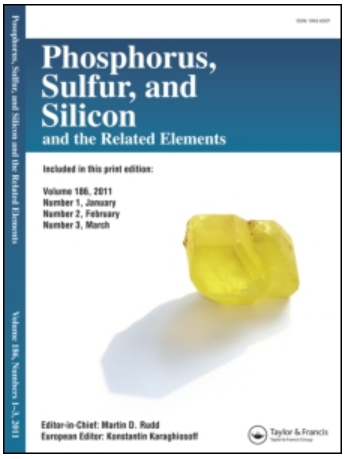

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A CONVENIENT SYNTHESIS OF POLYFUNCTIONALLY SUBSTITUTED HETEROCYCLIC SYSTEMS DERIVED FROM 4-METHYL-2H-l,4-BENZOXAZIN-3-ONE

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A CONVENIENT SYNTHESIS OF POLYFUNCTIONALLY SUBSTITUTED HETEROCYCLIC SYSTEMS DERIVED FROM 4-METHYL-2H-1,4-BENZOXAZIN-3-ONE

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Cycloaddition of 2-[(N-phenyl)thiocarboxamido-]-4-methyl-2H-1,4-benzoxazin-3-one (**2**) to α,β-unsaturated compounds gave spiro pyridine derivatives. Reaction of compound **2** with some halo compounds afforded thiazolidine derivatives. 2-Ethoxymethylenyl-4-methyl-1,4-benzoxazine-3-thione underwent cyclocondensation reactions with some bidentate reagents. Condensed tricyclic systems have been prepared through the reaction of 3-dicyanomethylenyl-4-methyl-2H-1,4-benzoxazine with the appropriate reagents.

Keywords: 4-methyl-2H-1,4-benzoxazin-3-one; spiro pyridine; thiazolidine; pyrazolo-1,4-benzoxazine; phenoxazine

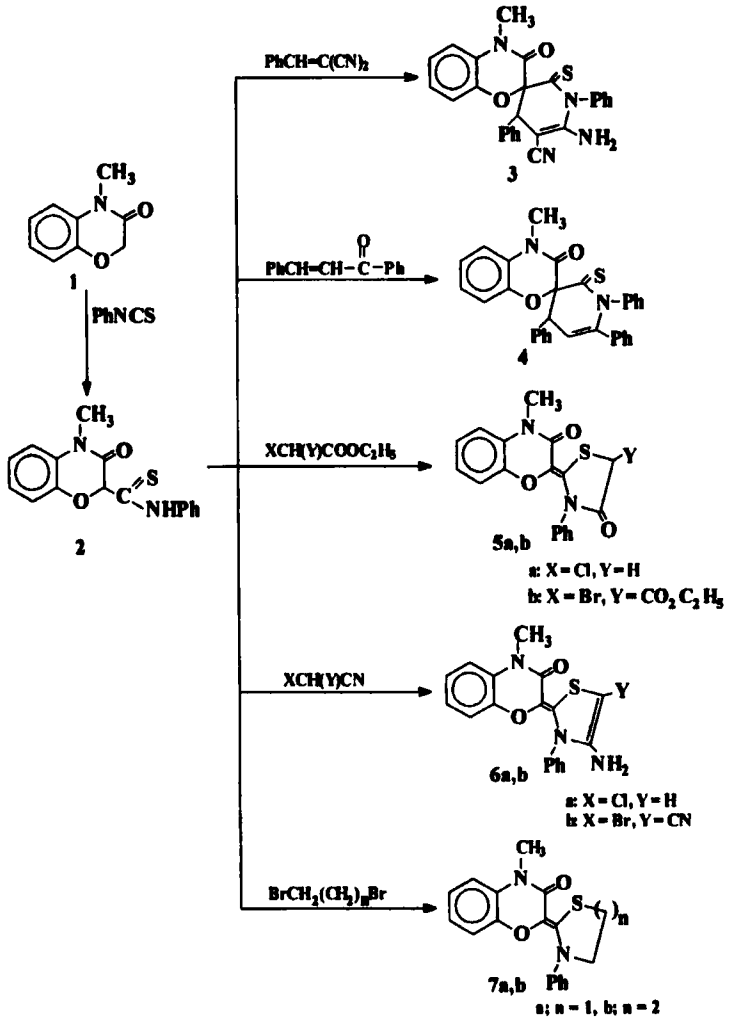
INTRODUCTION

Heterocyclic annelated benzoxazines continue to attract considerable attention which mainly arises from the large variety of interesting pharmacological activities observed with benzoxazine derivatives, which includes antibacterial,[1–5] antifungal,[6] anthelmintic,[7] antifilarial,[7] anti-inflammatory,[8,9] analgesic,[8,9] antipyretic,[8] and anticancer[10] properties. In view of the above structure-activity relationship we reported herein the synthesis of some fused and spiro heterocyclic systems containing benzoxazine moiety.

