One-Pot Microwave-Assisted Selective Azido Reduction/Tandem Cyclization in Condensed and Solid Phase with Nickel Boride

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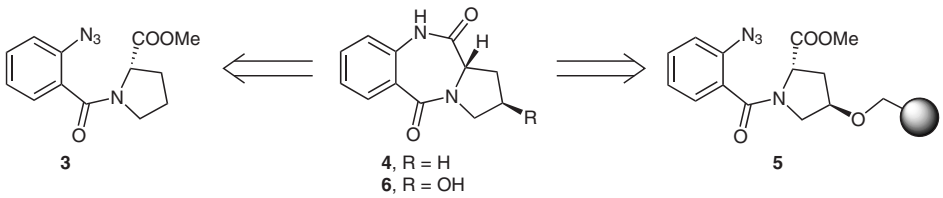
Abstract: An efficient and inexpensive method using microwave-assisted irradiation with Ni_2B for the syntheses of aromatic amines, pyrrolobenzodiazepines as well as pyrroloquinazolinones was developed. This protocol was applied in the tandem resin-cleavage, azido reduction, and cyclization of compounds **3** and **5** that afforded substituted pyrrolo[2,1-*c*][1,4]benzodiazepines **4** and **6** in a one-pot manner. The microwave-assisted irradiation reactions enhanced yields with very short reaction times in contrast to the conventional thermal reactions.

Key words: pyrrolo[2,1-*c*][1,4]benzodiazepines, pyrroloquinazolinones, azido reductive cyclization, nickel boride, microwave irradiation

The search towards efficient and mild methodologies for the reduction of azido/nitro groups to amines continues to challenge the chemists involved in the construction of organic molecules with enhanced complexity and functions. A large number of organic azides have attracted much interest not only as excellent protecting groups, but also as key intermediates for the synthesis of medicinally active compounds, such as carbohydrates, nucleosides, N-heterocycles, pyrrolo[2,1-*c*][1,4]benzodiazepines (PBDs), lactams, fused pyrroloquinazolinones, quinolines, and cyclic imides.[1] Several mild methodologies have been reported for the reduction of aromatic azido derivatives into the corresponding amines with the goal for the construction of heterocyclic moieties.[2] A great number of reagents have been described in the literature for azido group reductions using borohydrides,[3] triphenylphosphine,[4] benzyltriethylammonium tetrathiomolybdate,[5] hexamethyldisilathiane,[6] samarium iodide,[7] radical initiators,[8] and others. Use of nickel boride is shown to be an alternative way of main importance in hydrogenation processes, especially in selective hydrogenation reactions.[9] Several of these methodologies are not suitable if labile groups are present during the reduction process. During the past few years, we have investigated several synthetic strategies including solid-supported ones for the conversion of azido and nitro aromatic compounds to the corresponding amines.[10]

In such a scenario, microwave-assisted (MWA) approach has been applied in a variety of synthetic transformations for time as well as energy-saving aspects.[11,12a] It is well known that microwave-assisted irradiation is more selective in comparison to thermal reactions by favoring faster reactions and preventing decomposition of reactants and products.[12b] Despite its increasing importance and recent usage, there are few reports on the application of MWA for the reduction of azido and nitro groups.[13] During the course of PBD and pyrroloquinazolinone syntheses, we noted that Ni_2B was another choice to obtain such heterocyclic compounds. The main advantage of using this protocol consists in producing compounds **4** and **6** from azido derivatives **3** and **5** in a one-pot manner (Scheme 1).

PBDs are tricyclic low molecular weight compounds produced by various *Streptomyces* species, and are known to exhibit the DNA-binding interactions with potent antitumor or antibiotic activity.[14] PBD-5,11-diones have also been utilized as key intermediates in the synthesis of naturally occurring and synthetically modified PBD imines such as tomaymycin and chicamycin.[15–17] Moreover, the tricyclic ring system has been extensively utilized in the preparation of a number of pharmaceutically important moieties used as templates for the design and assembly of



Scheme 1 Retrosynthetic analysis of pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-diones

