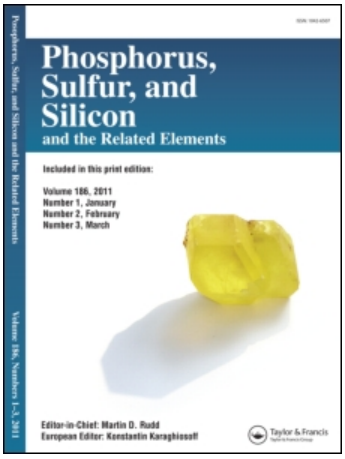

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Synthesis of New Fused 1,5-Benzodiazepines, Part 3

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Synthesis of New Fused 1,5-Benzodiazepines, Part 3*

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1,3-Dihydro-4-phenyl-1,5-benzodiazepin-2-one ***1a*** *was treated with some ylidenecyanothioacetamides to give the corresponding pyrido(2,3-b)benzodiazepines* ***3–6****. Treatment of compound* ***1a*** *with a mixture of thiophen-2-aldehyde and thiourea or guanidine gave the corresponding 1,3-thiazino- and pyrimido(4,5-b)benzodiazepines* ***7*** *and* ***8****. 3-Arylidene derivatives* ***9a–e*** *and* ***10*** *were synthesized. Compound* ***10*** *was subject to react with 2-(1-methylthio-1′-anilinomethylidene)malononitrile to give oxazino-benzodiazepine* ***11****. Thieno(3,2-b)benzodiazepines* ***12a,b*** *and* ***13*** *were synthesized via the reaction of compound* ***1b*** *with sulfur and some active nitriles. [1,3-Dihydro-4-phenyl(1,5)-benzodiazepin-2-ylidene]malononitrile* ***15*** *was used as synthon to obtain novel pyrido-, pyrano-, benzo-, and thienobenzodiazepines* ***16–20****, respectively. The reaction of compound* ***1b*** *with* CS_2 *or PhNCS along with 1,1,3-tricyano-2-aminoprop-1-ene, 2-(1-methylthio-1′-anilinomethylidene)malononitrile, or 1,3-dibromopropane gave the corresponding polyfused benzodiazepines* ***21–23****, respectively.*

Keywords 1,3-Dihydro-4-phenyl-1,5-benzodiazepin-2-one; pyridobenzodiazepines; pyrimidobenzodiazepines; thiazinobenzodiazepines; oxazinobenzodiazepines; thienobenzodiazepines

INTRODUCTION

Benzodiazepines have been widely employed in clinical practices as anxiolytics,[1] sedative-hypnotics,[2] anticonvulsant vasopressin antagonists,[3] and anticipated CNS-depressants.[4] Interestingly, benzothienobenzodiazepine (Y-931), dibenzo[b,f]diazepine (clozapine), and thienobenzodiazepine (olanzapine) are known as typical effective antipsychotics.[5,6]

This prompted us to continuate our previous work[7,8] to synthesize some new fused and spiro benzodiazepines. So, we report herin the synthesis of novel pyridine, pyran, thiophene, pyrimidine, oxazine, thiazine, and naphthyridine rings fused with benzodiazepine moiety.

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*For Part 1 and Part 2, see references 7 and 8.

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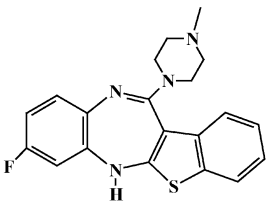
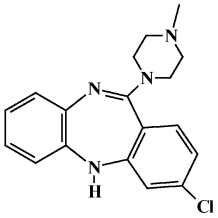
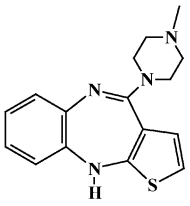


