) Moreover, compound **3** was reacted with potassium thiocyanate in the presence of hydrochloric acid to give **16**a, which was also prepared by treatment of **2** with thiosemicarbazide in ethanol in poor yield. Compound **16**a on refluxing with pyridine gave the cyclized product **17.** Compound **17** was obtained directly from both fusion of **3** with ammonium thiocyanate and refluxing of **2** with thiosemicarbazide in pyridine. Also, refluxing **16a** with pyridine gave **17** analogous results has been reported (Shiba *et al.*, 1997).

Structure **17** was established by chemical reactions. Thus, compound **17** was reacted with methyl iodide in sodium hydroxide to give derivative **18**. Also, treatment of **17** with acetic anhydride afforded the acetyl derivative **19** (Scheme 3).



Scheme 2. Synthesis of 1,3,4-oxadiazole and 1,3,4-thiadiazole derivatives



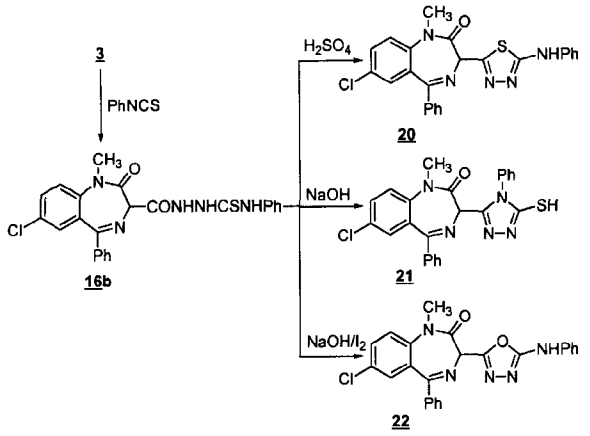
Scheme 3. Synthesis of 1,3,4-triazoles derivatives

In continuation of our study, thiosemicarbazide **16**b was prepared from the reaction of **3** with phenylisothiocyanate. Subsequent, treatment of **16**b with sulfuric acid, sodium hydroxide, or Iodine in sodium hydroxide under-went chemoselective heterocyclization to give thiadiazole **20**, triazole **21** and oxadiazole **22** respectively (Scheme 4). The new compounds were tested against antibacterial activity. The data obtained from this microbiological screaning (Table I), showed that thiadiazole systems attached with Diazepam exhibits high potent

Table I. Diameter of the inhibition zone (mm)

Comp.	*B. subtilis*	*E. coli*	Compd.	*B. subtilis*	*E. coli*	Compd	*B. subtilis*	*E. coli*
4	10	8	**11**	10	11	**18**	8	14
5	8	9	**12a**	10	9	**19**	6	12
7	11	8	**12b**	8	8	**20**	11	14
6	9	8	**14**	9	10	**21**	13	7
8	10	7	**15**	12	14	**22**	10	8
9	15	8	**17**	9	13	**Ampicillin**	14	15
						Diazepam	15	13

It is apparent from the data listed in the Table I. Some compounds show very promising activity. It caused inhibition zones vary between 10-14 mm in diameter. The results could be grouped under four different cate-gories:
1-The compounds **15** and **20** exhibits dual high activity against both G+ and G- bacteria.
2-The compounds **7,8,9** and **21** exhibit higher activity against G- than those against G+.
3-The compounds **17,18** and **19** exhibits higher activity against G+ than those againstG-.
4-The rest compounds exhibits moderate activity against G+ and G- bacteria.



Scheme 4. Synthesis of thiadiazole, trizole and oxadiazole derivatives

activity against both *E. coli* and *B. subtilis*. It encourage further studies and it will be the goal of future chemotherpeutic investigations.

MATERIALS AND METHODS

Melting points were determined on Fisher-Jones electric melting point apparatus and are uncorrected. The infrared spectra (IR) were recorded for potassium bromide disk on a Pye-Unicam SP 1000 spectrophotometer. Magnetic resonance (^{1}H-NMR) spectra were carried out at ambient temperature (~25°C) with a Varian EM-390 spectrometer using tetramethylsilane (TMS) as an internal standard. Elemental analyses were performed at the Microanalytical Unit, Cairo University, Cairo, Egypt, and the results for the indicated elements were within ±0.4% of the theoretical values.