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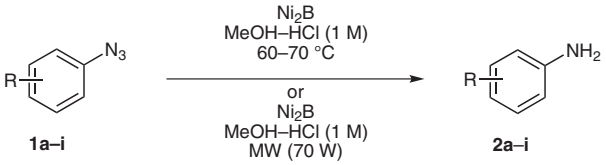
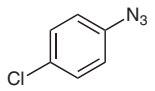
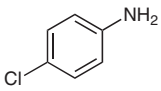
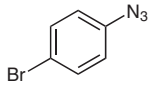
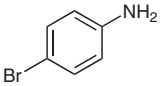
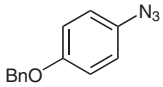
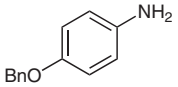
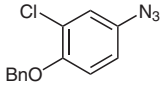
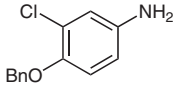
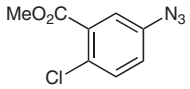
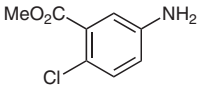
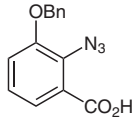
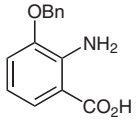
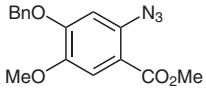
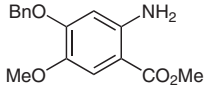
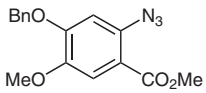
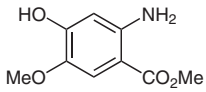
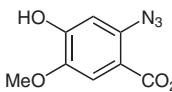
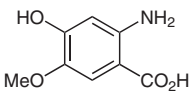
peptidomimetic agents,[18] anxiolytic drugs,[19] anticonvulsants,[20] herbicides,[21] and anticancer agents.[22]

Our investigation began by examining Ni_2B in acidic media as a mild reaction condition for the conversion of azido compounds to the corresponding amines through thermal and MWA approaches. The structure of nickel boride has remained unclear for the last 40 years, however, its annealing behavior was investigated and accepted to lead to crystalline Ni_2B.[23] The nickel boride (Ni_2B, amorphous fine black granules) was freshly prepared by mixing $Ni(OAc)_2$ and $NaBH_4$.[23] Previously, Seltzman and co-workers[23d] reported the reduction of iodine-substituted arylnitro compounds to the corresponding amino derivatives with Ni_2B. Table 1 summarizes the azido reductions with Ni_2B. The azido starting materials **1a–i** were synthesized according to reported methods.[10c–e] Initially, the reduction reactions were carried out using **1a–i** and an excess of Ni_2B (3 equiv) in MeOH–HCl (1.0 M) for 10–20 minutes at 60–70 °C. The corresponding amines **2a–i** was obtained in good yields (72–88%). The reactions were monitored by the disappearance of starting material as indicated by TLC and GC analysis. It was interesting to observe that the substituted azido acid derivatives (entries **f** and **i**) did not dimerize after reductions using the Ni_2B reagent system as observed previously.[24] It was also interesting to note that products **2c**,**d**,**f**,**g** were selectively obtained without any detected amount of debenzylated side products.

Therefore, with aim to increase the yields along with the shortening of the reaction times, we decided to explore the microwave-assisted irradiation process as the heating source for the conversion of aryl azides into amines. This

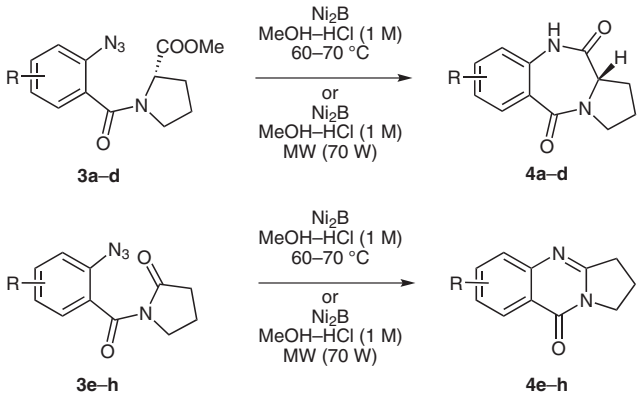
Table 1 Ni_2B Reduction of Azido Derivatives to the Corresponding Amines