* Corresponding Author.

RESULTS AND DISCUSSION

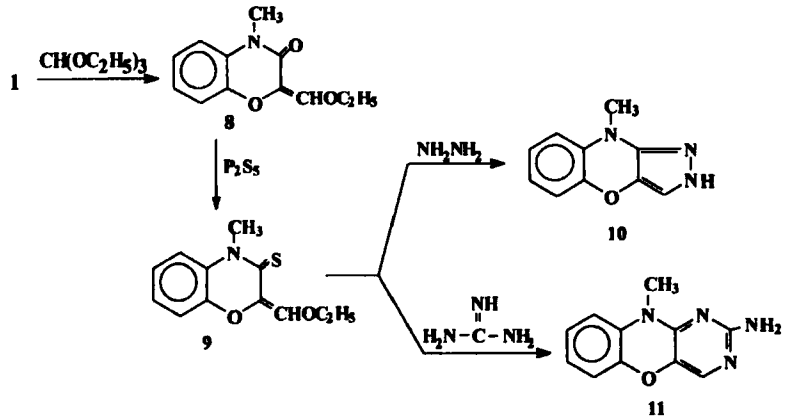
Reaction of 4-methyl-2H-1,4-benzooxazin-3-one[11] (1) with phenylisothiocyanate in DMF using TEA as a catalyst afforded 2-[(N-phenyl)thiocarboxamido-]-4-methyl-2H-1,4-benzoxazin-3-one (2) via addition of the active methylene of compound 1 to the isothiocyanate (Scheme 1).



SCHEME 1

Compound **2** undergoes cycloaddition reactions with benzylidenemalononitrile and chalcone in presence of pyridine as a catalyst to give the corresponding spiro pyridine[12,13] derivatives **3** and **4**, respectively (Scheme 1). Cyclization of compound **2** with equimolar amounts of α-halo carbonyl compounds, namely ethyl chloroacetate and diethyl bromomalonate in alkaline medium, afforded the corresponding thiazolidin-4-one derivatives $\mathbf{5_{a,b}}$ respectively, in good yields. Reaction of compound **2** with an equimolar amount of α-halo nitriles, namely chloroacetonitrile and/or bromomalononitrile via a similar procedure, yielded 4-thiazoline derivatives $\mathbf{6_{a,b}}$ respectively, in good yields.[14] In addition, compounds $\mathbf{7_{a,b}}$ were obtained in good yields by reaction of compound **2** with a dihalo compound (1,2-dibromoethane and 1,3-dibromopropane) under PTC conditions (Scheme 1)

Reaction of compound **1** with triethylorthoformate in an equimolar ratio in refluxing acetic anhydride affords 2-ethoxymethylenyl-4-methyl-1,4-benzoxazin-3-one (**8**). The ^{1}H-NMR spectrum of compound **8** showed the disappearance of the methylene group of the benzoxazine nucleus and the appearance of new peaks at 8.6, 3.9 and 1.1 ppm due to =CH, OCH_2, and CH_3, respectively (Scheme 2).



SCHEME 2

On refluxing compound **8** with phosphorus pentasufide in dry toluene, 2-ethoxymethylenyl-4-methyl-1,4-benzoxazine-3-thione (**9**) was obtained in good yield. The IR spectrum showed the disappearance of C=O group.

Condensation of compound **9** with hydrazine hydrate and guanidine hydrochloride in boiling ethanol in presence of sodium ethoxide yielded the corresponding fused heterocyclic systems **10** and **11**, respectively. The structures of these compounds were confirmed by elemental analyses, IR, and ^{1}H-NMR spectra (Scheme 2).

