A FACILE SYNTHESIS OF NOVEL TRICYCLIC COMPOUNDS, TETRAZOLOQUINOXALINES AND 1,2,4-TRIAZOLOQUINOXALINES

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Abstract - Novel 5-methyltetrazolo[1,5-a]quinoxalin-4-ones (5) and 5-methyl-1,2,4-triazolo[4,3-a]quinoxalin-4-ones (7) could be synthesized from 1-methyl-3-chloroquinoxalin-2-ones (3) and 1-methyl-3-hydrazinoquinoxalin-2-ones (6), respectively. Further extensive study was carried out to synthesize 4- or 7-substituted and 4,7-disubstituted tetrazolo[1,5-a]quinoxalines (10) and 1,2,4-triazolo[4,3-a]quinoxalines (12).

Recently, it has been reported that 4-methyltetrazolo[1,5-a]quinazolin-5-one (PP-389)[1] and 5-methyl-1,2,4-triazolo[3,4-b]benzothiazole (tricyclazole)[2] have been excellent fungicides against *Pyricularia oryzae* and inhibited the pathway of melanine biosynthesis.

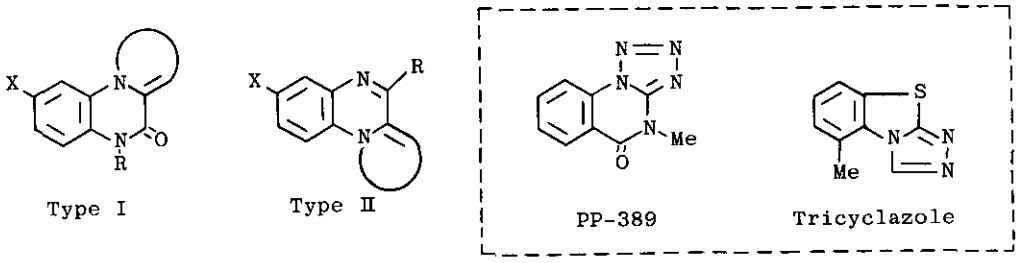
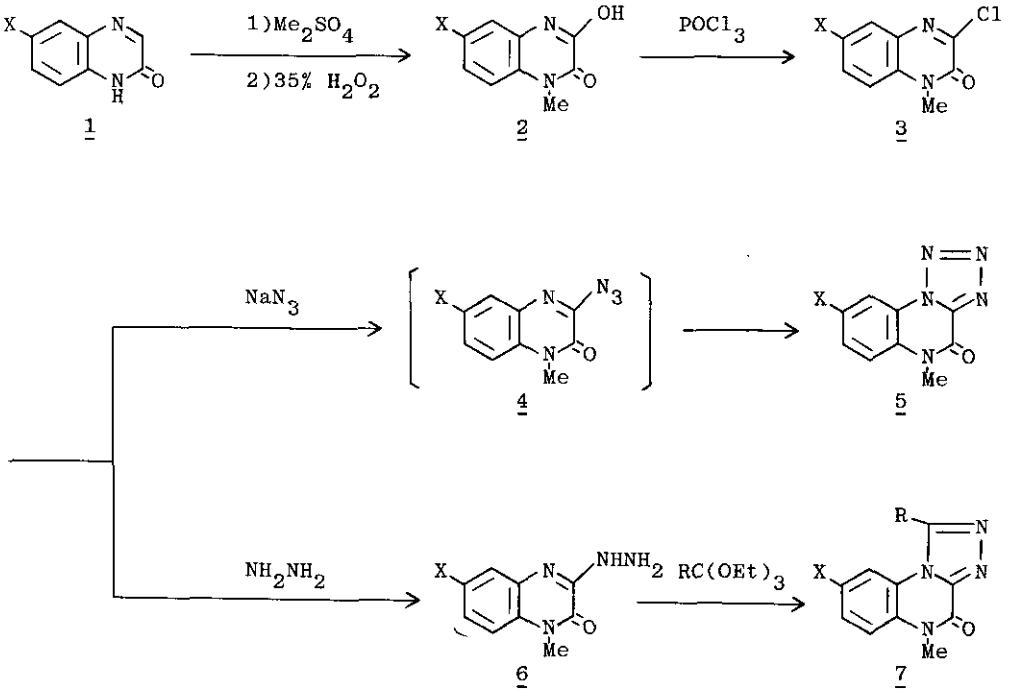


Figure 1.

