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NEW SYNTHETIC APPROACH TO PYRIDAZINO[4,5-*b*]INDOLES BY Pd(0)-CATALYZED CROSS-COUPLING REACTION

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Abstract 5-Iodo-2-methylpyridazin-3(2*H*)-one readily underwent Suzuki coupling with protected anilinoboronic acids to yield the corresponding arylpyridazinones which proved to be suitable starting compounds to a ring closure – a 4 step pathway - to pyridazino[4,5-*b*]indoles.

Among fused indole ring systems, β-carbolines and related derivatives have attracted recently considerable attention in the literatures[1,2] mainly because of their potential biological activity. Our recent studies in the area of the synthesis of new pyridazine derivatives[3,4] as well as our novel results in ring closure strategies by Pd(0)-catalysis[5,6] prompted us to elaborate new cyclizations to azacarbolines starting from halopyridazines. Particularly, the easily accessable 5-iodo-2-methylpyridazin-3(2*H*)-one[7] (**1**) proved to be a convenient starting material for these studies.

In this paper we describe a new ring closure strategy to some aza-ß-carboline derivatives: 3-methylpyridazino[4,5-*b*]indol-4(3*H*)-ones (**6**). Although synthetic procedures have already been described to this[8,9] and related[10] ring systems, all these implied the cyclisation of the pyridazine moiety starting from an indole derivative. Our approach, in turn, is starting from a pyridazine compound and involves an indolization step.

A visual demonstration of the difference between the retrosynthetic analyses of the present and earlier pathways is shown in Figure 1 (approaches A and B, respectively). This comparison reveals that the basic feature of the new strategy is the cross-coupling reaction of a halopyridazinone with an appropriate phenylboronic acid. A few such and similar conversions have recently appeared.[11-13]

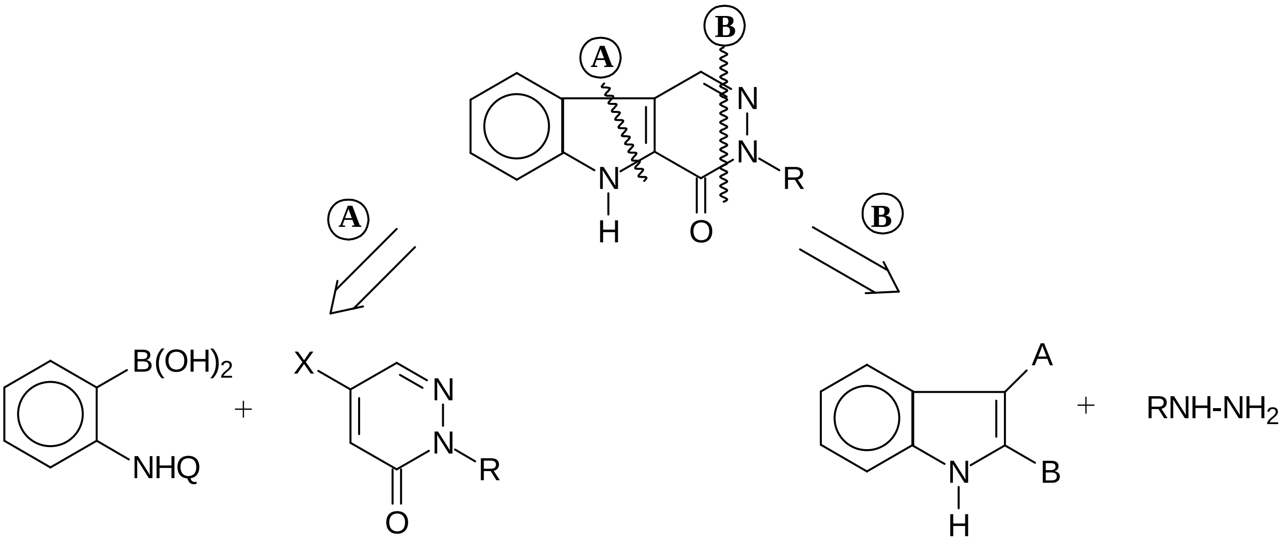

Figure 1

Retrosynthetic analysis of present (route A) and earlier (route B) synthetic strategies for cyclization to 3-alkylpyridazino[4,5-*b*]indol-4(3*H*)-ones (Q = protective group; X = halogen atom; R = alkyl; A and B = functional groups suitable for condensation reactions with hydrazines).