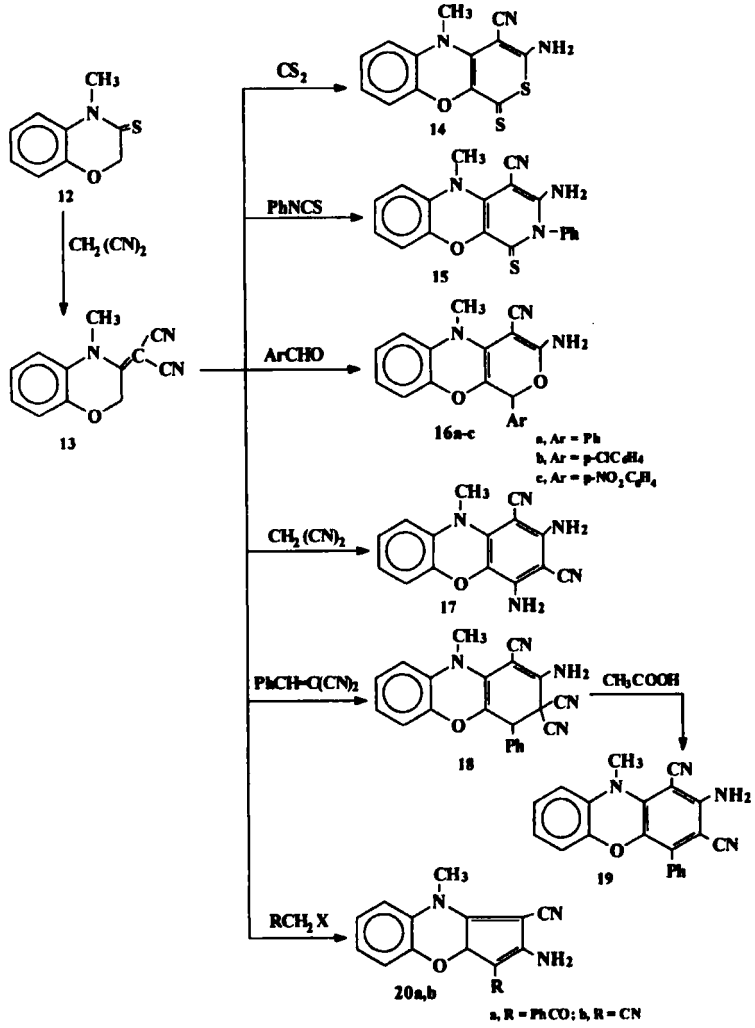
Interestingly, refluxing compound **1** with phosphorus pentasufide in dry pyridine yielded the corresponding thione derivative[15] **12** in good yield. Compound **12** undergoes condensation reaction with malononitrile in dioxan in presence of TEA to give 3-dicyanomethylenyl-4-methyl-2H-1,4-benzoxazine (**13**). The IR spectrum of this compound showed the absence of a C=S absorption band, but exhibited an absorption band at 2207 cm^{-1} due to CN groups (Scheme 3)

Compound **13** was allowed to react with carbon disulfide using solid-liquid phase-transfer catalysis technique [dioxan/K_2CO_3/tetrabutylammonium-bromide (TBAB)] to give compound **14**. Moreover, cycloaddition of compound **13** to phenylisothiocyanate in refluxing DMF in the presence of TEA yielded **15** in good yield (Scheme 3).

The reaction of compound **13** with aromatic aldehydes (benzaldehyde, 4-chlorobenzaldehyde, and 4-nitrobenzaldehyde) in refluxing ethanol in the presence of anhydrous sodium acetate afforded compounds **16$_{a,b,c}$**. The formation of these compounds was assumed to proceed via the generation of an aldol adduct as an intermediate, followed by cyclization (Scheme 3).

Reaction of malononitrile with compound **13** in refluxing dioxan in the presence of piperidine as a catalyst gave compound **17**. The reaction mechanism was assumed to follow a preliminary formation of a carbanion of the active methylene group of compound **13**, followed by nucleophilic attack on the cyano group of malononitrile. This imino intermediate then underwent intramolecular cyclization through the addition of the methylene to the cyano group to give compound **17**. The reaction of **13** with benzylidenemalononitrile in ethanol in presence of piperidine as a catalyst gave tricyanophenoxazine derivative **18** which lost HCN molecule upon heating in acetic acid to give compound **19**.

Compounds **20$_{a,b}$** were prepared in good yields by reacting compound **13** with active halo compounds, namely phenacyl bromide and chloroacetonitrile under PTC conditions. The reaction mechanism was follow a first alkylation of compound **13** at the 2-position, followed by addition of the methylene group to the cyano group to give the cyclized compounds.



SCHEME 3

EXPERIMENTAL

Melting points were uncorrected and were determined on Kofler melting point apparatus. IR (cm^{-1}) spectra were obtained (KBr disc) on a Nicolet

710 FT-IR Spectrophotometer. ^{1}H-NMR spectra were recorded at 60 MHz on a Varian EM 360 L Spectrometer. The chemical shift is expressed in δ values (ppm) from TMS as an internal reference. Elemental analyses were carried out on an elemental analyzer 240 °C.