Y-931



clozapine



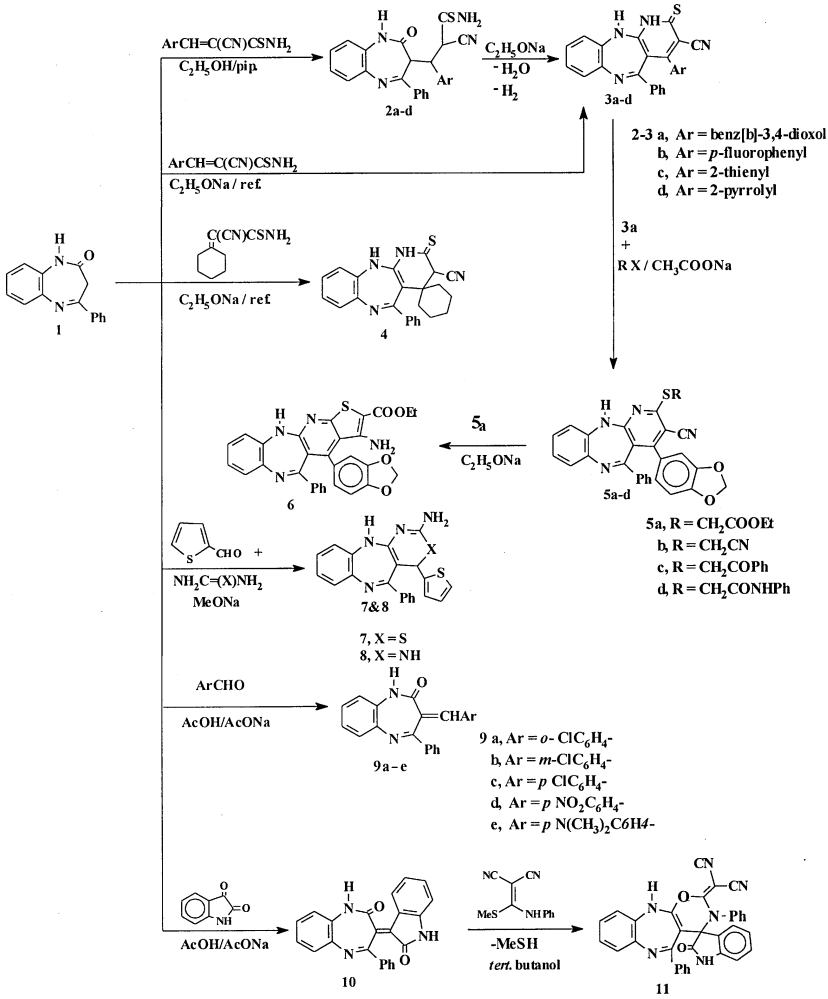
olanzapine

SCHEME 1

RESULTS AND DISCUSSION

The reaction of 1,3-dihydro-4-phenyl-1,5-benzodiazepin-2-one $\mathbf{1_a}$[9] with a variety of arylidenecyanothioacetamides namely; benzo[b]-3,4-dioxolmethylidene-, *p*-fluorobenzylidene-, thien-2-ylidene-, or pyrrol-2-ylidenecyanothioacetamide in the presence of piperidine as a catalyst, afforded the corresponding 3-substituted benzodiazepines $\mathbf{2_{a–d}}$, which in turn were cyclized in the presence of sodium ethoxide to afford 3-cyano-pyrido[2,3-b][1,5]benzodiazepine–2-thione derivatives $\mathbf{3_{a–d}}$. Compounds $\mathbf{3_{a–d}}$ and **4** were also prepared in one step *via* the reaction of compound $\mathbf{1_a}$ with the same arylidenecyanothioacetamides or cyclohexylidenecyano thio-acetamide in alcoholic sodium ethoxide. IR spectra of compounds $\mathbf{2_{a–d}}$ showed the absorption bands corresponding to NH_2, CN, and C=O groups at 3320, 3200, 2210, and 1690 Cm^{-1}, respectively, whereas IR spectra of compounds $\mathbf{3_{a–d}}$ and **4** showed the disappearance of the absorption bands corresponding to NH_2 and C=O groups and the appearance of the absorption bands corresponding to NH groups (cf. Scheme 2, Table I). Compound $\mathbf{3_a}$ was treated with some active halo compounds, namely ethyl chloroacetate, chloroacetonitrile, phenacyl bromide, or chloroacetanilide, in the presence of sodium acetate, to afford the corresponding S-alkylated derivatives $\mathbf{5_{a–d}}$. Compound $\mathbf{5_a}$ underwent intramolecular cyclization,[10] affording the corresponding thieno[3′,2′:5,6]pyrido[2,3-b]-1,5-benzodiazepine derivative **6** on refluxing with sodium ethoxide. IR spectrum of compound **6** showed the disappearance of the absorption band corresponding to the CN group and ^{1}H-NMR spectrum revealed a broad signal at δ 5.4–5.0 of the NH_2 group, which was exchangeable with deuterium on addition of D_2O (c.f. Scheme 2, Table I).

Treatment of compound $\mathbf{1_a}$ with a mixture of thiophen-2-aldehyde and thiourea or guanidine in the presence of sodium methoxide[11] gave the corresponding 1,3-thiazino- and pyrimido[4,5-b][1,5]benzodiazepine derivatives **7** and **8**, respectively (c.f. Scheme 2, Table I).



SCHEME 2

3-Arylidene-1,5-benzodiazepine derivatives **9a–e** and **10** were synthesized through the reaction of compound **1a** with some aromatic carbonyl reagents including *o*-, *m*-, and *p*-chlorobenzaldehyde; *p*-nitrobenzaldehyde; *p*-N,N-dimethylaminobenzaldehyde; or isatine in glacial acetic acid and fused sodium acetate as a catalyst. Compound **10** was subjected to react with 2-(1-methylthio-1′-anilinomethylidene)malononitrile[12] in *tert*. butanol to afford the corresponding 1,3-oxazine[6,5-b](1,5)benzodiazepine derivative **11**. IR spectrum of