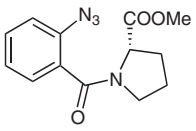
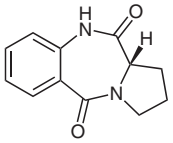
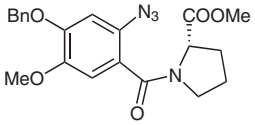
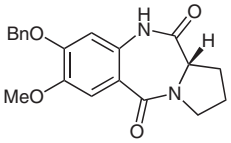
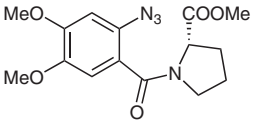
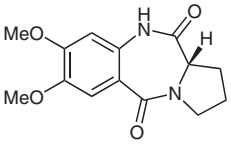
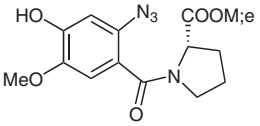
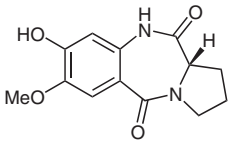
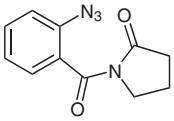
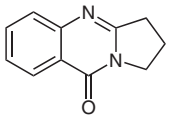
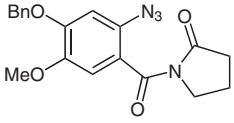
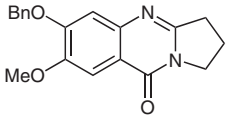
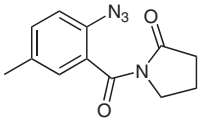
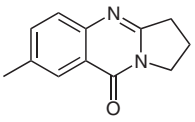
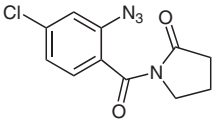
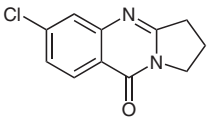


Entry	Substrate **1**	Product **2**[a]	Thermal reaction		MWA reaction	
			Time (min)	Yield (%)[b]	Time (min)	Yield (%)[b]
a			10	82	1	93
b			10	77	1	84
c			10	88	1	95
d			10	80	1	90
e			10	75	1	88
f			15	75	1	82
g			10	80	1	90
h			15	75	1	88
i			20	72	1	80

[a] All compounds were characterized by GC, ^1H and ^{13}C NMR, FT-IR, and EI-MS.
[b] Isolated yields.

Table 2 Synthesis of PBD-5,11-diones **4a–d** and Pyrroloquinazolinones **4e–h** through Reductive Cyclization Using Ni_2B



Entry	Substrate **3**	Product **4**[a]	Thermal reaction		MWA reaction	
			Time (min)	Yield (%)[b]	Time (min)	Yield (%)[b]
a			20	72	2	90
b			20	76	2	88
c			23	80	2	90
d			30	75	2	85
e			15	82	2	92
f			20	80	2	90
g			20	75	2	80
h			15	72	2	85

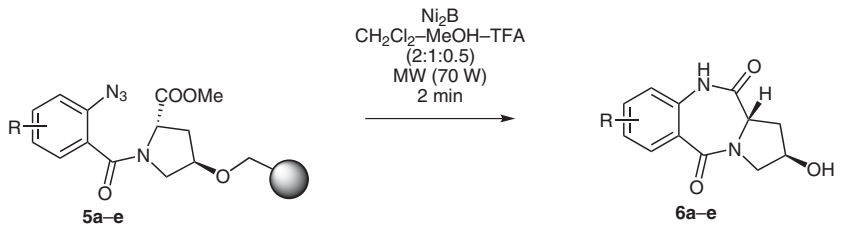
[a] All compounds were characterized by GC, ^1H and ^{13}C NMR, FT-IR and EI-MS.
[b] Isolated yields.