2-[(N-Phenyl)thiocarboxyamido-]-4-methyl-1,4-benzoxazin-(2H)-3-one (2)

An equimolar mixture of compound **1** (1.51 g, 0.01 mol), phenylisothiocyanate (1.2 mL), and triethylamine (0.9 mL) in 30 mL of dimethylformamide was refluxed for 6 h. The reaction mixture was concentrated, cooled, and poured on ice-water. The precipitate was collected by filtration and crystallized from ethanol. Yield: 2.18 g (73 %); mp 192 °C; $C_{16}H_{14}N_2O_2S$ (298.35); Calc: C, 64.40; H, 4.73; N, 9.39. Found: C, 64.09; H, 4.52; N, 9.22. IR ν = 3261 (NH), 1689 (C=O); ^{1}H-NMR ($CDCl_3$) δ = 9.6 (br, 1 H, NH), 7.0–8.1 (m, 9 H, arom.), 6.5 (s, 1 H, CH), 2.8 (s, 3 H, CH_3).

Spiro[(4-methyl-1,4-benzoxazin-2H-3-one)-2,3′-(1,4-diphenyl-3,4-dihydropyridine-2-thione)] (3 and 4)

General Procedure

To a solution of compound **2** (1.43 g, 0.005 mol) in dioxane (30 mL) was added benzylidenemalononitrile (0.77 g, 0.005 mol)) and/or chalcone (1.04 g, 0.005 mol) and a catalytic amount of pyridine. The reaction mixture was refluxed for 5 h, the solvent was evaporated under reduced pressure, and the remaining product was triturated with cold water. The resulting precipitate was collected by filtration, dried, and crystallized from the appropriate solvent.

Spiro[(4-methyl-1,4-benzoxazin-2H-3-one)-2,3′-(6-amino-5-cyano-1,4-diphenyl-3,4-dihydropyridine-2-thione)] (3)

Yield: 1.53 g (68 %); mp 153 °C (dioxan); $C_{26}H_{20}N_4O_2S$ (452.51); Calc: C, 69.00; H, 4.45; N, 12.38. Found: C, 68.76; H, 4.29; N, 12.16. IR ν = 3341, 3276 (NH_2), 2201 (CN), 1691 (C=O); ^{1}H-NMR (DMSO) δ = 7.0–7.9 (m, 14 H, arom.), 5.7–5.5 (br, 2 H, NH_2), 4.3 (s, 1 H, CH), 2.8 (s, 3H, CH_3).

Spiro[(4-methyl-1,4-benzoxazin-2H-3-one)-2,3'-(1,4,6-triphenyl-3,4-dihydropyridine-2-thione)] (4)

Yield: 1.49 g (61 %); mp 223–224 °C (ethanol); $C_{31}H_{24}N_2O_2S$ (488.58); Calc: C, 76.20; H, 4.95; N, 5.73. Found: C, 76.01; H, 4.88; N, 5.61. IR ν = 1699 (C=O); ^{1}H-NMR (DMSO) δ = 7.1–8.0 (m, 19 H, arom.), 6.3 (d, 1 H, HC=), 4.1 (d, 1 H, CH), 2.8 (s, 3H, CH_3).

4-Methyl-2-[3-phenyl-1,3-thiazolidin-2-enyl (1,3-thiazol-Δ^4-ine-2-yl)]-1,4-benzoxazin-3-one ($5_{a,b}$ and $6_{a,b}$)

General Procedure

A mixture of compound **2** (1.42 g, 0.006 mol), potassium hydroxide (0.34 g, 0.006 mol), and dry DMF (40 mL) was treated with the appropriate halo compound (0.006 mol). The reaction mixture was refluxed for 4 h. The reaction mixture was filtered while hot. After cooling, the filtrate was poured on ice-cooled water. The precipitate was collected by filtration and crystallized from ethanol.

4-Methyl-2-(3-phenyl-4-oxo-1,3-thiazolidin-2-enyl)-1,4-benzoxazin-3-one (5_a)

Yield: 1.42 g (70 %); mp 281 °C; $C_{18}H_{14}N_2O_3S$ (338.37); Calc: C, 63.88; H, 4.17; N, 8.28. Found: C, 63.53; H, 4.00; N, 8.03. IR ν = 1698, 1687 (2 C=O), 1623 (C=C); ^{1}H-NMR (DMSO) δ = 7.0–7.8 (m, 9 H, arom.), 4.2 (s, 2 H, CH_2), 2.8 (s, 3 H, CH_3).