TABLE I Analytical and Spectral Data of the New Compounds

Product no	M.P (°C)[a] cryst. solvent	Yield (%)	Mol. form. (mol. w.t.)	Analytical data (cal./found)[b] C	H	N	S	IR (Cm^{-1})[c]	H-NMR (δ ppm)[d]
2_a	166 (EtOH)	80	$C_{26}H_{20}N_4O_3S$ (468.53)	66.50 66.77	4.30 4.65	11.96 11.70	6.84 6.65	3433, 3366, 3211(NH, NH_2), 2214(CN), 1898 (CO), 1432(CS).	10.2(s, 1H, NH), 8.0–7.3(m, 12H, arom.), 6.3(m, 1H, CH—Ar), 7.0[br, 1H, CH(CN)], 5.5–5.2(br, 2H, NH_2), 4.0(s, 2H, CH_2), 3.5(d, 1H, $CH_{benzdiazepine}$).
2_b	187 (Dioxane)	86	$C_{25}H_{19}FN_4OS$ (442.51)	67.86 67.69	4.33 4.56	12.66 12.43	7.25 7.10	3321, 3300, 3201(NH, NH_2), 2224(CN), 1890 (CO), 1430(CS).	10.0(s, 1H, NH), 8.1–7.5(m, 13H, arom.), 6.2(t, 1H, CH—Ar), 7.2[br, 1H, CH(CN)], 5.5–5.1(br, 2H, NH_2), 3.8(d, 1H, $CH_{benzodiazepine}$).
2_c	177 (Acetic acid)	90	$C_{23}H_{18}N_4OS_2$ (430.54)	64.16 64.32	4.21 4.04	13.01 13.32	14.89 14.76	3400, 3326, 3241(NH, NH_2), 2240(CN), 1893 (CO), 1442(CS).	10.0(s, 1H, NH), 8.2–7.7(m, 12H, arom.), 6.0(m, 1H, CH—Ar), 5.9[br, 1H, CH(CN)], 5.3–5.0(br, 2H, NH2), 3.7(d, 1H, $CH_{benzodiazepine}$).
2_d	219 (DMF)	66	$C_{23}H_{19}N_5OS$ (413.50)	66.81 66.93	4.30 4.54	16.94 16.75	7.75 7.93	3344, 3312, 3265(2NH, NH_2), 2211(CN), 1700 (CO), 1422(CS).	10.2(s, 1H, NH), 9.2(s, 1H, $NH_{pyrrole}$), 8.0–7.5(m, 12H, arom.), 6.1(m, 1H, CH—Ar), 5.7[br, 1H, CH(CN)], 5.3–4.9(br, 2H, NH_2), 3.5(d, 1H, $CH_{benz.}$)
3_a	290 (Dioxane)	85	$C_{26}H_{16}N_4O_2S$ (448.5)	69.63 69.43	3.60 3.43	12.49 12.51	7.15 7.34	3333, 3200(NH), 2242 (CN), 1430(CS).	13.4(s, 1H, NH), 10.0(s, 1H, NH), 8.2–7.1 (m, 13H, arom.).
3_b	266 (EtOH)	80	$C_{25}H_{15}FN_4O$ (422.48)	71.07 71.23	3.58 3.30	13.26 13.42	7.59 7.32	3321, 3211(NH), 2211 (CN), 1436(CS).	12.4(s, 1H, NH), 9.4(s, 1H, NH), 8.3–7.6 (m, 12H, arom.).

3c	270 (DMF)	71	$C_{23}H_{14}N_4S_2$ (410.00)	67.30 67.43	3.44 3.55	13.65 13.48	15.62 15.78	3300, 3241(NH), 2251 (CN), 1440(CS).	10.4(s, 1H, NH), 9.4(s, 1H, NH), 8.3–7.7 (m, 12H, arom.).
3d	240-3 (DMF)	67	$C_{23}H_{15}N_5S$ (393.46)	70.21 70.43	3.84 3.72	17.80 17.69	8.15 8.32	3341, 3231(NH), 2231 (CN), 1432(CS).	11.4(s, 1H, NH), 9.9(s, 1H, NH), 8.0–7.1 (m, 12H, arom.).
4	222 (EtOH)	68	$C_{24}H_{22}N_4S$ (398.52)	72.33 72.44	5.56 5.73	14.06 14.31	8.08 8.23	3266, 3200(2NH), 2133 (CN), 1444(CS).	12.4(s, 1H, NH), 8.4(s, 1H, NH), 8.3–7.8 (m, 9H, arom.), 3.8(s, 1H, CH, CN), 3.0–1.0(m, 10H, $5CH_2$).
5a	220 (EtOH)	69	$C_{30}H_{22}N_4O_4S$ (534.59)	67.40 67.43	4.15 4.31	10.48 10.51	6.00 6.23	3280(NH), 2233(CN).	11.0(s, 1H, NH), 8.3–7.7(m, 12H, arom.), 4.2(s, 2H, SCH_2), 4.0(s, 2H, CH_2).
5b	210 (Benzene)	64	$C_{28}H_{17}N_5O_2S$ (487.53)	68.98 68.64	3.51 3.70	14.35 14.49	6.58 6.43	3220(NH), 2143(CN), 1734(CO).	13.0(s, 1H, NH), 8.0–7.4(m, 12H, arom.), 4.4–4.3(m, 4H, $CH_{2\ ester} + SCH_2$), 3.9(s, 2H, CH_2) 1.3–1.1(t, 3H, CH_3).
5c	222 (EtOH)	44	$C_{34}H_{22}N_4O_3S$ (566.63)	72.07 72.33	3.91 3.72	9.89 9.71	5.66 5.87	3224(NH), 2220 (CN), 1690 (CO).	9.0(s, 1H, NH), 8.3–7.7(m, 17H, arom.), 4.0(s, 2H, SCH_2), 3.7(s, 2H, SCH_2).
5d	238 (DMF)	76	$C_{34}H_{23}N_5O_3S$ (581.65)	70.21 70.43	3.99 3.85	12.04 12.24	5.51 5.78	3210, 3122(2NH), 2218 (CN), 1690 (CO).	9.0(s, 1H, NH), 8.3–7.7(m, 17H, arom. + NH), 4.0(s, 2H, CH_2), 3.7(s, 2H, SCH_2).
6	>330 (DMF)	50	$C_{30}H_{22}N_4O_4S$ (534.59)	67.40 67.66	4.15 4.33	10.48 10.57	6.00 6.12	3421, 3350, 3210(NH, NH_2), 1734(CO).	10.0(s, 1H, NH), 8.4–7.4(m, 12H, arom.), 6.0–5.5(br, 2H, NH_2), 4.4–4.3(q, 2H, $CH_{2\ ester}$), 3.9(s, 2H, CH_2) 1.3–1.1(t, 3H, CH_3).
7	305 (Dioxane)	80	$C_{21}H_{16}N_4S_2$ (388.50)	64.92 64.62	4.15 4.36	14.42 14.48	16.50 16.81	3344, 3200, 3182($NH + NH_2$).	13.0(s, 1H, NH), 8.2–7.5(m, 12H, arom.), 5.4–5.0(br, 2H, NH_2).