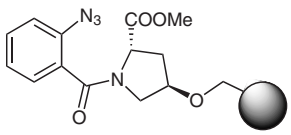
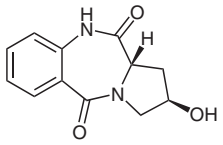
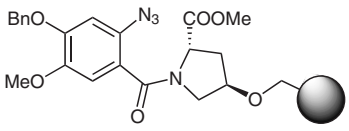
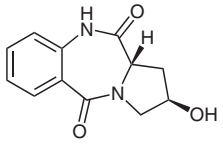
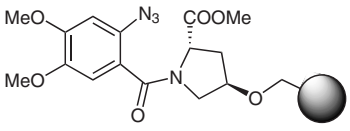
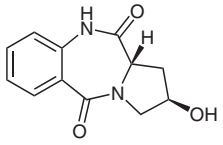
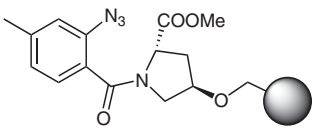
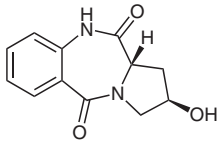
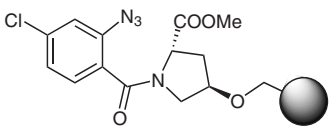
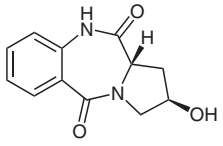
simple process and reaction conditions render particularly attractive for the efficient preparation of biologically and medicinally interesting molecules. The same reactions as depicted in Table 1 were carried out under MWA irradiation in a sealed vessel. Reaction times were reduced to one minute for azides **2a**–**i**, the yields (80–95%) were better than using thermal heating, as shown in Table 1. Further, it was also observed that applying the described protocol, temperatures of the reaction mixture inside the reaction vessel reached values of 39 °C (1 min) and 52 °C (2 min) for MWA irradiation reductions applying a potency of 70 W. These temperatures were lower than used in the thermal conditions, preventing in this way degradation of reactants and products, and favoring the enhancement of yields.

Next, we performed the reactions using **3a**–**d**[10c–e] as these compounds are interesting intermediates for PBD-5,11-dione syntheses. Table 2 summarizes the selective reduction of **3a**–**d** to amines followed by tandem cyclization affording **4a**–**d** in good to excellent yields (72–80%) in 20–30 minutes in condensed-phase, and 85–92% yields in 2 minutes in microwave-assisted reactions. As expected, azido derivatives **3a**–**d** showed better results in the reduction followed by cyclization to the corresponding PBD-5,11-diones **4a**–**d**. In addition, fused pyrroloquinazolinones (deoxyvasicinones) **4e**–**h** were also synthesized efficiently by using this Ni_2B reagent system. These derivatives **4e**–**h** are particularly interesting compounds as precursors for vasicinone and its derivatives that possess several pharmacological properties such as bronchodilation,[25] antitumour,[26] and antimycobacterial.[27]

Recently, we reported a versatile solid-phase combinatorial approach for PBD-5,11-diones with high diversity of a library of compounds, and in vitro activity against *Mycobacterium tuberculosis* assays.[28] In the same context, a solid-phase approach was developed for reductive cyclization of azido/nitro derivatives to the corresponding PBD-5,11-diones employing Al/$NiCl_2 \cdot 6H_2O$ and Al/NH_4Cl in a two-steps manner.[29] Thus, it is plausible to expect that using MWA, compounds **6a**–**e** might be obtained

Table 3 One-Pot Microwave-Assisted Solid-Phase Synthesis of PBD-5,11-diones by Reductive Cyclization and Resin Cleavage with Ni_2B



Entry	Substrate **5**	Product **6**[a]	Time (min)	Yield (%)[b]
a			2	80
b			2	73
c			2	64
d			2	78
e			2	81

[a] All compounds were characterized by ^1H and ^{13}C NMR, FT-IR and EI-MS.
[b] Isolated yields.

by Ni_2B reduction protocol from solid-supported **5a**–**e**.[10d] The C2-hydroxy substituted PBD-5,11-diones **6a**–**e** were obtained by a different protocol as used before. In the new approach Ni_2B was used with CH_2Cl_2–MeOH–TFA (2:1:0.5) as solvent. After MWA irradiation (2 min) of the mixture, **6a**–**e** was obtained in good yields ranging from 64–81% and lower reaction times than described previously, as depicted in Table 3. The sequence of this one-pot solid-phase synthesis of **6** by a reductive cyclization and resin cleavage seems to follow resin cleavage and/or reduction and tandem ring-closing (Table 3).

In conclusion, an efficient MWA methodology employing Ni_2B for the preparation of aromatic amines, pyrrolobenzodiazepines as well as pyrroloquinazolinones has been developed. The nickel boride reagent is easy to prepare, inexpensive, safe to handle, stable, and not pyrophoric, and no inert atmosphere is required. Interestingly, the microwave-assisted irradiation reactions enhanced yields with very short reaction times in contrast to the conventional thermal reactions. The reaction conditions are particularly attractive and are an example of green chemistry approach. The possibility of performing reactions in a very short time period by MWA energy with the reaction mixture can be considered green chemistry (reducing energy consumption, time savings, increasing efficiency, water as solvent). This work is also an example of preventing major adverse effects to the environment due to the consumption of energy for heating and cooling, and use of eco-friendly solvent like water. Several groups have tried to overcome these problems by seeking efficient methods that use alternative energy sources such as ultrasound or microwave irradiation to facilitate chemical reactions. If one compares the energy efficiency of conventional oil-bath synthesis (heating by conduction and convection currents), and microwave-assisted reactions, it can be noted that for most chemical transformations a significant energy saving (up to 80-fold) can be expected using microwaves as an energy source on a laboratory scale.[30]