Ethyl 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one-3-carboxylate (2)

To a solution of **1** (2.84 gm, 0.01 mol) in dry benzene (20 ml), ethyl chloroformate (1.08 ml, 0.01 mol) was added, followed by the dropwise of triethyl amine (2 ml). The reaction mixture was refluxed for 5 h, cooled to room temperature and the separated solid was filtered and crystallized from ethanol to give **2** as pale yellow needles (80%); m.p. 199°C.

IR: 1610 (C=N), 1695 ($CONCH_3$), 1720 (COOR); ^{1}H NMR ($CDCl_3$): δ 1.81 (t, 3H, CH_3), 2.82 (s, 3H, NCH_3), 4.63 (q, 2H, CH_2), 3.26 (s, 1H, CH), 7.74 (br, 8H, ArH). Anal. Calc. for $C_{19}H_{17}ClN_2O_3$ (356.81): C, 63.95; H, 4.80; N, 7.85 Found: C, 63.80, H, 4.93; N, 7.71.

3-Carbohydrazide-7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzo-diazepin-2-one (3)

To a solution of **2** (3.57 gm, 0.01 mol) in ethanol (30 ml), hydrazine hydrate (15 ml, 80%) was added and the mixture was heated under refluxed for 5 h. Most of ethanol was removed under reduced pressure, cooled and diluted with water. (When a solid separated out it). The precipitate was filtered and recrystallized from ethanol to give **3** as yellow crystals (70%); m.p. 260°C; IR: 1615 (C=N), 1660 (CONH), 1690 ($CONCH_3$), 3190 (NH), 3300 (NH_2); ^{1}H NMR ($CDCl_3$): δ 2.81 (s, 3H, NCH_3), 3.12 (s, 1H, CH), 3.87 (br, 2H, NH_2), 7.22-7.53 (br, 8H, Ar-H), 8.62 (br, 1H, CONH). Anal. Calc. for $C_{17}H_{15}ClN_4O_2$ (342.78): C, 59.56; H, 4.41; N, 16.35. Found: C, 59.68; H, 4.54; N, 16.16.

3-(2-Thio-1,3,4-oxadiazol-5-yl)-7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (4)

A solution of **3** (3.43 gm, 0.01 mol) in ethanol (30 ml), potassium hydroxide (0.5 g) in water (5 ml) and carbon disulphide (2.28 ml, 0.03 mol) were added. The reaction mixture was heated under reflux till the evolution of hydrogen sulphide ceased. The mixture was cooled, diluted with cold water (30 ml) and acidified with acetic acid. The solid that separated was filtered and crystallized from ethanol to give **4** (70%); m.p. 290°C; IR: 1610, 1620 (2C=N), 1220 (C=S), 1695 ($CONCH_3$), 3120 (NH); ^{1}H NMR [$(CD_3)_2SO$]: δ 2.99 (s, 3H, NCH_3), 3.44 (s, 1H, CH), 7.11-7.39 (br, 8H, ArH), 9.22 (s, 1H, NH). Anal. Calc. for $C_{18}H_{13}ClN_4O_2S$ (384.83): C, 56.18; H, 3.40; N, 14.56; S,

8.33. Found C, 56.34; H, 3.58; N, 14.62; S, 8.21.

3-[2-Thio-3-(*N,N*-dimethylaminomethyl)-1,3,4-oxadiazol-5'-yl]-7-chloro-1,3-dihyd-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (5)

To a boiling solution of **4** (3.85 gm, 0.01 mol) in ethanol (50 ml) containing aqeous formaldehyde (40%, 1 ml), dimethylamine (0.45 ml, 0.01 mol) was added with stirring. The solution was heated for 10 min, and left overnight. The separated solid was filtered and crystallized from methanol to give **5** as brown crystals (52%); m.p. 299°C; IR: 1615, 1620 (2C=N), 1220 (C=S), 1685 ($CONCH_3$); ^1H NMR [$(CD_3)_2SO$]: 2.55 (s, 3H, CH_3), 3.00 (s, 1H, CH), 3.31-3.63 (s, 6H, $2CH_3$), 5.33 (s, 2H, NCH_2N), 7.00-7.32 (br, 8H, ArH). Anal. Calc. for $C_{21}H_{20}ClN_5O_2S$ (441.87): C, 57.08; H, 4.55; N, 15.85; S, 7.26. Found: C, 57.23; H, 4.69; N, 16.03; S, 7.38.