(Continued on next page)

TABLE I Analytical and Spectral Data of the New Compounds *(Continued)*

Product no	M.P (°C)[a] cryst. solvent	Yield (%)	Mol. form. (mol. w.t.)	Analytical data (cal./found)[b] C	H	N	S	IR (Cm^{-1})[c]	H-NMR (δ ppm)[d]
8	310 (Dioxane)	50	$C_{21}H_{15}N_5S$ (39.44)	68.27 68.54	4.09 4.23	8.96 8.88	8.68 8.92	3350, 3344, 3212, 3112 ($2NH + NH_2$).	11.0(s, 1H, NH), 8.3–7.7(m, 13H, arom. + NH), 6.4–6.0(br, 2H, NH_2).
9_a	288 (Benzene)	90	$C_{22}H_{15}ClN_2O$ (358.86)	73.64 73.90	4.21 4.42	7.81 7.92		3221(NH), 1700(CO).	13.5(s, 1H, NH), 8.1–7.6(m, 13H, arom.), 6.9(s, 1H, =CH).
9_b	300 (EtOH)	98	$C_{22}H_{15}ClN_2O$ (358.86)	73.64 73.40	4.21 4.00	7.81 7.78		3201(NH), 1702(CO).	14.5(s, 1H, NH), 8.2–7.3(m, 13H, arom.), 6.8(s, 1H, =CH).
9_c	321 (EtOH)	87	$C_{22}H_{15}ClN_2O$ (358.86)	73.64 73.39	4.21 4.45	7.81 7.70		3211(NH), 1700(CO).	11.5(s, 1H, NH), 8.1–7.6(m, 13H, arom.), 6.9(s, 1H, =CH).
9_d	278 (Acetic acid)	83	$C_{22}H_{15}N_3O_3$ 369.38	71.54 71.12	4.09 4.32	11.38 11.51		3231(NH), 1702(CO).	12.5(s, 1H, NH), 7.9–7.2(m, 13H, arom.), 6.9(s, 1H, =CH).
9_e	244 (EtOH)	95	$C_{24}H_{21}N_3O$ (367.44)	78.45 78.22	5.70 5.65	11.44 11.23		3221(NH), 1700(CO).	13.5(s, 1H, NH), 8.5–7.8(m, 13H, arom.), 7.4(s, 1H, =CH), 2.3(s, 6H, $N(CH_3)_2$].
10	>330 (DMF)	97	$C_{23}H_{15}N_3O_2$ 365.39	75.61 75.43	4.14 4.32	11.50 11.65		3321, 3231(2NH), $1720_{isatine}$, 1704(2CO).	13.5(s, 1H, NH), 10.0(s, 1H, $NH_{isatine}$), 8.2–7.5 (m, 13H, arom.).
11	165 (EtOH)	58	$C_{33}H_{20}N_6O_2$ (532.5)	74.43 74.12	3.79 3.55	15.78 15.54		3221(NH), 2180(CN).	13.0(s, 1H, NH), 10.2(s, 1H, $NH_{isatine}$), 8.0–7.2 (m, 18H, arom.).
12_a	181 (EtOH)	75	$C_{20}H_{16}N_4S$ (344.43)	69.74 69.56	4.68 4.60	16.27 16.46	9.31 9.50	3221, 3168(NH_2), 2100 (CN).	8.6–7.0 (m, 9H, arom.), 6.4–6.0(br, 2H, NH_2), 2.2–2.0(q, 2H, CH_2), 1.1–0.9(t, 3H, CH_3).

12$_b$	215 (Dioxan)	65	$C_{22}H_{21}N_3O_2S$ (391.49)	67.50 67.70	5.41 5.26	10.73 10.80	8.19 8.00	3331, 3240(NH_2), 1730 (CO).	7.6–7.0 (m, 9H, arom.), 5.4–5.0(br, 2H, NH_2), 4.3–4.0(q, 2H, $CH_{2\ ester}$), 2.3–2.0 (q, 2H, CH_2), 1.1–0.9(t, 3H, CH_3).
13	285 (EtOH)	57	C23H18N6S (410.50)	67.30 67.43	4.42 4.66	20.47 20.65	7.81 7.99	3331, 3300, 3210, 3145 (2NH_2), 2230(2CN).	8.6–7.0 (m, 9H, arom.), 5.1–4.6(br, 2H, $NH_{2\ thiophene}$), 4.1–3.8(br, 2H, NH_2), 2.2–2.0(q, 2H, CH_2), 1.1–0.9(t, 3H, CH_3).
14	>330 (DMSO)	43	$C_{30}H_{23}N_7S_2$ (545.8)	66.03 66.32	4.25 4.40	17.97 17.79	11.75 11.60	3350, 3310, 3230, 3185 (2NH_2), 2170(CN), 1433 (CS).	8.6–7.0 (m, 14H, arom.), 6.7(s, 2H, NH_2), 5.1–4.6(br, $2HNH_{2thiophene}$), 2.2–2.0(q, 2H, CH_2), 1.1–0.9(t, 3H, CH_3).
16$_a$	295 (Dioxan)	77	$C_{25}H_{17}N_5S$ (419.50)	71.58 71.63	4.08 4.30	1.69	7.45 7.17	3320, 3300, 3265($NH+NH_2$), 2169(CN), 1433 (CS).	12.0(s, 1H, NH), 8.0–7.5(m, 14H, arom.), 5.5–5.1(br, 2H, NH_2).
16$_b$	341 (Dioxan)	68	$C_{26}H_{17}N_5OS$ (447.51)	69.78 69.52	3.83 3.68	15.65 15.54	7.16 7.01	3330, 3300, 3235($NH+NH_2$), 2149(CN), 1433 (CS).	12.4(s, 1H, NH), 8.2–7.3(m, 14H, arom.), 5.4–5.0(br, 2H, NH_2).
17	300 (EtOH)	56	$C_{25}H_{16}N_4O$ (388.43)	77.31 77.56	4.15 4.34	14.42 14.23		3215, 3199(2NH), 2200 (CN), 1689(CO).	9.9(s, 1H, NH), 7.8–7.2(m, 15H, arom. + NH).
18	281 (EtOH)	56	$C_{25}H_{18}N_4O$ (390.44)	76.91 76.79	4.65 4.56	14.35 14.75		3387, 3215, 3199(NH, NH_2), 2220 (CN), 1689(CO).	10.4(s, 1H, NH), 8.0–7.5(m, 14H, arom.), 5.2–4.9(br, 2H, NH_2).
19	311 (EtOH)	60	$C_{27}H_{16}ClN_5$ (445.91)	72.73 72.55	3.62 3.76	15.71 15.57		3320, 3300, 3265($NH+NH_2$), 2169(CN).	13.4(s, 1H, NH), 8.0 −7.5(m, 13H, arom.), 5.0–4.6(br, 2H, NH_2).