In connection with our synthetic and biological studies,[3] we have now elaborated facile methods for the synthesis of novel tricyclic compounds, which are illustrated as type I and type II in Figure 1. They can be regarded as analogues of PP-389 and tricyclazole.

The type I compounds could be synthesized from 2(1H)-quinoxalinones (1). The N-methylations of 1 with dimethyl sulfate in aqueous sodium hydroxide, next the oxidations of the resulting products with 35% hydrogen peroxide afforded 1-methyl-3-hydroxyquinoxalin-2-ones (2). The chlorinations of 2 with phosphoryl chloride provided 1-methyl-3-chloroquinoxalin-2-ones (3). The reactions of 3 with sodium azide in DMF afforded 5-methyltetrazolo[1,5-a]quinoxalin-4-ones (5) in satisfactory yields. Wherein 1-methyl-3-azidoquinoxalin-2-ones (4) were formed at the first step in this reaction and the intramolecular cyclizations of 4 to 5 occurred immediately. The predominant existences of 5 were supported by the ir spectral data, which exhibited no absorption bands around 2200 cm^{-1}. On the other hand, 3 were converted into 1-methyl-3-hydrazinoquinoxalin-2-ones (6), which were refluxed in ethyl orthoformate or ethyl orthoacetate to give 5-methyl-1,2,4-triazolo[4,3-a]quinoxalin-4-ones (7). Scheme 1 shows the reaction pathway and



Scheme 1.* X= H, Cl, CF_3; R= H, Me

Table 1. Results for Tricyclic Compounds (5 and 7)

A) 5-Methyltetrazolo[1,5-a]quinoxalin-4-ones (5)

Compound	X	Yield(%)	mp(°C)
5a	H	87	240.0-241.0
5b	Cl	96	249.0-250.0
5c	CF_3	85	186.0-187.0

B) 5-Methyl-1,2,4-triazolo[4,3-a]quinoxalin-4-ones (7)

Compound	X	R	Yield(%)	mp(°C)
7a	H	H	85	300<
7b	H	Me	98	300<
7c	Cl	H	98	300<
7d	Cl	Me	97	300<
7e	CF_3	H	48	224.0-226.0
7f	CF_3	Me	75	269.0-270.0

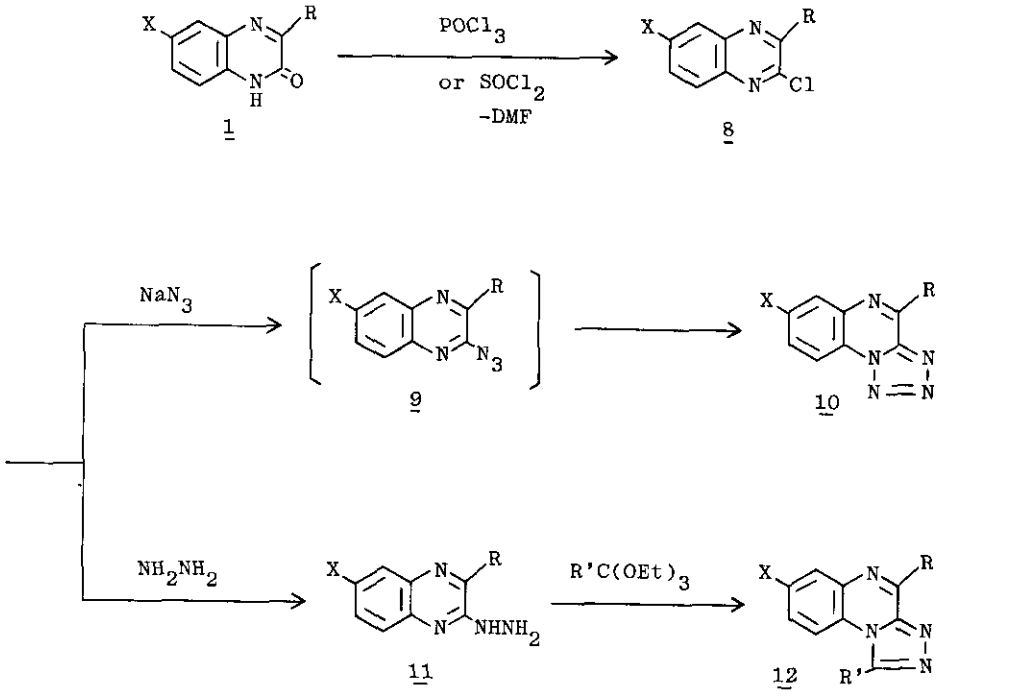
the results of these reactions are summarized in Table 1.