3-[2-(Carbethoxymethylmercapto)-1,3,4-oxadiazol-5-yl]-7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (6)

A mixture of **4** (3.85 gm, 0.01 mol) in ethyl chloroacetate (1.22 ml, 0.01 mol) and sodium acetate (4.10 gm, 0.05 mol) in ethanol (50 ml) was refluxed for 4 h. The solid separated after cooling washed with dilute HCl (1%, 100 ml) and crystallized from benzene to give **6** as brown powder (75%); m.p. 213°C; IR: 1613, 1620, 1628 (3C=N), 1695 ($CONCH_3$), 1760 ($COOC_2H_5$); ^1H NMR (CF_3COOD): δ 1.91 (t, 3H, $CH_2\underline{CH_3}$), 2.73 (s, 3H, $NC\underline{H_3}$), 4.81 (q, 2H, $C\underline{H_2}CH_3$), 3.16 (s, 1H, CH), 3.61 (s, 2H, SCH_2CO), 7.00-7.30 (m, 8H, ArH). Anal. Calc. for $C_{22}H_{19}ClN_4O_4S$ (470.92): C, 56.11; H, 4.07; N, 11.90; S, 6.81. Found: C, 56.36; H, 4.29; N, 11.71; S, 6.86.

3-(3-Amino-3-thio-1,2,4-triazol-5-yl)-7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (7)

A mixture of **4** (3.8 gm, 0.01 mol), hydrazine hydrate (0.50 ml, 0.015 mol) and water (2 ml) was stirred for 3 h, and heated under reflux for 5 h. The separated solid was filtered and recrystallized from ethanol to give **7** as dark brown powder (60%); m.p. 200°C; IR: 1605, 1618 (2C=N), 1215 (C=S), 1685 (C=O), 3280 (NH), 3400 cm^{-1} (NH_2); ^1H NMR (CF_3COOD): δ 2.93 (s, 3H, NCH_3), 3.33 (s, 1H, CH), 5.63 (s, 2H, NH_2), 7.92 (br, 1H, NH), 7.12-7.40 (m, 8H, ArH). Anal. Calc. for $C_{18}H_{15}ClN_6OS$ (398.87): C, 54.20; H, 3.79; N, 21.07; S, 8.04 Found: C, 54.43; H, 3.88; N, 21.23; S, 8.31.

3-[4-(Formylamino)-3-thio-1,2,4-triazol-5-yl]-7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (8)

Equimolar quantities of **7** (3.99 g, 0.01 mol) and formic acid (0.5 ml) in dry benzene (20 ml) were refluxed for 2 h, excess of solvent was removed by evaporation and the reaction mixture cooled. The precipitated product was filtered and recrystallized from benzene to give **8** (45%); m.p. >300°C; IR: 1615, 1620 (2C=N), 1220 (C=S), 1680, 1650 (2C=O), 3260, 3300 (2NH). Anal. Calc. for $C_{19}H_{15}ClN_6O_2S$ (426.88): C, 53.46; H, 3.54; N, 19.69; S, 7.51 Found: C, 53.79, H, 3.83, N, 19.42, S, 7.79.