4-Methyl-2-(5-carbethoxy-3-phenyl-4-oxo-1,3-thiazolidin-2-enyl)-1,4-benzoxazin-3-one (5_b)

Yield: 1.72 g (70 %); mp 201 °C; $C_{21}H_{18}N_2O_5S$ (410.43); Calc: C, 61.45; H, 4.42; N, 6.82. Found: C, 61.13; H, 4.22; N, 6.60. IR ν = 1712 ($C=O_{ester}$), 1698, 1687 (2 C=O), 1616 (C=C); ^{1}H-NMR (DMSO) δ = 7.1–7.8 (m, 9 H, arom.), 5.3 (s, 1 H, CH), 4.0 (q, 2 H, CH_2), 2.8 (s, 3H, NCH_3), 1.1 (t, 3 H, CH_3).

4-Methyl-2-(4-amino-3-phenyl-1,3-thiazol-Δ^4-ine-2-yl)-1,4-benzoxazin-3-one (6_a)

Yield: 1.54 g (76 %); mp 199°C; $C_{18}H_{15}N_3O_2S$ (337.38); Calc: C, 64.07; H, 4.48; N, 12.45. Found: C, 63.70; H, 4.29; N, 12.25. IR ν = 3412, 3370 (NH_2), 1689 (C=O), 1626, 1607 (C=C); ^{1}H-NMR (DMSO) δ = 7.1–7.9 (m, 9 H arom. + 1 H vinylic), 5.4- 5.2 (br, 2 H, NH_2), 2.8 (s, 3 H, CH_3).

4-Methyl-2-(4-amino-5-cyano-3-phenyl-1,3-thiazol-Δ^4-ine-2-yl)-1,4-benzoxazin- 3-one (6_b)

Yield: 1.50 g (69 %); mp 251 °C; $C_{19}H_{14}N_4O_2S$ (362.39); Calc: C, 62.97; H, 3.89; N, 15.46. Found: C, 62.67; H, 3.78; N, 15.29. IR ν = 3431, 3353 (NH_2), 3201 (CN), 1689 (2 C=O), 1626, 1607 (C=C); ^{1}H-NMR (DMSO) δ = 7.1–7.8 (m, 9 H, arom.), 5.7- 5.5 (br, 2 H, NH_2), 2.8 (s, 3 H, CH_3).

4-Methyl-2-[3-phenyl-1,3-thiazolidin-2-enyl(1,3-tetrahydrothiazin-2-enyl)]-1,4-benzoxazin-3-one ($7_{a,b}$)

General Procedure

A mixture of 3 g anhydrous potassium carbonate, compound **2** (1.72 g, 0.006 mol), dry dioxan (40 mL), and catalytic amount of tetrabutylammonium bromide (TBAB) was treated with 0.006 mole of 1,2-dibromoethane (1.12 g) or 1,3-dibromopropane (1.21 g). The reaction mixture was stirred at 60 °C for 6 h. The reaction mixture was filtered. The filtrate was evaporated under reduced pressure The precipitate was crystallized from ethanol.

4-Methyl-2-(3-phenyl-1,3-thiazolidin-2-enyl)-1,4-benzoxazin-3-one (7_a)

Yield: 1.38 g (71 %); mp 217 °C; $C_{18}H_{16}N_2O_2S$ (324.38); Calc: C, 66.64; H, 4.97; N, 8.63. Found: C, 66.33; H, 4.80; N, 8.41. IR ν = 1683 (C=O), 1621 (C=C); ^{1}H-NMR ($CDCl_3$) δ = 6.9–7.8 (m, 9 H, arom.), 3.3 (t, 2 H, NCH_2), 3.1 (t, 2 H, SCH_2), 2.8 (s, 3 H, CH_3).

4-Methyl-2-(3-phenyl-1,3-tetrahydrothiazin-2-enyl)-1,4-benzoxazin-3-one (7_b)

Yield: 1.42 g (70 %); mp 233–234 °C; $C_{19}H_{18}N_2O_2S$ (338.41); Calc: C, 67.43; H, 5.36; N, 8.28. Found: C, 67.05; H, 5.19; N, 8.11. IR ν = 1687 (C=O), 1619 (C=C); ^{1}H-NMR ($CDCl_3$) δ = 6.8–7.7 (m, 9 H, arom.), 3.3 (t, 2 H, NCH_2), 3.1 (t, 2H, SCH_2), 2.8 (s, 3 H, CH_3), 1,5 (m. 2 H, CH_2).