As the type II compounds, unsubstituted tetrazolo[1,5-a]quinoxaline, 1,2,4-triazolo-[4,3-a]quinoxaline, and 1-methyl-1,2,4-triazolo[4,3-a]quinoxaline have already been reported,[4] whereas pharmaceutically interesting 4- or 7-substituted and 4,7-disubstituted tetrazolo[1,5-a]quinoxalines (10) and 1,2,4-triazolo[4,3-a]-quinoxalines (12) have not been synthesized so far. We now describe the synthesis of 10 and 12 from easily obtainable 3- or 6-substituted and 3,6-disubstituted compounds 1.[3]

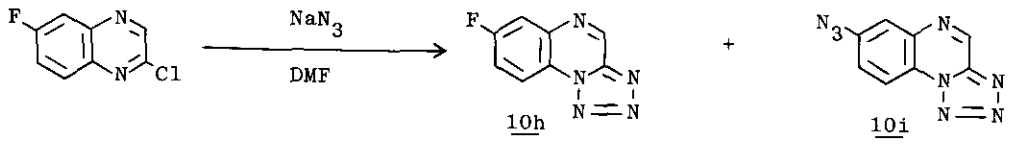
The chlorinations of 1 were carried out using phosphoryl chloride or thionyl chloride - DMF to provide 2-chloroquinoxalines (8), whose reactions with sodium azide in DMF at 120 °C afforded 10 in good yields. As well as the syntheses of 5, intramolecular cyclizations of 9 to 10 were checked by their ir spectral data. When 2-chloro-6-fluoroquinoxaline was allowed to react with sodium azide, a mixture of 7-fluorotetrazolo[1,5-a]quinoxaline (10h) and maybe ipso-substituted 7-azido-tetrazolo[1,5-a]quinoxaline (10i) was obtained. The formation of 10i was assumed by the mass spectral data. On the other hand, the reactions of 8 with hydrazine hydrate furnished 2-hydrazinoquinoxalines (11), which were converted into 12 by

similar procedures to those described in the syntheses of 7. The above results are summarized in Scheme 2, 3 and Table 2.

Most of the compounds synthesized in the present study showed fungicidal activities. Particularly, 7a, 10a, and 12d indicated excellent preventive activities against *Plasmodiophora brassicae*, *Sphaerotheca fuliginea*, and *Pyricularia oryzae*, respectively.



Scheme 2.* X= H, Cl, Br, CF_3; R= H, Me, NH_2; R'= H, Me



Scheme 3.