3-[4-Benzylidenamino-3-thio-1,2,4-triazol-5-phenyl-5-yl]-7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-bebenzodiazepin-2-one (9)

A solution of **7** (3.99 gm, 0.01 mol) in glacial acetic acid (20 ml) and benzaldehyde (1.06 ml, 0.01 mol) was refluxed for 3 h, the reaction mixture was then cooled, diluted with water, the separated solid was filtered and crystallized from benzene to give **9** (40%); m.p. > 300°C; IR: 1610, 1613, 1618 (3C=N), 1215 (C=S), 3300 cm^{-1} (NH); ^1H NMR (CF_3COOD): δ 2.78 (s, 3H, NCH_3), 3.13 (s, 1H, CH), 6.51 (s, 1H, azomethine H), 7.23-7.66 (m, 13H, ArH), 7.82-7.85 (br, 1H, NH). Anal. Calc. for $C_{25}H_{19}ClN_6OS$ (486.97): C, 61.66; H, 3.93; N, 17.26; S, 6.58 Found: C, 61.91; H, 3.68; N, 17.30; S, 6.81.

Hydrazone derivatives (10a,b)

A mixture of **3** (3.43 gm, 0.01 mol) and acetophenone or p-tolualdehyde (1.2 ml, 0.01 mol) in absolute ethanol (25 ml) was heated under reflux for 8 h, the solid separated after concentration and crystallization from methanol gave **10**a or **10**b respectively.

10a- (50%); m.p. 205°C; IR: 1600, 1620 (2C=N), 1650, 1690 (2C=O), 3000 cm^{-1} (NH); ^1H NMR ($CDCl_3$): δ 1.92 (s, 3H, CH_3), 2.83 (s, 3H, NCH_3), 3.00 (s, 1H, CH), 7.31-7.79 (m, 13H, Ar-H), 8.36 (s, 1H, NH). Anal. Calc. for $C_{25}H_{21}ClN_4O_2$ (444.91).

10b- (65%); m.p. 290°C; IR: 1610, 1618 (2C=N), 1660, 1680 (2C=O), 3300 cm^{-1} (NH); ^1H NMR($CDCl_3$): δ 2.55 (s, 3H, Ar-CH_3), 2.82 (s, 3H, NCH_3), 2.99 (s, 1H, CH), 8.66 (s, 1H, =CH), 7.11-7.53 (br, 12H, ArH), 8.56 (br, 1H, NH). Anal. Calc. for $C_{25}H_{21}ClN_4O_2$ (444.91): C, 67.50; H, 4.77; N, 12.60 Found: C, 67.39; H, 4.88; N, 12.81.

3-[4-Acetyl-5-methyl-5-phenyl-1,3,4-oxadiazolin-2-yl]-7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (11)

A mixture of **10**a (4.45 gm, 0.01 mol) and acetic anhydride (10 ml) was refluxed for 2 h, the excess acetic anhydride was distilled and the solid was recrystallized from ethanol to give **11** (60%); m.p. > 300°C; IR: 1610, 1620 (2C=N), 1655, 1680 (2C=O); ^1H NMR (CF_3COOD): δ 1.98 (s, 3H, CH_3), 2.93 (s, 3H, NCH_3), 2.97 (s, 1H, CH), 3.11 ($COCH_3$), 7.11-8.23 (br, 13H, ArH). Anal. Calc. for $C_{27}H_{23}ClN_4O_3$ (486.94): C, 66.59; H, 4.76; N, 11.51 Found: C, 66.68; H, 4.67; N, 11.32.

3-[2-Phenyl-1,3,4-oxadiazol-5-yl]-7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (12a)

To a mixture of 3 (3.43 gm, 0.01 mol) and benzoic acid

(1.22 gm, 0.01 mol), excess phosphorus oxychloride was added. The mixture was heated under reflux for 10 h. Cooled, the separated solid was filtered and crystallized from methanol to give 12a (50%); m.p. 263°C; IR: 1613, 1615, 1622 (3C=N), 1660 (C=O), 1200 (C-O-C). Anal. Calc. for $C_{24}H_{17}ClN_4O_2$ (428.87): C, 67.21; H, 4.00; N, 13.06 Found: C, 67.32; H, 3.81; N, 13.28.