The extensive literature[14,15] on Suzuki coupling of haloazines reveals that iodo derivatives participate in these transformations with special ease. We have found, accordingly, that 5-iodo-2-methylpyridazin-3(2*H*)-one (**1**) readily reacts with arylboronic acids to yield 5-arylpyridazinones in excellent yields. Thus, reaction of **1** with phenylboronic acid gave 2-methyl-5-phenylpyridazin-3(2*H*)-one (**2**) and, some substituted arylboronic acids (containing pivaloylamino groups in order to allow subsequent ring closures to the target ring system) also reacted in analogous way and to afford the arylpyridazinones (**3a,b**).

These protected aniline derivatives (**3**) seemed to be convenient starting compounds for internal ring closures following our earlier established cyclisation protocol. Thus, after deprotection to the amine (**4**), these compounds were diazotated to a diazonium salt which, *in situ*, was subjected to an aza-transfer azidation reaction to an aryl azide (**5**). Heat treatment of this azide generates a nitrene which – according to our expectations on the base of our earlier experience with related systems[5,6] – should attack one of the adjacent positions of the pyridazine ring as shown with the dotted and continuous arrow in structure (**5**).

When **5** was refluxed in *o*-dichlorobenzene for 1 h, formation of one single product was experienced, and its NMR spectral study revealed (appearance of the significantly deshielded singlet of H-6 and disappearance of the singnals H-4 in **5**) that compound (**6**) was formed selectively (*i.e.* the attack shown

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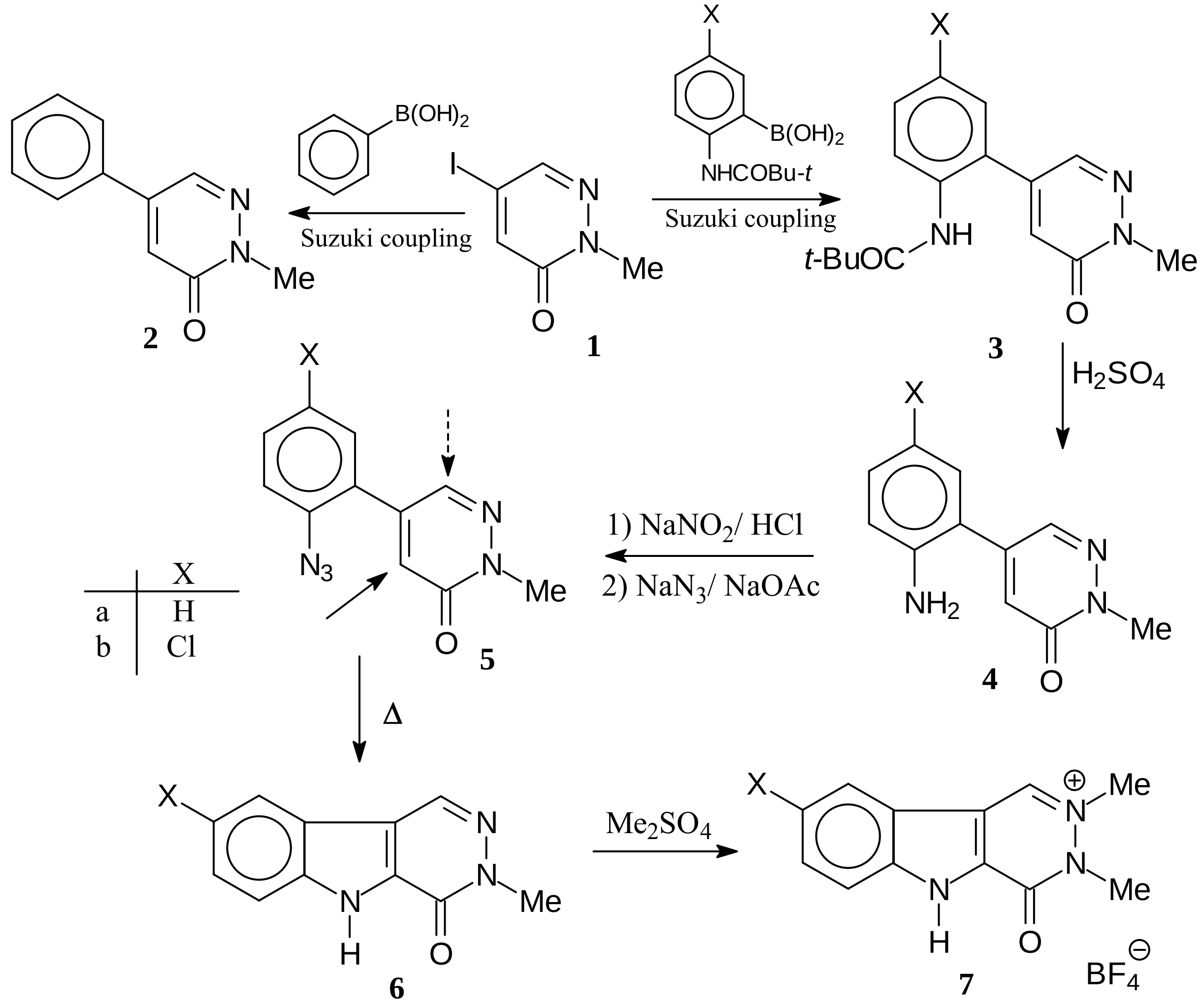
disappearance of the singnals H-4 in **5**) that compound (**6**) was formed selectively (*i.e.* the attack shown by the continuous arrow did occur). The physical data of the tricyclic compound (**6a**) proved to be identical with those published for this compound[9] synthesised by a different procedure.