Table 2. Results for Tricyclic Compounds (10 and 12)

A) Tetrazolo[1,5-a]quinoxalines (10)

Compound	X	R	Yield(%)	mp(°C)
10a	Cl	H	87	236.0-237.0
10b	Br	H	98	246.5-248.0
10c	CF_3	H	84	143.0-144.0
10d	H	Me	81	152.0-153.0
10e	F	Me	93	161.0-162.0
10f	Br	Me	68	169.0-170.0
10g	H	NH_2	98	291.5-293.0

B) 1,2,4-Triazolo[4,3-a]quinoxalines (12)

Compound	X	R	R'	Yield(%)	mp(°C)
12a	F	H	H	85	300<
12b	F	H	Me	80	217.0-218.0
12c	Cl	H	H	90	287.0-288.0
12d	Cl	H	Me	83	213.0-214.0
12e	Br	Me	H	96	288.0-289.0
12f	Br	Me	Me	92	235.0-236.0

EXPERIMENTAL

Pmr spectra were obtained on a JEOL FX-90 Spectrometer locked on tetramethylsilane as an internal reference. Ir spectra were measured on a JASCO A-3 Infrared Spectrophotometer. Mass spectra were measured on a JEOL D-300, JMA-3500 and DX-300, JMA-3100. Elemental analyses were measured on an Elemental Analyzer model 1106 (Carlo Erba Strumentazione). Chemical purities were determined on a Shimazu Liquid Chromatograph LC-3A. All melting points are uncorrected.

Typical procedures for the syntheses of 5a-c from 1. Dimethyl sulfate (120 ml) was added to a solution of 1 (X= Cl; 36.1 g, 200 mmol) in 2N sodium hydroxide (1200 ml) at room temperature. After stirring at room temperature for 8 h, the reaction product was extracted with chloroform and the chloroform layer was washed with water, next dried over anhydrous sodium sulfate. Removal of the solvent gave a solid, which was washed with diethyl ether/n-hexane (1/3) to afford 29.2 g

(75%) of 1-methyl-6-chloroquinoxalin-2-one, mp 118.0-119.0 °C; ir(KBr): 3450, 3050, 1650, 1583, 1549, 1450, 1421, 1300, 1202, 1162, 1101, 1063, 922, 888, 828 cm^{-1}; pmr ($CDCl_3$) δ 3.64(3H, s, CH_3), 7.23(1H, d, J= 8.4 Hz, H-8), 7.54(1H, d d, J= 8.4, 2.4 Hz, H-7), 7.82(1H, d, J= 2.4 Hz, H-5), 8.27(1H, s, H-3). 35% Hydrogen peroxide (10 ml) was added to a suspension of the N-methylated compound (5.84 g, 30.0 mmol) in 5% sodium hydroxide (200 ml), and then the reaction temperature was elevated to 70-80 °C and maintained for 5 h. After cooling, the resulting solid was collected and suspended in water (200 ml). The suspension was adjusted to pH 1 with hydrochloric acid and the solid was collected, washed with water, and dried in vacuo to afford 4.60 g (73%) of 2 (X= Cl), mp >300 °C; ir(KBr): 3400, 2125, 1665, 1496, 1372, 1132, 784, 665 cm^{-1}; pmr(DMSO-d_6) δ 3.52(3H, s, CH_3), 7.16(3H, br s, aromatic protons); ms m/z 210(M^+, base peak), 182, 153.

2 (X= Cl; 3.16 g, 15.0 mmol) was refluxed in phosphoryl chloride (50 ml) for 1.5 h. After removal of excess phosphoryl chloride under reduced pressure, crude product was dissolved in ethyl acetate and washed with 1% sodium hydroxide, next with water and dried over anhydrous sodium sulfate. Removal of the solvent gave 2.53 g (74%) of 3 (X= Cl), mp 159.0-160.0 °C; ir(KBr): 3410, 1662, 1578, 1455, 1161, 1099, 1070, 804 cm^{-1}; pmr($CDCl_3$) δ 3.72(3H, s, CH_3), 7.25(1H, d, J= 9.0 Hz, H-8), 7.57(1H, d d, J= 9.0, 1.8 Hz, H-7), 7.73(1H, d, J= 1.8 Hz, H-5); ms m/z 228(M^+, base peak), 200, 199, 164, 124.