3-[2-Toulyl-1,3,4-oxadiazol-5-yl]-7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (12b)

To a solution of 10b (4.44 gm, 0.1 mol) in acetic acid (80 ml), ferric chloride (1 g) and water (4 ml) were added. The reaction mixture was stirred for 1 h, then diluted with water (100 ml). It was allowed to stand for 72 h, the separated solid filtered and recrystallized from ethanol to give 12b (55%); m.p. 272°C; IR: 1605, 1615, 1618 (3C=N), 1660 (C=O), 1200 (C-O-C); ^{1}H NMR($CDCl_3$): δ 1.82 (s, 3H, Ar-CH_3), 2.91 (s, 3H, N-CH_3), 3.22 (s, 1H, CH), 7.10-7.42 (m, 12H, Ar-H). Anal. Calc. for $C_{25}H_{19}ClN_4O_2$ (442.89): C, 67.79; H, 4.32; N, 12.65 Found: C, 67.98; H, 4.61; N, 12.88.

Acetyl derivative (13)

Acetyl chloride (0.80 ml, 0.11 mol) was gradually added to a solution of **3** (3.43 gm, 0.01 mol) in dry pyridine (15 ml) with stirring and cooling. The reaction mixture was then heated under reflux for 30 min, excess of pyridine was distilled under reduced pressure. The mixture was cooled and poured on crushed ice. The separated solid was filtered and crystallized from ethanol to give 13 (75%); m.p. 198°C; IR: 1608 (C=N), 1593, 1595, 1650 (3C=O), 3190, 3400 (2NH); ^{1}H NMR ($CDCl_3$): δ 2.76 (s, 3H, NCH_3), 2.89 (s, 3H, $COCH_3$), 3.16 (s, 1H, CH), 7.17-7.56 (m, 8H, Ar-H), 10.12 (s, 1H, NH), 10.26 (s, 1H, NH). Anal. Calc. for $C_{19}H_{17}ClN_4O_3$ (384.82): C, 59.30; H, 4.45; N, 14.56 Found: C, 59.16; H, 4.59; N, 14.71.

3-[2-Methyl-1,3,4-oxadiazol-5-yl]-7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (14)

A mixture of **13** (3.85 gm, 0.01 mol) and polyphosphoric acid (30 ml) was heated in oil bath at 150-170°C for 2 h, the reaction mixture was cooled and poured into ice cold water (400 ml). On partial neutralization with sodium carbonate, the solid that separated out was filtered and crystallized from methanol to give **14** (60%); m.p. 250°C; IR: 1608, 1620 (2C=N), 1655 (C=O), 1230 (C-O-C); ^{1}H NMR($CDCl_3$): δ 2.68 (s, 3H, NCH_3), 2.72 (s, 3H, CH_3), 3.22 (s, 1H, CH), 7.18-7.30 (m, 8H, ArH). Anal. Calc. for $C_{19}H_{15}ClN_4O_2$ (366.80): C, 62.21; H, 4.12; N, 15.28 Found: C, 26.93; H, 4.28; N, 15.39.

3-[2-Methyl-1,3,4-thiadiazol-5-yl]-7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (15)

A mixture of **13** (3.85 gm, 0.01 mol) and phosphorous pentasulphide (7 g) was heated at 150-160°C in an oil bath for 2 h, after cooling, the mixture was treated with excess of dilute sodium hydroxide solution. The solid product thus separated was filtered and recrystallized to give **15** (40%); m.p. 240°C; IR: 1605, 1618 (2C=N), 1655 (C=O), 1400 (C-S-C). Anal. Calc. for $C_{19}H_{15}ClN_4OS$ (382.86): C, 59.58; H, 3.95; N, 14.64; S, 8.38 Found: C, 59.72; H, 4.21; N, 14.83; S, 8.49.

3-(Carbothiosemicarbazide)-7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (16a)

Method (A)

A mixture of **3** (3.43 gm, 0.01 mol), potassium thiocyanate (1.94 gm, 0.02 mol) and conc. hydrochloric acid (2 ml) in ethanol (50 ml) was refluxed for 8 h, the solid produced after concentration of the solvent was filtered and crystallized from ethanol to give **16**a (65%); m.p. 200 °C; IR: 1610 (C=N), 1630, 1650 (2C=O), 1150 (C=S), 3110-3340 (NH); ^{1}H NMR ($CDCl_3$): δ 2.91 (s, 3H, NCH_3), 3.00 (s, 1H, CH), 7.12-7.31 (m, 8H, ArH), 7.93-8.44 (br, 2H, NHNH), 9.12 (br, 2H, $CSNH_2$). Anal. Calc. for $C_{18}H_{16}ClN_5O_2S$ (401.87): C, 53.79; H, 4.01; N, 17.43; S, 7.98 Found: C, 53.91; H, 3.88; N, 17.52; S, 8.19.