	X
a	H
b	Cl

Since **6a** proved to be insoluble in water the methylation of **6a** to a quaternary salt has also been accomplished for omprovement of water-solubility for biological investigations. We found that treatment with dimethyl sulfate afforded the methyl substituted salt (**7**).

Our new procedure has the synthetically favorable feature that certain substituents can be introduced to position 8 relatively easily as exemplified by the preparation of the 8-chloro derivative (**6b**).

EXPERIMENTAL

Melting Points were determined by a Büchi apparatus and are uncorrected. The IR spectra were recorded with a Nicolet Magna 750 FT-IR and Perkin-Elmer 1600 FT-IR spectrophotometers; the NMR spectra were measured on a Varian VXR-200 spectrometer.

*General procedure for the synthesis of arylpyridazines (**2**) and (**3**)*

A mixture of 5-iodo-2-methyl-3(2*H*)-pyridazinone (**1**) (0.236 g, 1 mmol) and tetrakis-(triphenylphosphine)-palladium(0) (0.058 g, 0.05 mmol) in dimethoxyethane (6 mL, over $SnCl_2$ distilled) was stirred for 30 min at rt under argon. The appropriate arylboronic acid (1.25 mmol) and a sodium carbonate solution (2M, 1 mL) were then added and the mixture was refluxed for 8 h. The reaction mixture was poured onto ice-water (8 mL) and was extracted with chloroform (3x10 mL) and the extract was dried over Na_2SO_4. Evaporation of the solvent gave a crude product which was suspended with ether and the precipitated crystals were filtered off.

2-Methyl-5-phenylpyridazin-3(2*H*)-one (2)

In this case we started from 4 mmol (0.94 g) of 5-iodo-2-methylpyridazin-3(2*H*)-one (**1**).

Yellow crystals (0.603 g, 81%); **mp**: 118-119 ^{o}C (recryst. from diisopropyl ether); **IR** (KBr): 3060, 1659, 1592, 1443, 1300, 770 cm^{-1}; ^{1}**H NMR** ($CDCl_3$) δ: 8.03 (d, 1H, *J* = 2.3 Hz, H-6), 7.08 (d, 1H, *J* = 2.3 Hz, H-4), 7.8-7.2 (m, 5H, H-Ph), 3.83 (s, 3H, N-CH_3); ^{13}**C NMR** ($CDCl_3$) δ: 135.46, 130.07, 129.23, 126.68, 124.09, 39.78; **Anal. Calcd** for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.04. Found: C, 70.66; H, 5.48; N, 15.12.

2-[(2*H*)-2-Methyl-3-oxo-5-pyridazinyl]-*N*-pivaloylanilide (3a)

In this case we started from 20 mmol (4.72 g) of 5-iodo-2-methylpyridazin-3(2*H*)-one (**1**).