Commercially available chemical reagents were used without further purification. Anhyd THF, CH_2Cl_2, MeOH, and DMF were prepared by distillation under N_2 over sodium/benzophenone, CaH_2, Na/P_2O_5, and CaH_2/molecular sieves, respectively. Solvents for extraction and column chromatography were distilled prior to use. Wang resin (0.8–1.0 mmol/g, 100–200 mesh, 1% DVB) was purchased from Lancaster. NaN_3 was handled with care for the preparation of various substituted azido derivatives by wearing safety glasses, facemask, gloves, and reactions were performed in a fume hood. All the microwave reactions were performed in CEM Discover LabMate equipment in a closed vessel (built-in infrared sensor) with cooling system. IR spectra were recorded as thin films on KBr discs and the wave numbers are expressed in cm^{-1}. All the polymer-bound intermediates were monitored by FT-IR spectra. Melting points were measured with an electrothermal apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on Varian Gemini 200, Bruker WH Avance 300, and Varian Unity 400 MHz spectrometers using TMS as the internal standard. Chemical shifts are reported in parts per million (ppm) downfield from TMS. Coupling constants are reported in hertz (Hz). Mass spectra were recorded on a Quattro-LC ESI-MS, and on a LSIMS-VG-Autospec (FAB and EI-MS) equipment. Column chromatography was performed using silica gel (100–200 mesh). TLC analyses were performed with silica gel plates using I_2, $KMnO_4$, and UV-lamp for visualization. The final yields of the purified products were determined on the basis of loading of the polymeric support starting from the Wang resin.

4-Chloroaniline (2a); Typical Procedure

1-Azido-4-chlorobenzene (**1a**; 50 mg, 0.326 mmol) was dissolved in MeOH (2.0 mL), and then Ni_2B (76 mg, 0.980 mmol) and aq 1 M HCl (1.0 mL) were added. This reaction mixture was heated to 60 °C and stirred for 10 min. Progress of the reaction was monitored by the disappearance of starting material as indicated by TLC and GC analysis. The same reaction was also performed with microwave-assisted irradiation at 70 W using CEM Discover LabMate equipment in a closed vessel with the temperature monitored by a built-in infrared sensor for 1 min at 39 °C with cooling. The resulting mixture was filtered, and then the MeOH was evaporated under vacuum. Then, H_2O (10 mL) was added to the mixture and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), rotaevaporated under reduced pressure to afford pure compound **2a**; yield: thermal, 34 mg (82%); MWA, 38 mg (93%); mp 70–71 °C.

FT-IR (KBr): 3477, 3375, 3198, 1880, 1618, 1509, 1288, 1180, 1079, 1015, 647, 546 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.12 (d, *J* = 8.87 Hz, 2 H), 6.63 (d, *J* = 8.87 Hz, 2 H), 3.67 (br s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 116.5, 123.7, 129.5, 144.8.

EI-MS: *m*/*z* = 127 [M^+].

4-Bromoaniline (2b)

Yield: thermal, 77%; MWA, 84%.

Mp 60–62 °C. Spectroscopic and physical data are in agreement with those described in the literature.[31]

4-Benzyloxyaniline (2c)

Yield: thermal, 88%; MWA, 95%; mp 44–46 °C.

FT-IR: (KBr): 3411, 3373, 3287, 3204, 2897, 2847, 1632, 1591, 1462, 918, 827, 697 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.28–7.46 (m, 5 H), 6.83 (d, *J* = 8.73 Hz, 2 H), 6.66 (d, *J* = 8.73 Hz, 2 H), 4.51 (s, 2 H), 3.44 (br s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.1, 141.1, 137.3, 128.7, 128.1, 127.4, 117.1, 116.8, 70.6.

EI-MS: *m*/*z* = 199 [M^+].

4-Benzyloxy-3-chloroaniline (2d)

Yield: thermal, 80%; MWA, 90%; mp 57–58 °C.