Method (B)

Equimolecular quantities of **2** and thiosemicarbazide (0.92 gm, 0.01 mol) in ethanol (30 ml) was refluxed for 2 h, the reaction mixture was cooled. The solid that separated was filtered and crystallized from ethanol to give **16**a (60%).

3-[3-Thio-1,2,4-triazol-5-yl]-7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (17)

Method (A)

The above reaction is repeated while using pyridine in lieu of ethanol compound **17** was obtained (58%); m.p. 209°C; IR: 1605, 1610, 1628 (3C=N), 1650 (C=O), 1225 (C=S), 3200, 3300 (2NH); ^{1}H NMR(CF_3COOD): δ 2.76 (br, 3H, NCH_3), 2.98 (s, 1H, CH), 7.12-7.53 (m, 8H, Ar-H), 9.92 (br, 1H, NH), 10.32 (br, 1H, NH). Anal. Calc. for $C_{18}H_{14}ClN_5OS$ (383.85): C, 56.32; H, 3.68; N, 18.25; S, 8.35 Found: C, 56.11; H, 3.82; N, 18.30; S, 8.49.

Method (B)

A mixture of **3** (3.43 gm, 0.01 mol) and ammonium thiocyanate (1.52 gm, 0.02 mol) was heated at 210°C for 2 h, after cooling, the solid mass was triturated with warm water and the solid suspended was collected to give **17** (50%).

Method (C)

Refluxing of **16**a in pyridine for 6 h, the solid mass was then filtered to give **17** (60%).

Action of methyl iodide on 17: Formation of 18:

A mixture of **17** (3.84 gm, 0.01 mol), methyl iodide (1.42 ml, 0.01 mol) and sodium hydroxide (0.20 gm, 0.05 mol) in ethanol (70 ml) was heated under reflux for 1 h. The separated solid was washed with dil hydrochloric acid

(1%) and recrystallized from acetic acid to give **18** (70%); m.p. 210°C; IR: 1605, 1608, 1616 (3C=N), 1648 (C=O), 3105 (NH); ^{1}H NMR (CF_3COOD): 2.73 (s, 3H, NCH_3), 2.84 (s, 3HSCH_3), 3.16 (s, 1H, CH), 7.22-7.43 (m, 8H, ArH), 10.11 (br, 1H, NH). Anal. Calc. for $C_{19}H_{16}ClN_5OS$ (397.88): C, 57.35; H, 4.05; N, 17.60; S, 8.06 Found: C, 57.56; H, 3.95; N, 17.41; S, 8.38.

Action of acetic anhydride on 17: Formation of 19

A solution of **17** (3.84 gm, 0.01 mol) in acetic anhydride (20 ml) was refluxed for 4 h. Cooled and poured into water. The separated solid was collected and recrystallized from ethanol to give **19** (60%); m.p. 233°C; IR: 1610, 1628 (2C=N), 1250 (C=S), 1650, 1680 (2C=O), 3200 (NH); ^{1}H NMR($CDCl_3$): δ 2.73 (s, 3H, NCH_3), 2.98 (s, 1H, CH), 3.21 (s, 3H, $COCH_3$), 10.20 (br, 1H, NH). Anal. Calc. for $C_{20}H_{16}ClN_5O_2S$ (425.89): C, 56.41; H, 3.79; N, 16.45; S, 7.53 Found: C, 56.59; H, 3.92; N, 16.61; S, 7.78.