(Continued on next page)

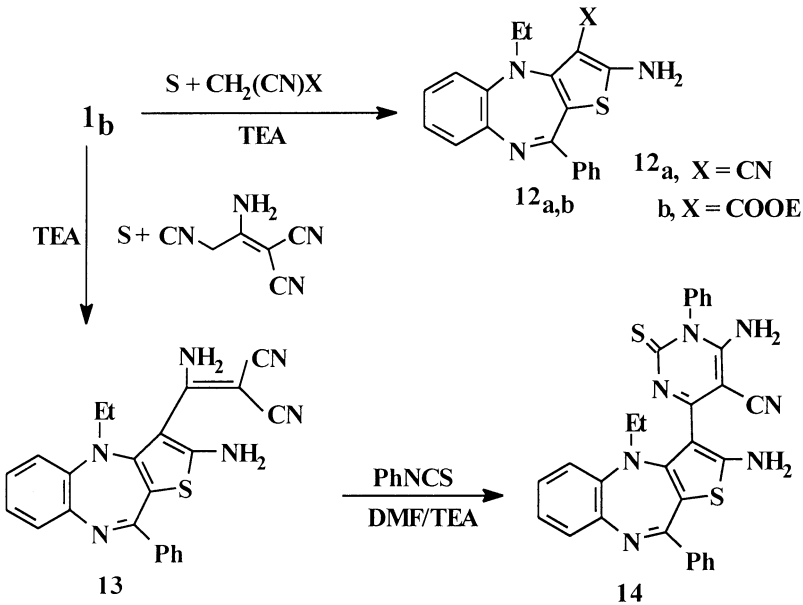
TABLE I Analytical and Spectral Data of the New Compounds *(Continued)*

Product no	M.P (°C)[a] cryst. solvent	Yield (%)	mol. form. (mol. w.t.)	Analytical data (cal./found)[b] C	H	N	S	IR (Cm^{-1})[c]	H-NMR (δ ppm)[d]
20	175 (EtOH)	85	$C_{18}H_{12}N_4S$ (316.38)	68.33 68.55	3.82 3.66	17.71 17.62	10.13 10.29	3320, 3300, 3235($NH+NH_2$), 2221(CN).	10.0(s, 1H, NH), 7.9–7.2 (m, 9H, arom.), 5.1(s, 2H, NH_2).
21$_a$	301 (Bnzene)	86	$C_{24}H_{18}N_6S_2$ (454.57)	63.42 63.64	3.99 3.82	18.49 18.60	14.11 14.37	3331, 3300, 3210, 3145 ($2NH_2$), 2130(CN), 1443(CS).	8.6–7.0 (m, 9H, arom.), 6.4–6.0(br, 2H, NH_2), 5.1–4.6(br, $2HNH_2$), 2.2–2.0(q, 2H, CH_2), 1.1–0.9(t, 3H, CH_3).
21$_b$	295 (EtOH)	85	$C_{30}H_{23}N_7S$ (513.62)	70.16 70.36	4.15 4.36	19.09 19.26	6.24 6.46	3300, 3250, 3200, 3135 ($2NH_2$), 2130(CN), 1433(CS).	8.5–7.3 (m, 14H, arom.), 6.0–5.6(br, 2H, NH_2), 5.0–4.5(br, $2HNH_2$), 2.3–2.1(q, 2H, CH_2), 1.1–0.8(t, 3H, CH_3).
22$_a$	285 (EtOH)	87	$C_{28}H_{19}N_5S_2$ (489.61)	68.69 68.44	3.91 3.80	14.30 14.12	13.10 13.31	2219, 2210(2CN), 1422(CS).	8.3–7.3 (m, 9H, arom.), 2.2–2.0(q, 2H, CH_2), 1.1–0.9(t, 3H, CH_3).
22$_b$	287 (EtOH)	77	$C_{34}H_{24}N_6S$ (548.66)	74.43 74.21	4.41 4.19	15.32 15.02	5.84 5.71	2233, 2200 (2CN), 1422(CS).	8.0–7.0 (m, 14H, arom.), 2.2–2.0(q, 2H, CH_2), 1.1–0.9(t, 3H, CH_3).
23	311 (Dioxane)	65	$C_{21}H_{20}N_2OS_2$ (390.52)	66.29 66.01	5.30 5.12	7.36 7.14	16.85 16.90	2966, 2877(CH), 1704 (CO).	8.3–7.3 (m, 9H, arom.), 3.5–2.4(m, 6H, $3CH_2$), 2.2–2.0(q, 2H, CH_2), 1.1–0.9(t, 3H, CH_3).