2-Ethoxymethylenyl-4-methyl-1,4-benzoxazin-3-one (8)

A mixture of compound **1** (3.02 g, 0.02 mol) and triethylorthoformate (3.26 g, 0.022 mol) was refluxed in acetic anhydride (20 mL) for 4 h. The reaction mixture was poured into ice-cooled water (500 mL). The precipitated solid was collected by filtration and crystallized from ethanol. Yield: 3.16 g (72 %); mp 117 °C; $C_{12}H_{13}NO_3$(219.23); Calc: C, 65.73; H, 5.97; N, 6.39. Found: C, 65.40; H, 5.81; N, 6.21. IR ν = 2991 (CH, aliph.), 1690 (C=O); ^{1}H-NMR ($CDCl_3$) δ = 8.6 (s, 1H, =CH), 7.2–7.8 (m, 4 H, arom.), 3.9 (q, 2 H, CH_2), 2.8 (s, 3 H, N-CH_3); 1.1 (t, 3 H, CH_3).

2-Ethoxymethylenyl-4-methyl-1,4-benzoxazine-3-thione (9)

A mixture of compound **8** (2.19 g, 0.01 mol) and phosphorus pentasufide (2.22 g, 0.01 mol) in dry pyridine (30 mL) was refluxed for 5 h. After cooling, the reaction mixture was poured into ice-cooled water. The solid product was collected by filtration, washed thoroughly with water, dried, and crystallized from ethanol. Yield: 1.90 g (80 %); mp 136–137 °C; $C_{12}H_{13}NO_2S$ (235.29); Calc: C, 61.25; H, 5.57; N, 5.95. Found: C, 60.95; H, 5.44; N, 5.79. IR ν = 2963 (CH, aliph.), 1167 (C=S); ^{1}H-NMR: ($CDCl_3$) δ = 8.2 (s, 1 H, =CH), 7.0–7.7 (m, 4 H, arom.), 3.9 (q, 2 H, CH_2), 2.8 (s, 3 H, N-CH_3); 1.1 (t, 3 H, CH_3),

Pyrazolo[4,3-b]-1,4-benzoxazine and pyrimido[5,4-b]-1,4-benzoxazine (10 and 11)

A mixture of compound **9** (1.18 g, 0.005 mol) and the proper bidentate reagent (0.005 mol) in absolute ethanol (50 mL) was stirred at r.t. for 4 h. Then sodium ethoxide (0.012 g of Na in 5 mL ethanol) was added, and the mixture was refluxed until the evolution of H_2S was ceased (10 h) and

then was concentrated and cooled. The precipitate formed was filtered off, washed with water, and recrystallized from ethanol.

9-Methylpyrazolo[4,3-b]-1,4-benzoxazine (10)

Yield: 0.62 g (66 %); mp 293 °C; $C_{10}H_9N_3O$ (187.19); Calc: C, 64.16; H, 4.84; N, 22.44. Found: C, 63.85; H, 4.66; N, 22.28. IR ν = 3306 (NH), 1602 (C=N); ^{1}H-NMR (DMSO) δ = 11.9–11.7 (br, 1 H, NH), 7.0–7.6 (m, 4 H, arom.), 6.6 (s, 1 H, HC=), 2.8 (s, 3 H, CH_3).

2-Amino-10-methylpyrimido[5,4-b]-1,4-benzoxazine (11)

Yield: 0.82 g (77 %); mp 276 °C; $C_{11}H_{10}N_4O$ (214.22); Calc: C, 61.67; H, 4.70; N, 26.15. Found: C, 61.87; H, 4.88; N, 26.34. IR ν = 3346, 3261 (NH_2), 1611 (C=N); ^{1}H-NMR (DMSO) δ = 8.6 (s, 1 H, N-CH=), 7.1–7.7 (m, 4 H, arom.), 5.9–5.7 (br, 2 H, NH_2) 2.8 (s, 3 H, CH_3).

3-Dicyanomethylenyl-4-methyl-(2H)-1,4-benzoxazine (13)

An equimolar mixture (0.01 mol) of compound **14** (1.79 g), malononitrile (0.66 g), and triethylamine (1.01 g) in 50 mL of dimethylformamide was refluxed until the evolution of H_2S ceased (10 h). The reaction mixture was cooled and poured on cold water. The separated solid was filtered off and crystallized from ethanol. Yield: 1.77 g (84 %); mp 191 °C; $C_{12}H_9N_3O$(211.21); Calc: C, 68.23; H, 4.29; N, 19.89. Found: C, 67.93; H, 4.09; N, 19.70. IR ν = 2205 (2 CN), 1621 (C=C); ^{1}H-NMR ($CDCl_3$) δ = 7.0–7.8 (m, 4 H, arom.), 3.8 (s, 2 H, CH_2), 2.8 (s, 3 H, CH_3).