FT-IR (KBr): 3409, 3301, 3208, 3061, 3032, 2911, 2859, 1627, 1509, 1272, 1225, 1012, 921, 855, 747, 696 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.47 (d, *J* = 7.46 Hz, 2 H), 7.40 (t, *J* = 7.46 Hz, 2 H), 7.29 (t, *J* = 7.47 Hz, 1 H), 6.81 (d, *J* = 8.76 Hz, 1 H), 6.77 (d, *J* = 3.27 Hz, 1 H), 6.52 (dd, *J* = 8.72, 3.12 Hz, 1 H), 5.11 (s, 2 H), 3.46 (br s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 146.9, 141.5, 138.8, 128.4, 128.3, 127.5, 124.3, 116.9, 117.2, 113.9, 72.1.

EI-MS: *m*/*z* = 233 [M^+].

Methyl 5-Amino-2-chlorobenzoate (2e)

Yield: thermal, 75%; MWA, 88%; mp 68–70 °C.

FT-IR (KBr): 3458, 3366, 3228, 3010, 2947, 2838, 1727, 1628, 1611, 1488, 1444, 1334, 1044, 988, 788, 656 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.22 (d, *J* = 8.48 Hz, 1 H), 7.16 (d, *J* = 3.32 Hz, 1 H), 6.77 (dd, *J* = 8.48, 3.21 Hz, 1 H), 3.96 (s, 3 H), 3.77 (br s, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 167.1, 146.7, 132.6, 131.1, 122.2, 119.2, 117.8, 52.9.

EI-MS: *m*/*z* = 185 [M^+].

2-Amino-3-(benzyloxy)benzoic Acid (2f)

2-Azido-3-(benzyloxy)benzoic acid (**1f**; 0.050 g, 0.185 mmol) was dissolved in MeOH (2.0 mL), then Ni_2B (0.070 g, 0.557 mmol) and aq 1 M HCl (1.0 mL) were added. This reaction mixture was heated to 60 °C and stirred for 10 min. The resulting mixture was filtered and the MeOH was evaporated under vacuum. Then, H_2O (10 mL) was added to the residue and extracted with CH_2Cl_2 (10 mL). Next, the aqueous layer was carefully neutralized with aq 5% $NaHCO_3$ until pH 7.0. The aqueous solution was extracted with EtOAc (3 × 20 mL), dried (Na_2SO_4), rotaevaporated under reduced pressure to afford the pure compound **2f** as a brown solid; yield: thermal, 33 mg (75%); MWA, 37 mg (82%); mp 141–142 °C.

FT-IR: (KBr): 3491, 3348, 3064, 3029, 2922, 2866, 1673, 1612, 1577, 1463, 1399, 1275, 1214, 1158, 1087, 1041, 902, 845, 796 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47 (d, *J* = 9.29 Hz, 1 H), 7.26–7.36 (m, 5 H), 6.86 (d, *J* = 8.80 Hz, 1 H), 6.72 (br s, 1 H), 6.49 (t, *J* = 7.82, 8.31 Hz, 1 H), 5.64 (br s, 1 H), 5.00 (s, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 174.4, 173.1, 146.1, 142.4, 136.6, 128.2, 123.6, 115.0, 114.5, 109.6, 76.9, 70.7, 22.6.

EI-MS: *m*/*z* = 243 [M^+].

Methyl 2-Amino-4-(benzyloxy)-5-methoxybenzoate (2g)

Yield: thermal, 80%; MWA, 90%; mp 131–132 °C.

FT-IR (KBr): 3468, 3356, 3030, 2947, 1676, 1617, 1587, 1560, 1514, 1462, 1426, 1384, 1303, 1258, 1200, 1170, 992, 872, 835, 740, 695 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.24–7.39 (m, 6 H), 6.08 (s, 1 H), 5.08 (s, 2 H), 3.82 (s, 3 H), 3.80 (s, 3 H), 1.26 (d, *J* = 15.86 Hz, 2 H).

EI-MS: *m*/*z* = 287 [M^+].

Methyl 2-Amino-4-hydroxy-5-methoxybenzoate (2h)

Yield: thermal, 75%; MWA, 88%; mp 148–149 °C.

FT-IR (KBr): 3410, 3304, 3000, 2958, 2850, 1670, 1598, 1576, 1508, 1446, 1302, 1231, 1175, 1061, 1023, 952, 869, 843, 784, 629, 448 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.22 (s, 1 H), 6.15 (s, 1 H), 5.48 (br s, 2 H), 3.84 (s, 3 H), 3.83 (s, 3 H).