Yellow product (5.49 g) was recrystallized from diisopropyl ether (3.65 g, 64%, pale brown crystals); **mp**: 135-136 ^{o}C; **IR** (KBr): 3248, 2965, 1690, 1647, 1573, 1519, 1448, 1285, 1160, 996 cm^{-1}; ^{1}**H NMR** ($CDCl_3$) δ: 7.83 (d, 1H , *J* = 7.8 Hz, H-6'), 7.78 (d, 1H, *J* = 2.2 Hz, H-6), 7.57 (s, 1H, NH), 7.47-7.24 (m, 3H, H-3', 4', 5'), 6.82 (d, 1H, *J* = 2.2 Hz, H-4), 3.77 (s, 3H, NCH_3), 1.24 (s, 9H, H-$(CH_3)_3$); ^{13}**C NMR** ($CDCl_3$) δ: 176.75(NH**CO**), 160.20, 143.04, 136.96, 134.61, 130.48, 129.20, 128.14, 125.94, 125.21, 127.04, 39.91, 39.52, 27.36; **Anal. Calcd** for $C_{16}H_{19}N_3O_2$: C, 67.35; H, 6.71; N, 14.73. Found: C, 67.25; H, 6.80; N, 14.65.

2-[(2*H*)-2-Methyl-3-oxo-5-pyridazinyl]-4-chloro-*N*-pivaloylanilide (**3b**)

Starting from 6.8 mmol (1.60 g) of **1**, the yellow crude product (1.88 g) was recrystallized from diisopropyl ether (1.65 g, 79%, pale yellow crystals); **mp**: 167-168 ^{o}C; **IR** (KBr): 3280, 1690, 1650, 1590, 1560, 1510 cm^{-1}; ^{1}**H NMR** ($CDCl_3$) δ: 7.85 (d, 1H, *J* = 8.6 Hz, H-6'), 7.75 (d, 1H, *J* = 2.2 Hz, H-6,), 7.51 (s, 1H, NH,), 7.42 (dd, 1H, *J* = 8.6, 2.4 Hz, H-5'), 7.25 (d, 1H, *J* = 2.4 Hz, H-3'), 6.82(d, 1H, *J* = 2.2Hz, H-4), 3.77 (s, 3H, NCH_3,), 1.24 (s, 9H, $C(CH_3)_3$,); ^{13}**C NMR** ($CDCl_3$) δ: 176.79, 159.94, 141.72, 136.37, 133.26, 131.17, 130.41, 129.33, 128.91, 127.34, 126.40, 40.06, 39.59, 27.34. **Anal. Calcd** for

$C_{16}H_{18}N_3O_2Cl$: C, 60.09; H, 5.67; N, 13.14. Found: C, 60.17; H, 5.76; N, 13.09.

5-(2-Aminophenyl)-2-methylpyridazin-3(2*H*)-one (4a)

2-[(2*H*)-2-Methyl-3-oxo-5-pyridazinyl]-*N*-pivaloylanilide (**3a**) (0.57 g, 2.0 mmol) was added to 20% sulphuric acid (35 mL) and was refluxed for 3 h. Upon cooling, the pH of the mixture was adjusted to 8 by addition of aqueous (25%) ammonia. The mixture was then extracted with $CHCl_3$ (1x100 mL, 2x50 mL), and the crude product (0.521 g) obtained after evaporation of the organic layer was recrystallized from acetonitrile to yield yellow crystals (0.278 g, 69%,); **mp**: 126.5-127.5 °C; **IR** (KBr): 3406, 3316, 3228, 3046, 1653, 1599, 1487, 1293, 756 cm^{-1}; **^{1}H NMR** ($CDCl_3$) δ: 7.92 (d, 1H, *J* = 2.2 Hz, H-6), 7.27-6.75 (m, 4H, H-Ar), 7.02 (d, 1H, *J* = 2.2 Hz, H-4), 3.91 (s, 2H, NH_2,), 3.81 (s, 3H, NCH_3); **^{13}C NMR** ($CDCl_3$) δ: 160.68, 143.78, 143.59, 137.30, 130.80, 129.51, 126.65, 119.03, 116.47, 119.64, 39.91; **Anal. Calcd** for $C_{11}H_{11}N_3O$: C, 65.66; H, 5.51; N, 20.88. Found: C, 65.72; H, 5.47; N, 20.76.