2-Amino-1-cyano-10-methyl-3-thiaphenoxazine-4-thione (14)

To a mixture of anhydrous potassium carbonate (3 g), dry benzene (40 mL), compound **13** (2.1 g, 0.01 mol), and a catalytic amount of TBAB was added carbon disulfide (0.7 mL, 0.01 mol). The reaction mixture was stirred of 9 h at 60 °C. The reaction mixture was filtered, and the filtrate was dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The solid residue was triturated with petroleum ether (60–80 °C) and crystallized from ethanol where upon compound **14** was obtained. Yield:

1.15 g (80 %); mp 302 °C; $C_{13}H_9N_3OS_2$ (287.35); Calc: C, 54.33; H, 3.15; N, 14.62. Found: C, 54.66; H, 3.24; N, 14.78. IR ν = 3305, 3246 (NH_2), 2199 (CN), 1129 (C=S); ^{1}H-NMR (DMSO) δ = 7.0–7.7 (m, 4 H, arom.), 5.1–4.8 (br, 2 H, NH_2), 2.8 (s, 3 H, CH_3).

2-Amino-1-cyano-10-methyl-3-phenyl-3-azaphenoxazine-4-thione (15)

An equimolar mixture of compound **13** (2.1 g, 0.01 mol), phenylisothiocyanate (1.35 g), and triethylamine (1.01 g) in 30 mL of dimethylformamide was refluxed for 7 h. The reaction mixture was concentrated, cooled, and poured into ice-water. The precipitate was collected by filtration and crystallized from ethanol. Yield: 1.4 g (81 %); mp 347 °C; $C_{19}H_{14}N_4OS$ (346.39); Calc: C, 65.87; H, 4.07; N, 16.17. Found: C, 65.50; H, 3.97; N, 16.01. IR ν = 3411, 3356 (NH_2), 2201 (CN), 1131 (C=S); ^{1}H-NMR (DMSO) δ = 7.1–7.9 (m, 9 H, arom.), 5.2–5.0 (br, 2 H, NH_2), 2.8 (s, 3 H, CH_3).

2-Amino-4-aryl-1-cyano-10-methyl-(4H)-3-oxaphenoxazine ($16_{a,b,c}$)

General Procedure

To a solution of compound **13** (2.1 g, 0.005 mol) and the proper aromatic aldehyde (0.005 mol) in absolute ethanol (25 mL) was added anhydrous sodium acetate (2 g). The reaction mixture was refluxed for 7 h. The reaction mixture was filtered while hot, concentrated, and cooled. The formed precipitate was filtered off, washed with water, dried, and crystallized from appropriate solvent.

2-Amino-1-cyano-10-methyl-4-phenyl-(4H)-3-oxaphenoxazine (16_a)

Yield: 1.22 g (77 %); mp 206 °C (ethanol); $C_{19}H_{15}N_3O_2$ (317.33); Calc: C, 71.91; H, 4.76; N, 13.24. Found: C, 71.59; H, 4.59; N, 13.03. IR ν = 3386, 3251 (NH_2), 2211 (CN); ^{1}H-NMR (DMSO) δ = 7.1–8.0 (m, 9 H, arom.), 6.0–5.8 (br, 2 H, NH_2), 5.1 (s, 1 H, CH), 2.8 (s, 3 H, CH_3).

2-Amino-1-cyano-10-methyl-4-(4-chlorophenyl)-(4H)-3-oxaphenoxazine (16_b)

Yield: 1.28 g (73 %); mp 266 °C (dioxan); $C_{19}H_{14}N_3O_2Cl$ (351.82); Calc: C, 64.86; H, 4.01; N, 11.94. Found: C, 64.60; H, 3.88; N, 11.73. IR

ν = 3660, 3299 (NH_2), 2203 (CN); ^{1}H-NMR (DMSO) δ = 7.1–8.0 (m, 8 H, arom.), 5.8–5.6 (br, 2 H, NH_2), 5.2 (s, 1 H, CH), 2.8 (s, 3 H, CH_3).

2-Amino-1-cyano-10-methyl-4-(4-nitrophenyl)-(4H)-3-oxaphenoxazine (16_c)

Yield: 1.48 g (82 %); mp 212 °C (dioxan); $C_{19}H_{14}N_4O_4$ (362.33); Calc: C, 62.98; H, 3.89; N, 15.46. Found: C, 62.61; H, 3.71; N, 15.27. IR ν = 3402, 3359 (NH_2), 2205 (CN); ^{1}H-NMR (DMSO) δ = 7.3–8.2 (m, 8 H, arom.), 6.1–5.9 (br, 2 H, NH_2), 5.5 (s, 1 H, CH), 2.8 (s, 3 H, CH_3).