3-[1-Phenyl(carbothiosemicarbazide)]-7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (16b)

A methanolic solution of **3** (3.43 gm, 0.01 mol) and phenyl isothiocyanate (1.35 ml, 0.01 mol) were refluxed for 4 h. The contents were poured onto crushed-ice, filtered and crystallized from ethanol to give 16b (65%); m.p. 230°C; IR: 1608 (C=N), 1620, 1645 (2C=O), 1200 (C=S), 3100, 3250 (2NH); ^{1}H NMR($CDCl_3$): δ 2.83 (s, 3H, NCH_3), 3.21 (s, 1H, CH), 7.00-7.51 (br, 8H, Ar-H), 7.86-8.11 (br, 2H, NHNH), 9.61 (br, 2H, CSNHPh). Anal. Calc. for $C_{24}H_{20}ClN_5O_2S$ (477.91): C, 60.31; H, 4.21; N, 14.65; S, 6.70 Found: C, 60.49; H, 4.51; N, 14.89; S, 6.87.

3-[(2-Phenylamino)-1,3,4-thiadiazol-5-yl]-7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (20)

Compound **16**b (4.78 gm, 0.01 mol) was dissolved in cold concentrated sulfuric acid (5 ml, 0.05 mol) and the contents were kept at room temperature for 5 h, stirred occasionally and then poured into crushed-ice. The resulting solid was collected and crystallized from benzene to give **20** (70%); m.p. 198°C; IR: 1590, 1610, 1620 (3C=N), 1430 (C-S-C), 1660 (C=O), 3380 (NH); ^{1}H NMR (CF_3COOD): δ 2.82 (s, 3H, NCH_3), 2.93 (s, 1H, CH), 7.11-7.39 (m, 13H, Ar-H), 8.45 (br, 1H, NHPh). Anal. Calc. for $C_{24}H_{18}ClN_5OS$ (459.95): C, 62.67; H, 3.94; N, 15.23; S, 6.97 Found: C, 62.88; H, 3.82; N, 15.44; S, 7.16.

3-[1-Phenyl-2-mercapto-1,3,4-triazol-5-yl]-7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (21)

Compound **16**b (4.78 gm, 0.01 mol) was refluxed in sodium hydroxide solution (20 ml, 80%) for 5 h, cooled, poured onto excess of water, stirred and filtered. The filtrate on acidification gave a solid which was filtered and crystallized from methanol to give **21** (68%); m.p. 215°C; IR: 1608, 1615, 1618 (3C=N), 1650 (C=O), 2500 (SH); ^{1}H NMR(CF_3COOD): δ 2.97 (s, 3H, NCH_3), 3.16 (s, 1H, CH), 7.22-7.63 (m, 13H, ArH), 8.66 (s, 1H, SH). Anal. Calc. for $C_{24}H_{18}ClN_5OS$ (459.95): C, 62.67; H, 3.94; N, 15.23; S, 6.97 Found: C, 62.88; H, 3.82; N, 15.44; S, 7.16.

3-[(2-Phenylamino)-1,3,4-oxadiazol-5-yl]-7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (22)

To a solution of **16**b (4.78 gm, 0.01 mol) dissolved in minimum quantity of ethanol, 6N sodium hydroxide (15 ml) was added. The solution of iodine (5%) in potassium iodide was then added dropwise and the reaction mixture was kept at 10°C. The addition of iodine was continued till the colour of iodine persisted and the reaction mixture was refluxed for 4 h at 70-80°C on water-bath. It was cooled and then poured onto crushed-ice. The product thus obtained was filtered and crystallized from ethanol to give **22** (60%); m.p. 253°C; IR: 1590, 1620, 1630 (3C=N), 1665 (C=O), 3100 (NH). Anal. Calc. for $C_{24}H_{18}ClN_5O_2$ (443.88): C, 64.94; H, 4.09; N, 15.78 Found: C, 64.71; H, 4.31; N, 15.89.

Antibacterial activity

Most of the new target synthesized compounds were tested for their antibacterial activity *in vitro* against bacterial strains such as *B. subtilis* (gram positive) and *E. coli* (gram negative) employing the cup-plate method technique (Cruickshank *et al.*, 1975) at 50-100 μg/ml concentration (The results are list in Table I). The results showed all the compounds exhibit a marked degree of activity against both gram positive and gram negative bacteria at the minimum inhibitory concentration (MIC) of 50 μg/ml in comparison to ampicillin which was taken as standard drug.

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