5-(2-Amino-5-chlorophenyl)-2-methylpyridazin-3(2*H*)-one (**4b**)

Starting from 5.2 mmol (1.66 g) of **3b**, the yellow crude product (**4b)** (1.07 g) was recrystallized from acetonitrile (0.92 g, 79%, yellow crystals); **mp**: 182-183 °C; **IR** (KBr): 3390, 3330, 3240, 1640, 1570, 1490, 1400, 1290 cm^{-1}; **^{1}H NMR** ($CDCl_3$ + DMSO-d_6) δ: 7.90 (d, 1H, *J* = 2.2, Hz, H-6), 7.14 (dd, 1H, *J* = 8.6 Hz, 2.4 Hz, H-5'), 7.04 (d, 1H, *J* = 2.4 Hz, H-3'), 6.91 (d, 1H, *J* = 2.2 Hz, H-4), 6,79 (d, 1H, *J* = 8.6 Hz, H-6'), 3.75 (s, 3H, NCH_3,); **^{13}C NMR** ($CDCl_3$ + DMSO-d_6) δ: 160.70, 145.07, 143.16, 137.48, 130.58, 129.13, 127.07, 121.58, 120.56, 118.19, 40.15; **Anal. Calcd** for $C_{11}H_{10}N_3OCl$: C, 56.06; H, 4.28; N, 17.83. Found: C, 56.13; H, 4.32; N, 17.76.

5-(2-Azidophenyl)-2-methylpyridazin-3(2*H*)-one (5a)

5-(2-Aminophenyl)-2-methyl-3(2*H*)-pyridazinone (**4a**) (1.006 g, 5 mmol) was dissolved in 37% hydrochloric acid (40 mL) and was cooled at 0°C with stirring. Aqueous sodium nitrite solution (0.73 g, 10.62 mmol of sodium nitrite in 27 mL of water) was added dropwise at such a rate that the temperature of the reaction mixture did not exceed 5 °C. The mixture was stirred at this temperature for 1.5 h. A solution of sodium azide (0.664 g, 10.62 mmol) and anhydrous sodium acetate (5.744 g, 70.02 mmol) in water (24 mL) was then added at 0-5°C and the mixture was stirred for an additional 1 h at this temperature. Then the mixture was neutralized with saturated of sodium carbonate solution and extracted with dichloromethane (1x100, 2x50 mL). The organic layer was evaporated without heating and the residue was suspended with ether to yield white crystals (0.532 g, 47%) which were filtered off . The product decomposed on air and was therefore stored under argon atmosphere in a refrigerator;

IR (KBr): 2930, 2132, 1661, 1595, 1570, 1290 cm^{-1}; **^{1}H NMR** ($CDCl_3$) δ: 7.93 (d, 1H, *J* = 2.2 Hz, H-6), 7.52-7.25 (m, 4H, H-Ar), 6.97 (d, 1H, *J* = 2.2 Hz, H-4), 3.83 (s, 3H, N-CH_3); **^{13}C NMR** ($CDCl_3$) δ:

160.51, 141,92, 137.64, 137.26, 131.12, 130.29, 127.63, 125.37, 118.93, 125.47, 39.86.

5-(2-Azido-5-chlorophenyl)-2-methylpyridazin-3(2*H*)-one (5b)

It was prepared from **4b** according to the procedure given for **5a** (1.19 g, 90 %); **mp**: 161-162 °C (from acetonitrile); **IR** (KBr): 3030, 3010, 2120, 2100, 1660, 1600, 1560, 1470, 1370, 1290 cm^{-1}; **^{1}H NMR** ($CDCl_3$) δ: 7.88 (d, 1H, *J* = 2.2, Hz, H-6), 7.47 (dd, 1H, J_1 = 8.6 Hz, J_2 = 2.4 Hz, H-5'), 7.31 (d, 1H, *J* = 2.4 Hz, H-3'), 7.22 (d, 1H, *J* = 8.6 Hz, H-6'), 6.96 (d, 1H, *J* = 2.2 Hz, H-4), 3.83 (s, 3H, NCH_3,); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 160.25, 140.63, 136.69, 136.28, 130.96, 130.69, 130.07, 127.92, 127.44, 120.20, 39.96.