A solution of 3 (X= Cl; 1.40 g, 6.11 mmol) and sodium azide (0.42 g, 6.46 mmol) in DMF (15 ml) was heated at 120 °C for 1.5 h. After cooling, the reaction mixture was poured into water, and the resulting solid was collected, washed with water, and dried in vacuo. It was washed with ethanol to afford 1.38 g (96%) of 5b; ir (KBr): 3440, 1674, 1505, 1452, 1399, 1319, 1278, 1132, 1101 cm^{-1}; pmr(DMSO-d_6) δ 3.67(3H, s, CH_3), 7.70(2H, br s, H-6 and H-7), 8.32(1H, br s, H-9); ms m/z 235 (M^+), 207(base peak), 178, 152.

In a similar manner, 5a and 5c were synthesized.

5a; ir(KBr): 3400, 1670, 1588, 1434, 1336, 1257, 1130, 768 cm^{-1}; pmr(DMSO-d_6) δ 3.70(3H, s, CH_3), 7.30-7.83(3H, m, H-6, H-7, and H-8), 8.31(1H, d d, J= 6.0, 2.0 Hz, H-9); ms m/z 201(M^+), 173(base peak), 144, 118.

5c; ir(KBr): 3450, 1698, 1632, 1352, 1326, 1284, 1250, 1160, 1136, 1120, 1084 cm^{-1}; pmr(DMSO-d_6) δ 3.75(3H, s, CH_3), 8.02(2H, br s, H-6 and H-7), 8.58(1H, br s, H-9); ms m/z 269(M^+), 241(base peak), 216, 212, 186, 144.

Typical procedures for the syntheses of 7a-f from 3. A solution of 3 (X= Cl; 6.87 g, 30.0 mmol) and hydrazine hydrate (15.0 g, 300 mmol) in ethanol (170 ml) was refluxed for 1 h. The reaction mixture was cooled and the resulting solid was collected. It was washed with water, next with a small amount of ethanol and dried in vacuo to afford 5.40 g (80%) of 6 (X= Cl), mp 210.0-211.0 °C; ir(KBr): 3340, 1652, 1572, 1508, 1458, 1410, 1362, 1281, 1143, 1114, 1097, 1035, 960, 898, 792 cm^{-1}; pmr(DMSO-d_6) δ 3.55(3H, s, CH_3), 7.07-7.47(3H, m, aromatic protons). 6 (X= Cl; 1.00 g, 4.45 mmol) was refluxed in ethyl orthoformate (20 ml) for 2 h. After cooling, the resulting solid was collected and washed with ethanol, next dried in vacuo to afford 1.02 g (98%) of 7c; ir(KBr): 3440, 3120, 1659, 1520, 1459, 1386, 1359, 1335, 1262, 1191, 1123, 990, 879, 824, 643 cm^{-1}; ms m/z 234 (M^+, base peak), 205, 152.

In a similar manner, 7a-b and 7d-f were synthesized.

7a; ir(KBr): 3425, 1664, 1524, 1458, 1389, 1350, 1262, 1188, 771, 760 cm^{-1}; ms m/z 200(M^+), 171(base peak), 144, 118.

7b; ir(KBr): 3430, 1665, 1458, 1424, 1350, 1256, 1139, 758 cm^{-1}; ms m/z 214(M^+, base peak), 185, 144, 118.

7d; ir(KBr): 3440, 1679, 1451, 1420, 1280, 1253, 1140, 859, 830 cm^{-1}; ms m/z 248 (M^+, base peak), 219, 178, 152.

7e; ir(KBr): 3430, 1665, 1614, 1488, 1445, 1362, 1311, 1270, 1239, 1170, 1152, 1130, 1108, 1072, 970, 862 cm^{-1}; pmr(DMSO-d_6) δ 3.69(3H, s, CH_3), 7.83(2H, br s, H-6 and H-7), 8.72(1H, br s, H-9), 10.07(1H, s, H-1); ms m/z 268(M^+, base peak), 239, 186.