EI-MS: *m*/*z* =197 [M^+].

Amino-4-hydroxy-5-methoxybenzoic Acid (2i)

Yield: thermal, 72%; MWA, 80%; mp 169–171 °C.

FT-IR (KBr): 3485, 3324, 1710, 1576, 1508, 1441, 1384, 1297 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.26 (s, 1 H), 6.19 (s, 1 H), 5.55 (br s, 2 H), 3.92 (s, 3 H).

EI-MS: *m*/*z* = 183 [M^+].

(11a*S*)-2,3,5,10,11,11a-Hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione (4a); Typical Procedure

To a stirred solution of compound **3a** (0.100 g, 0.364 mmol) in MeOH (2.0 mL) and Ni_2B (0.137 g, 1.094 mmol) was added aq 1 M HCl (1.0 mL). The reaction mixture was heated to 60 °C followed by stirring for 20–30 min and the same amount of the reaction was repeated in microwave irradiation at 70 W for 2 min; temperature was maintained at 52 °C with (CEM Discover LabMate) cooling. The solvent was evaporated, neutralized to pH 7 with sat. aq 5% $NaHCO_3$ solution, and then extracted with EtOAc (3 × 25 mL). The combined organic phases were washed with brine (20 mL), dried (Na_2SO_4) and evaporated under reduced pressure. The crude product thus obtained was purified by column chromatography over a silica gel (60–120 mesh) employing EtOAc–hexane (75:25) as eluent to afford **4a**; yield: thermal, 56 g (72%); MWA, 71 g (90%); mp 218–219 °C; $[\alpha]_D^{23}$ +201 (*c* 1.0, MeOH).

FT-IR (KBr): 3223, 2952, 2873, 1688, 1625, 1476, 1449, 1413, 1268, 1213, 1154, 1103 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 9.22 (br s, 1 H), 8.01 (d, *J* = 8.03 Hz, 1 H), 7.45 (t, *J* = 8.03, 7.03 Hz, 1 H), 7.21–7.28 (m, 1 H), 7.05 (d, *J* = 8.03 Hz, 1 H), 4.07 (d, *J* = 6.57 Hz, 1 H), 3.75–3.86 (m, 1 H), 3.51–3.65 (m, 1 H), 2.71–2.82 (m, 1 H), 1.85–2.15 (m, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 171.2, 163.3, 135.1, 132.2, 130.8, 124.3, 123.0, 121.0, 56.8, 46.8, 26.1, 23.2.

EI-MS: *m*/*z* = 216 [M^+].

(11a*S*)-8-(Benzyloxy)-7-methoxy-2,3,5,10,11,11a-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione (4b)

Yield: thermal, 76%; MWA, 88%; mp 172–173 °C; $[\alpha]_D^{23}$ +239 (*c* 1.0, MeOH).

FT-IR (KBr): 3356, 2962, 2928, 2844, 1679, 1636, 1601, 1519, 1441, 1288, 1177, 1121, 1022, 883, 756, 697 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.81 (s, 1 H), 7.26–7.40 (m, 6 H), 6.49 (s, 1 H), 5.10 (s, 2 H), 4.00 (d, *J* = 6.44 Hz, 1 H), 3.91 (s, 3 H), 3.47–3.78 (m, 2 H), 2.63–2.71 (m, 1 H), 1.90–2.05 (m, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 170.8, 165.0, 149.4, 146.6, 135.7, 129.4, 128.5, 128.0, 127.1, 119.4, 112.3, 105.8, 76.9, 76.6, 708, 56.7, 56.1, 47.2, 26.1, 23.5.

EI-MS: *m*/*z* = 352 [M^+].

(11a*S*)-7,8-Dimethoxy-2,3,5,10,11,11a-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione (4c)

Yield: thermal, 80%; MWA, 90%; mp 178–180 °C; $[\alpha]_D^{23}$ +303 (*c* 1.0, MeOH).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.71 (br s, 1 H), 7.42 (s, 1 H), 6.48 (s, 1 H), 4.03–4.10 (m, 1 H), 3.93 (s, 3 H), 3.90 (s, 3 H), 3.72–3.82 (m, 1 H), 3.52–3.65 (m, 1 H), 2.70–2.78 (m, 1 H), 1.98–2.06 (m, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 190.6, 184.8, 171.6, 165.7, 149.3, 138.5, 131.4, 123.3, 96.5, 76.3, 75.6, 66.7, 45.6, 43.0.