3-Methylpyridazino[4,5-*b*]indol-4(3*H*)-one (6a)

A solution of 5-(2-azidophenyl)-2-methyl-3(2*H*)-pyridazinone (**5a**) (0.227 g, 1 mmol) in *o*-dichlorobenzene (10 mL) was refluxed for 1 h and the solvent was then removed under reduced pressure. The residue was suspended with ether and the resulting pale-yellow crystals were filtered off (0.145 g, 73%); **mp**: 288-290 °C (from *n*-butanol) (lit.,[9] 298-300 °C, *n*-butanol); **IR** (KBr): 3081, 1652, 1520, 1321, 1251, 736 cm^{-1}; **^{1}H NMR** ($CDCl_3$ + DMSO-d_6) δ: 12.59 (s, 1H, NH), 8.55 (s, 1H, H-1,), 8.01 (d, 1H , *J* = 8.0 Hz, H-9), 7.57 (d, 1H, *J* = 8.2 Hz, H-6), 7.42, (dd, 1H, *J* = 7.7, 8.2 Hz, H-7) 7.24 (dd, 1H, *J* = 7.4, 8.0 Hz, H-8), 3.82(s, 3H, N-CH_3); **^{13}C NMR** ($CDCl_3$ + DMSO-d_6) δ: 154.62, 139.07, 132.09, 131.37, 126.44, 120.95, 120.82, 120.53, 117.07, 112.78, 36.83; **Anal. Calcd** for $C_{11}H_9N_3O$: C, 66.32; H, 4.55; N, 21.09. Found: C, 66.42; H, 4.58; N, 21.12.

3-Methyl-8-chloropyridazino[4,5-*b*]indol-4(3*H*)-one (6b)

It was prepared from **5b** according to the procedure given for **6a** (0.200 g, 87 %); **mp**: 333-347 °C (recryst. from DMF); **IR** (KBr): 3410, 3110, 1640, 1580, 1530, 1450, 1380, 1280, 650, 580 cm^{-1}; **^{1}H NMR** (DMSO-d_6) δ: 12.93 (s, 1H, H-NH), 8.75 (s, 1H, H-1,), 8.29 (d, 1H , *J* = 2.0 Hz, H-9), 7.60 (d, 1H, *J* = 8.8 Hz, H-6), 7.49, (dd, 1H, *J* = 2.0, 8.8 Hz, H-7), 3.80 (s, 3H, N-CH_3); **^{13}C NMR** (DMSO-d_6) δ: 155.19, 138.40, 133.21, 133.15, 127.65, 126.60, 122.65, 121.54, 117.36, 115.27, 39.29; **Anal. Calcd** for $C_{11}H_8N_3OCl$: C, 56.55; H, 3.45; N, 17.98. Found: C, 56.49; H, 3.52; N, 17.86.

2,3-Dimethyl-4(3*H*)-oxopyridazino[4,5-*b*]indolinium tetrafluoroborate (7)

A suspension of 3-methylpyridazino[4,5-*b*]indol-4(3*H*)-one (**6a**) (0.2 g, 1.0 mmol) in dimethyl sulfate (5.0 mL, 52.6 mmol) was heated at 100°C for 7 h. After this period, dimethyl sulfate was removed under vacuum, the residue was treated with ice-water (5 g) and was stirred for 10 min. Hydrogen tetrafluoroboric acid (2 mL) was then given and the mixture was stirred additionally for 2 h. A colorless solid separated was filtered off (0.25 g) and was recrystallized from a mixture of acetonitrile-water to yield white crystals (0.11 g, 37%,); **mp**: 292-295 °C (from acetonitrile-water); **IR** (KBr): 3420, 3180, 1650, 1600, 1540, 1370, 1260, 1180, 1040, 740 cm^{-1}; ^{1}**H NMR** (DMSO-d_6) δ: 14.17 (s, 1H, NH,), 9.94 (s, 1H, H-1), 8.10 (d, 1H, *J* = 8.0 Hz, H-9), 7.80-7.40 (m, 3H, H-6, 7, 8), 4.45 (s, 3H, N(2)CH_3), 4.03 (s, 3H, N(3)CH_3); ^{13}**C NMR** (DMSO-d_6) δ: 151.72, 139.81, 138.19, 133.53, 128.79, 124.10, 121.35, 121.53, 114.21, 113.40, 47.52, 32.18; **Anal. Calcd** for $C_{12}H_{12}N_3OBF_4$: C, 47.88; H, 4.02; N, 13.96; Found: C, 47.75; H, 4.11; N, 13.86.

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