[a]Uncorrected.
[b]Satisfactory microanalyses obtained; C, ± 0.3%, H, ± 0.3%, N, ± 0.45%, S, ± 0.21.
[c]Measured on Nicolet 710 FT-IR spectrophotometer.
[d]Measured with a Varian EM 360 L using TMS as internal standard.

compound **11** showed an absorption band corresponding to the CN group at 2219 Cm^{-1} (c.f. Scheme 2, Table I).

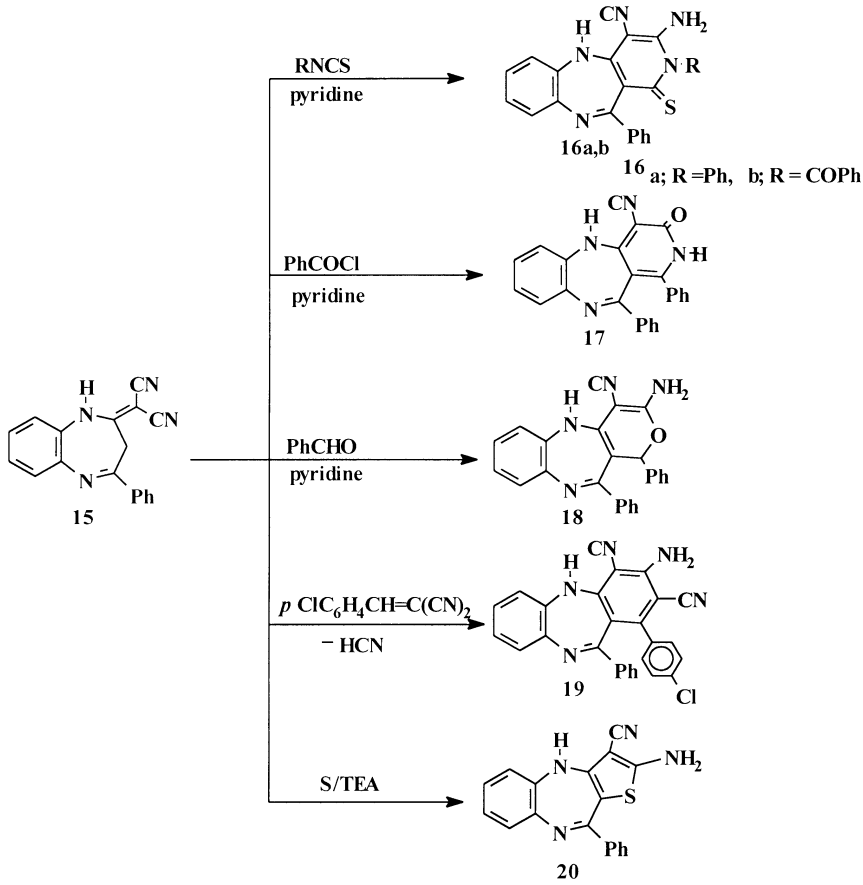
1,3-Dihydro-1-ethyl-4-phenyl-1,5-benzodiazepin-2-one $\mathbf{1_b}$[13] was allowed to react with elemental sulfur along with malononitrile, ethyl cyanoacetate, or 1,1,3-tricyano-2-aminoprop-1-ene to yield the corresponding thieno[3,2-b]benzodiazepines $\mathbf{12_{a,b}}$ and **13**, respectively. Treatment of compound **13** with phenyl isothiocyanate[14] in the presence of triethylamine as a base gave the corresponding 2-amino-3-pyrimidinyl thieno(3,2-b)-1,5-benzodiazepine derivative **14**. The reaction pathway for the formation of compound **14** was assumed to proceed via a nucleophilic attack of the ethylenic NH_2 group to the C=S group followed by a nucleophilic addition of the formed NH group to the CN group (c.f. Scheme 3, Table I).



SCHEME 3

[1,3-Dihydro-4-phenyl(1,5)benzodiazepin-2-ylidene]malononitrile **15**[8] was treated with phenyl isothiocyanate,[15] benzoyl isothiocyanate, benzoyl chloride,[15] or benzaldehyde[15] in pyridine to give the corresponding pyrido(4,3-b)benzodiazepinethiones $\mathbf{16_{a,b}}$, pyrido(4,3-b)benzodiazepinone **17**, or pyrano(4,3-b)benzodiazepine **18**, respectively. Moreover, treatment of compound **15** with *p*-chlorobenzylidenemalononitrile[12] in the presence of triethylamine afforded the corresponding 3-amino-2,4-dicyanobenz[b]-(1,5)benzodiazepine