7f; ir(KBr): 3580, 3400, 1684, 1624, 1460, 1418, 1330, 1295, 1272, 1259, 1155, 1118, 1091, 994, 875, 662 cm^{-1}; pmr(DMSO-d_6) δ 3.07(3H, s, CH_3-1), 3.69(3H, s, CH_3-5), 7.87(2H, br s, H-6 and H-7), 8.25(1H, br s, H-9); ms m/z 282(M^+, base peak), 253, 212, 186.

Typical procedures for the syntheses of 10a-g from 1. 1 (X= Cl, R= H; 36.1 g, 200 mmol) was refluxed in phosphoryl chloride (360 ml) for 1.5 h. After removal of excess phosphoryl chloride under reduced pressure, crude product was dissolved in chloroform, washed with 1% sodium hydroxide, next with water, and dried over anhydrous sodium sulfate. Removal of the solvent gave a solid, which was recrystallized from n-hexane/acetonitrile (10/1) to afford 33.0 g (83%) of 8 (X= Cl, R= H), mp 154.0-155.0 °C; pmr($CDCl_3$) δ 7.73(1H, d d, J= 8.9, 2.2 Hz, H-7),

7.96(1H, d, J= 8.9 Hz, H-8), 8.09(1H, d, J= 2.2 Hz, H-5), 8.77(1H, s, H-3); ms m/z 198(M^+, base peak), 163, 136.

A solution of 8 (X= Cl, R= H; 1.99 g, 10.0 mmol) and sodium azide (0.72 g, 11.1 mmol) in DMF (10 ml) was heated at 120 °C for 2 h. After cooling, the reaction mixture was poured into water and the resulting solid was collected, next washed with water and dried in vacuo. It was washed with ethanol to afford 1.79 g (87%) of 10a; ir(KBr): 3025, 1544, 1491, 1425, 1324, 1284, 1079, 834 cm^{-1}; pmr (DMSO-d_6) δ 7.99(1H, d d, J= 9.0, 1.8 Hz, H-8), 8.32(1H, d, J= 1.8 Hz, H-6), 8.62 (1H, d, J= 9.0 Hz, H-9), 9.75(1H, s, H-4); ms m/z 205(M^+), 177(base peak), 150, 115.

In a similar manner, 10b-g were synthesized.

10b; ir(KBr): 3020, 1545, 1491, 1424, 1320, 1180, 1076, 829 cm^{-1}; ms m/z 249(M^+), 221(base peak), 194, 142, 115.

10c; ir(KBr): 3425, 1432, 1312, 1170, 1145, 1122, 1079, 839 cm^{-1}; pmr($CDCl_3$) δ 8.18(1H, d d, J= 8.4, 1.8 Hz, H-8), 8.64(1H, d, J= 1.8 Hz, H-6), 8.79(1H, d, J= 8.4 Hz, H-9), 9.67(1H, s, H-4); ms m/z 239(M^+), 211(base peak), 192, 161.

10d; ir(KBr): 3400, 3000, 1508, 1474, 1406, 1370, 1332, 1175, 763 cm^{-1}; pmr($CDCl_3$) δ 3.10(3H, s, CH_3), 7.65-8.80(4H, m, aromatic protons); ms m/z 157(base peak), 130, 103, 90.

10e; ir(KBr): 3425, 3050, 1590, 1516, 1339, 1260, 1182, 1159, 908, 825 cm^{-1}; pmr (DMSO-d_6) δ 2.99(3H, s, CH_3), 7.55-8.75(3H, m, aromatic protons); ms m/z 203(M^+), 175(base peak), 148, 121.

10f; ir(KBr): 3400, 3050, 1558, 1493, 1395, 1168, 1059, 830 cm^{-1}; pmr($CDCl_3$) δ 3.09(3H, s, CH_3), 7.89(1H, d d, J= 8.4, 1.8 Hz, H-8), 8.32(1H, d, J= 1.8 Hz, H-6), 8.41(1H, d, J= 8.4 Hz, H-9); ms m/z 263(M^+), 235(base peak), 156, 129.