2,4-Diamino-1,3-dicyano-10-methylphenoxazine (17)

A mixture of compound **13** (1.06 g, 0.005 mol), malononitrile (033 g, 0.005 mol), and a catalytic amount of triethylamine was refluxed in dry dioxane (20 mL) for 7 h. On cooling, the precipitate was filtered off and crystallized from ethanol. Yield: 0.94 g (68 %); mp 181 °C; $C_{15}H_{11}N_5O$ (277.27); Calc: C, 64.97; H, 3.99; N, 25.26. Found: C, 64.65; H, 3.83; N, 25.07. IR ν = 3390, 3341 (2 NH_2), 2203 (2 CN); ^{1}H-NMR (DMSO) δ = 7.0–7.6 (m, 4 H, arom.), 5.4–5.1 (br, 4 H, 2 NH_2), 2.8 (s, 3 H, CH_3).

1,3,3-Tricyano-4-phenyl-10-methyl-3,4-dihydrophenoxazine (18)

To a solution of compound **13** (1.06 g, 0.005 mol) in absolute ethanol (30 mL) was added an equimolar amount of benzylidenemalononitrile (0.77 g) and few drops of piperidine. The reaction mixture was refluxed for 6 h and concentrated. The separated solid was collected by filtration and recrystallized from ethanol. Yield: 1.4 g (77 %); mp 179 °C; $C_{22}H_{15}N_5O$ (365.37); Calc: C, 72.31; H, 4.14; N, 19.16. Found: C, 72.60; H, 4.17; N, 19.26. IR ν = 3360, 3286 (NH_2), 2214 (CN), 2193 (2 CN); ^{1}H-NMR (DMSO) δ = 6.8–7.7 (m, 9 H, arom.), 5.2–5.0 (br, 2 H, NH_2), 4.6 (s,1 H, CH), 2.8 (s, 3 H, CH_3).

1,3-Dicyano-4-phenyl-10-methylphenoxazine (19)

A solution of compound **18** (0.73 g, 0.002 mol) in acetic acid (10 mL) was refluxed for 4 h. After cooling, the reaction mixture was added to ice-cold

water. The formed precipitate was collected by filtration and crystallized from ethanol. Yield: 0.58 g (86 %); mp 321 °C; $C_{21}H_{14}N_4O$ (338.35); Calc: C, 74.54; H, 4.17; N, 16.65. Found: C, 74.23; H, 4.03; N, 16.41. IR ν = 3411, 3352 (NH_2), 2203 (2 CN); ^{1}H-NMR (DMSO) δ = 7.0–7.9 (m, 9 H, arom.), 5.6–5.4 (br, 2 H, NH_2), 2.8 (s, 3 H, CH_3).

2-Amino-3-benzoyl(cyano)-1-cyano-9-methyl-1,3-cyclopentadieno-[5,1-b]-1,4-benzoxazine ($20_{a,b}$)

General Procedure

A mixture of 2 g anhydrous potassium carbonate, compound 13 (0.63 g, 0.003 mol), dry dioxan (30 mL) and a catalytic amount of TBAB was treated with 0.003 mole of phenacyl bromide (0.6 g) or chloroacetonitrile (0.22 g). The reaction mixture was stirred for 8 h at 60 °C. The reaction mixture was filtered, and the filtrate was evaporated under reduced pressure. The residue was triturated with pet.ether (40–60 °C) to give a solid which was crystallized from ethanol.

2-Amino-3-benzoyl-1-cyano-9-methyl-1,3-cyclopentadieno[5,1-b]-1,4-benzoxazine (20_a)

Yield: 0.7 g (71 %); mp 256 °C; $C_{20}H_{15}N_3O_2$ (329.34); Calc: C, 72.93; H, 4.59; N, 12.76. Found: C, 72.80; H, 4.51; N, 12.60. IR ν = 3436, 3361 (NH_2), 2207 (CN), 1698 (C=O); ^{1}H-NMR (DMSO) δ = 7.0–8.0 (m, 9 H, arom.), 5.2–5.0 (br, 2 H, NH_2), 2.8 (s, 3 H, CH_3).

2-Amino-1,3-dicyano-9-methyl-1,3-cyclopentadieno[5,1-b]-1,4-benzoxazine (20_b)

Yield: 0.63 g (84 %); mp 231 °C; $C_{14}H_{10}N_4O$ (250.25); Calc: C, 67.19; H, 4.03; N, 22.39. Found: C, 66.88; H, 3.90; N, 22.18. IR ν = 3440, 3382 (NH_2), 2207 (2 CN); ^{1}H-NMR(DMSO) δ = 7.0–8.0 (m, 4 H, arom.), 5.3–5.1 (br, 2 H, NH_2), 2.8 (s, 3 H, CH_3)

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