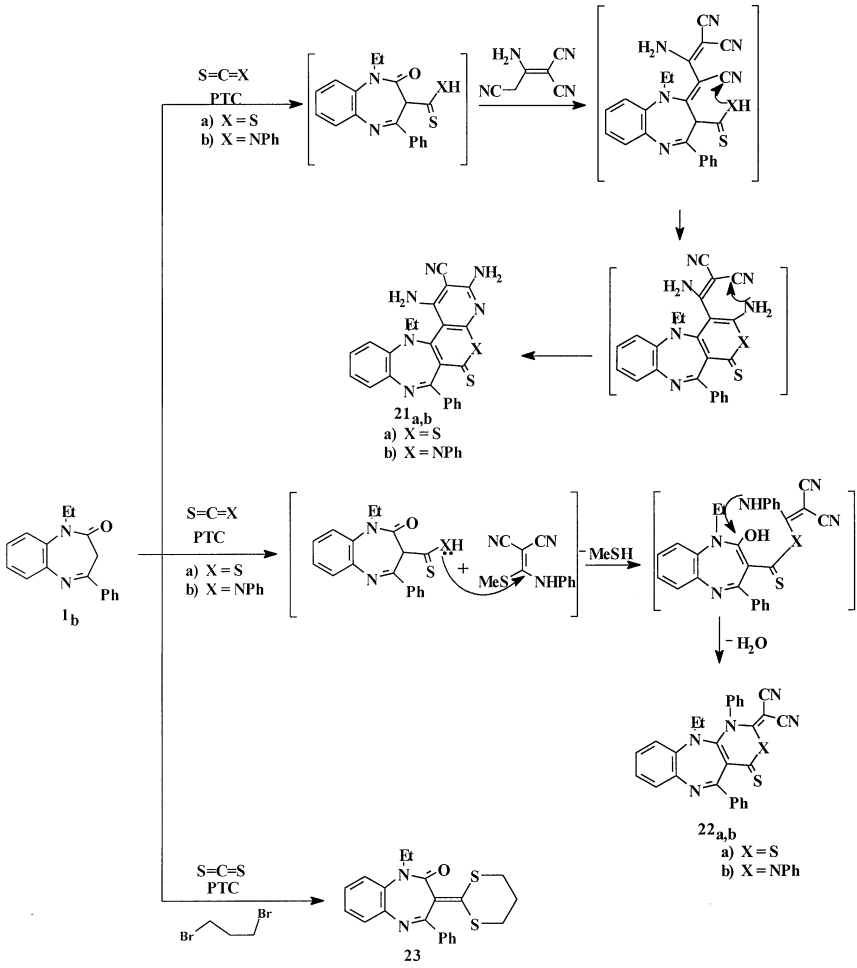
derivative **19**. Thieno[3,2-b]benzodiazepine **20** was synthesized through the reaction of compound **15** with elemental sulfur in the presence of triethylamine (c.f. Scheme 4, Table I).



SCHEME 4

Compound $\mathbf{1_b}$ was allowed to react with a mixture of CS_2 or PhNCS and 1,1,3-tricyano-2-aminoprop-1-ene under PTC conditions (dioxane/K_2CO_3/tetrabutylammonium bromide [TBAB]) to afford pyridothiopyrano[4,3-b]-1,5-benzodiazepine $\mathbf{21_a}$ and [1,5]-benzodiazepino[6,5-c][1,8]naphthyridine $\mathbf{21_b}$, respectively. The reaction pathway[16] was indicated in Scheme 5. Also, treatment of compound $\mathbf{1_b}$ with a mixture of CS_2 or PhNCS and 2(1-methylthio-1′-anilinomethyl-idene)malononitrile[12] under PTC conditions afforded the corresponding 1,3-thiazino(4,5-b)-1,5- benzodiazepine $\mathbf{22_a}$ and

pyrimido-1,5-benzodiazepine **22$_b$** derivatives, respectively. Morever, the reaction of compound **1$_b$** with CS_2 and 1,3-dibromopropane in a 1:1:1 molar ratio under the same PTC conditions afforded the corresponding 3[1,3-dithi-2-ylidene]benzodiazepin-2-one derivative **23** (c.f. Scheme 5, Table I).



SCHEME 5

EXPERIMENTAL

All melting points were determined on a Koffler melting points apparatus and are uncorrected. IR spectra were obtained on a Nicolet 710

FT-IR spectrometer. ^{1}H-NMR spectra were recorded on a Varian EM 360 at 60 MHz using TMS as an internal reference and DMSO-d_6 as a solvent. Elemental analyses were performed on a perkin-Elmer CHN-2400°C analyzer model.

Synthesis of Compounds $2_{a–d}$

A mixture of compound $\mathbf{1_a}$ (0.01 mol, 2.36 gm), the appropriate arylidenecyanothioacetamide (0.01 mol), including benz[b]-3,4-dioxolmethylidene- (2.32 g), *p*-fluorobenzylidene- (2.06 g), thiene-2-ylidene- (1.94 g), or pyrrol-2-ylidenecyanothioacetamide (1.77 g), and catalytic amount of piperidine (0.2 mL) was refluxed in dioxane (20 mL) for 2 h. The formed precipitate was filtered off and crystallized from an appropriate solvent to give compounds $\mathbf{2_{a–d}}$ (cf. Scheme 2, Table I).

Synthesis of Compounds $3_{a–d}$ (Method A)

The appropriate compound $\mathbf{2_{a–d}}$ (0.01 mol) was suspended in sodium ethoxide solution (0.23 g Na in 30 mL absolute ethanol) and refluxed for 3 h. The solid that formed after cooling was collected by filteration, washed with water, and crystallized from the suitable solvent to give the compounds $\mathbf{3_{a–d}}$ (cf. Scheme 2, Table I).

Synthesis of Compounds $3_{a–d}$ and 4 (Method B)

A mixture of compound $\mathbf{1_a}$ (0.01 mol, 2.36 gm), the appropriate ylidenecyanothioacetamide (0.01 mol), and sodium ethoxide (0.23 g of Na in 40 mL absolute ethanol) was refluxed for 2 h. The formed precipitate was filterd off, dried, washed with water, and crystallized from an appropriate solvent to give compounds $\mathbf{3_{a–d}}$ and **4**, respectively (cf. Scheme 2, Table I).

Synthesis of Compounds $5_{a–d}$

A mixture of compound $\mathbf{3_a}$ (0.005 mol, 4.48 gm), (0.005 mol) from the appropriate halo compound (chloroacetonitrile [0.31 mL], ethyl chloroacetate [0.54 mL], phenacyl bromide [0.93 g] or chloroacetanilide [0.85 g]) and sodium acetate (0.005 mol, 0.41 gm) in ethanol (20 mL) was refluxed for 2 h. The precipitate that was obtained was filtered off, washed with water, and crystallized from the appropriate solvent to give the compounds $\mathbf{5_{a–d}}$, respectively (cf. Scheme 2, Table I).