10g; ir(KBr): 3350, 3140, 1658, 1565, 1530, 1432, 768, 759 cm^{-1}; ms m/z 186(M^+), 158(base peak), 131, 105.

The reaction of 8 (X= F, R= H) with sodium azide. When 8 (x= F, R= H) was allowed to react with sodium azide as described above, a mixture of 10h (X= F, R= H) and 10i (X= N_3, R= H) was obtained, and then both compounds could not be separated by recrystallization. Therefore, the formations of 10h and 10i were checked by the mass spectral data [10h: m/z 189(M^+), 161(base peak), 134; 10i: m/z 212(M^+), 184, 156(base peak), 129].

Typical procedures for the syntheses of 12a-f from 8. A solution of 8 (X= Cl, R= H; 10.0 g, 50.3 mmol) and hydrazine hydrate (25.0 g, 500 mmol) in ethanol (300 ml) was refluxed for 1 h, the reaction mixture was cooled, and the resulting

solid was collected. It was washed with water, next with a small amount of ethanol and dried in vacuo to afford 9.10 g (93%) of 11 (X= Cl, R= H), mp 235.5-237.0 °C; ir(KBr): 3150, 1610, 1583, 1538, 1402, 1328, 1304, 1182, 1077, 1040, 988, 900, 829 cm^{-1}; pmr($CDCl_3$) δ 7.49(2H, br s, H-7 and H-8), 7.72(1H, br s, H-5), 8.33(1H, s, H-3); ms m/z 194(M^+, base peak), 179, 177, 164, 137.

11 (X= Cl, R= H; 6.0 g, 30.8 mmol) was refluxed in ethyl orthoformate (100 ml) for 6 h. After cooling, the resulting solid was collected and washed with ethanol, next dried in vacuo to afford 5.67 g (90%) of 12c; ir(KBr): 3425, 3100, 1552, 1495, 1458, 1355, 1190, 899, 826, 601 cm^{-1}; pmr(DMSO-d_6) δ 7.86(1H, d d, J= 9.0, 1.8 Hz, H-8), 8.15(1H, d, J= 1.8 Hz, H-6), 8.51(1H, d, J= 9.0 Hz, H-9), 9.43(1H, s, H-4), 10.13(1H, s, H-1); ms m/z 204(M^+, base peak), 177, 150.

In a similar manner, 12a-b and 12d-f were synthesized.

12a; ir(KBr): 3440, 3100, 1598, 1558, 1462, 1358, 1250, 1208, 834, 635, 620 cm^{-1}; ms m/z 188(M^+), 161(base peak), 134.

12b; ir(KBr): 3440, 3045, 1479, 1430, 1402, 1258, 1222, 821, 621 cm^{-1}; pmr(DMSO-d_6) δ 3.09(3H, s, CH_3), 7.30-8.65(3H, m, aromatic protons), 9.26(1H, s, H-4); ms m/z 202(M^+), 161(base peak), 134.

12d; ir(KBr): 3425, 3050, 1547, 1492, 1420, 819, 602 cm^{-1}; pmr(DMSO-d_6) δ 3.04 (3H, s, CH_3), 7.71(1H, d d, J= 9.0, 2.4 Hz, H-8), 8.03(1H, d, J= 2.4 Hz, H-6), 8.27(1H, d, J= 9.0 Hz, H-9), 9.20(1H, s, H-4); ms m/z 218(M^+, base peak), 177, 150.

12e; ir(KBr): 3450, 3090, 1503, 1400, 1359, 1202, 880, 810, 599 cm^{-1}; ms m/z 262 (M^+, base peak), 235, 156.

12f; ir(KBr): 3430, 1502, 1424, 1365, 1199, 888, 816, 600 cm^{-1}; ms m/z 276(M^+, base peak), 235, 156, 129.

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