Synthesis of Compound 6

Compound **5$_a$** (0.01 mol, 5.34 g) was suspended in sodium ethoxide solution (0.35 g Na in 30 mL absolute ethanol) and refluxed for 3 h. The solid that formed after cooling was filtered off, washed with water, and crystallized from the ethanol to give the compound **6** (cf. Scheme 2, Table I).

Synthesis of Compounds 7 and 8: General Procedure

To a stirred solution of compound **1$_a$** (0.003 mol, 0.7 g) in methanol (25 mL), thiophene-2-aldehyde (0.003 mol, 0.28 mL), thiourea (0.003 mol, 0.22 g) or guanidine hydrochloride (0.003 mol, 0.28 g) and sodium methoxide (0.23 g Na in 5 mL methanol) were added. The reaction mixture was refluxed for 2 h, evaporated *in vacuo* and the residue was triturated with pet. ether (60–80°C). The solid product was collected by filtration and crystallized (cf. Scheme 2, Table I).

Synthesis of Compounds 9 and 10: General Procedure

A mixture of compound **1$_a$** (4.72 g, 0.005 mol); the appropirate carbonyl reagent (0.005 mol), including *o*-chloro- (0.7 g), *m*-chloro- (0.7 g), *p*-hloro- (0.7 g), *p*-nitro- (o.75 g), *p* N,N-dimethylaminobenzaldehyde (0.73 g), or isatin (0.73 g); and fused sodium acetate (2.3 g) in glacial acetic acid (20 mL) was refluxed for 4 h. On cooling, the precipitated solid was filtered, dried, washed with water, and crystallized from appropirate solvent (cf. Scheme 2, Table I).

Synthesis of Compound 11

Equimolar amount (0.003 mol) of compound **10** (0.28 g) and 2(1-methylthio-1′-anilinomethylidene)malononitrile (0.64 g) were dissolved in *tert.* butanol (30 mL) containing few drops of triethyl amine. The reaction mixture was refluxed until the evolution of MeSH ceased (12 h), evaporated *in vacuo*, and the remaining residue was triturated with pet. ether (40–60°C). The solid formed was collected by filtration and crystallized (cf. Scheme 2, Table I).

Synthesis of Compounds 12 and 13: General Procedure

A mixture of compond **1$_b$** (0.002 mol, 0.53 g); elemental sulfur (0.002 mol, 0.096 g); the appropirate active methylene (0.003 mol) including malononitrile (0.1 g), ethyl cyanoacetate (0.23 mL), or 1,1,3-tricyano-2-aminoprop-1-ene (0.26 g), and triethylamine (0.003 mol,

0.32 mL) in dioxane (20 mL) was refluxed for 3 h. The solid that formed on cooling was filtered off and crystallized from an appropirate solvent (cf. Scheme 3, Table I).

Synthesis of Compound 14

A mixture of compound **13** (0.002 mol, 0.82 g), phenyl isothiocyanate (0.002 mol, 0.23 mL), and a catalytic amount of triethylamine was refluxed in dimethylformamide (20 mL) for 2 h. The formed precipitate was filtered off and crystallized to give compound **14** (cf. Scheme 3, Table I).

Synthesis of Compounds $16_{a,b}$–18: General Procedure

Equimolar amounts (0.003 mol) of compound **15** (0.89 g) and phenyl isothiocyanate (0.35 mL), benzoyl isothiocyanate (0.4 mL), benzoyl chloride (0.34 mL) or benzaldehyde (0.32 mL) in pyridine (20 mL) was refluxed for 5 h. After cooling, the reaction mixture was poured into a mixture of ice water (100 mL) and HCl (5 mL). The separated solid was then collected by filtration, washed with water, and crystallized from appropirate solvent (Scheme 4, Table I).

Synthesis of Compounds 19

(0.003 Mol) of compound **15** (0.89 g), *p*-chlorobenzylidene-malononitrile (0.7 g), and triethylamine (0.2 mL) in dioxane (20 mL) was refluxed for 4 h. On cooling, the precipitated solid was filtered off, dried, and crystallized (cf. Scheme 4, Table I).

Synthesis of Compound 20

A mixture of compound **15** (0.003 mol, 0.89 g), elemental sulfur (0.003 mol, 0.1 g), and a catalytic amount of triethylamine was refluxed in dioxane (20 mL) for 2 h. The formed precipitate was filtered off and crystallized to give compound **20** (cf. Scheme 3, Table I).

Synthesis of Compounds 21–23: General Procedure

A mixture of anhydrous potassium carbonate (3 g), dry dioxane (30 mL), compound $\mathbf{1_b}$ (0.003 mol, 0.79 g), carbon disulfide (0.003 mol, 0.22 mL) or phenyl isothiocyanate (0.003 mol, 0.36 mL) and TBAB (0.003 g) was stirred for 2 h. at room temperature and stirred for 2 h at 60°C. To the

reaction mixture, the appropirate reagent (0.003 mol), namely, 1,1,3-tricyano-2-aminoprop-1-ene (0.39 g), 2(1-methylthio-1'-anilinomethylidene)malononitrile (0.64 g), or 1,3-dibromopropane (0.6 mL), was added. The reaction mixture was stirred for 5 h at 60°C until the completion of the reaction (TLC). The reaction mixture was filtered off and the filtrate evaporated in vacuo. The residual solid was washed with water and then crystallized from the appropriate solvent (cf. Scheme 5, Table I).

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