EI-MS: *m*/*z* = 276 [M^+].

(11a*S*)-8-Hydroxy-7-methoxy-2,3,5,10,11,11a-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione (4d)

Yield: thermal, 75%; MWA, 85%; mp 254–255 °C; $[\alpha]_D^{23}$ +276 (*c* 0.5, MeOH).

FT-IR (KBr): 2960, 2925, 2843, 1683, 1631, 1607, 1521, 1438, 1284, 1204, 1173, 1115, 1060, 1025, 884, 757 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.80 (br s, 1 H), 7.40 (s, 1 H), 6.50 (s, 1 H), 6.00–6.10 (br s, 1 H), 4.00–4.10 (m, 1 H), 3.95 (s, 3 H), 3.70–3.80 (m, 1 H), 3.55–3.65 (m, 1 H), 2.70–2.80 (m, 1 H), 1.90–2.10 (m, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$) δ = 175.1, 170.1, 155.1, 149.5, 135.8, 122.5, 117.0, 112.8, 61.5, 60.7, 51.7, 30.7, 28.2.

EI-MS: *m*/*z* = 262 [M^+].

1,2,3,9-Tetrahydropyrrolo[2,1-*b*]quinazolin-9-one (4e)

Yield: thermal, 82%; MWA, 92%; mp 104–106 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.24 (dd, *J* = 1.5, 8.3 Hz, 1 H), 7.57–7.70 (m, 2 H), 7.38–7.52 (m, 1 H), 4.16–4.21 (t, *J* = 7.5 Hz, 2 H), 3.12–3.18 (t, *J* = 7.5 Hz, 2 H), 2.24–2.34 (m, 2 H).

EI-MS: *m*/*z* = 186 [M$^+$].

6-(Benzyloxy)-7-methoxy-1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazolin-9-one (4f)
Yield: thermal, 80%; MWA, 90%; mp 157–158 °C.

FT-IR (KBr): 2955, 2931, 2849, 1662, 1611, 1501, 1453, 1401, 1371, 1288, 1261, 1175, 1137, 1076, 1028, 846, 777 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.53 (s, 1 H), 7.25–7.46 (m, 5 H), 7.00 (s, 1 H), 5.22 (s, 2 H), 4.16 (t, *J* = 7.34 Hz, 2 H), 3.99 (s, 3 H), 3.10 (t, *J* = 7.34, 8.08 Hz, 2 H), 2.18–2.34 (m, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 176.8, 173.1, 168.4, 164.5, 155.4, 148.0, 147.4, 146.7, 133.3, 128.3, 125.0, 115.6, 89.9, 75.3, 65.7, 51.6, 49.1, 39.1, 31.5.

ESI-MS: *m*/*z* = 323 [M + H]$^+$.

2-Methyl-6,7,8,9-tetrahydro[2,1-*b*]quinazoline-11-one (4g)
Yield: thermal, 75%; MWA, 80%; mp 119–121 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.01 (s, 1 H), 7.55 (s, 2 H), 4.12 (t, *J* = 5.07 Hz; 2 H), 3.08 (t, *J* = 5.0 Hz, 2 H), 2.51 (s, 3 H), 1.90–2.20 (m, 4 H).

EI-MS: *m*/*z* = 214 [M$^+$].

3-Chloro-6,7,8,9-tetrahydro[2,1-*b*]quinazoline-11-one (4h)
Yield: thermal, 72%; MWA, 85%; mp 132–133 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.24 (d, *J* = 6.56 Hz, 1 H), 7.66 (s, 1 H), 7.47 (d, *J* = 6.65 Hz, 1 H), 4.04 (t, *J* = 7.42 Hz, 2 H), 3.03 (t, *J* = 8.0 Hz, 2 H), 1.95–2.10 (m, 4 H).

EI-MS: *m*/*z* = 234 [M$^+$].

(2*R*,11a*S*)-2-Hydroxy-1,2,3,10,11,11a-hexahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione (6a); Typical Procedure
To a suspension of resin **5a** (0.200 g, 0.72 mmol/g) in CH_2Cl_2 (4.0 mL) and MeOH (2.0 mL) was added TFA (1.0 mL) and Ni_2B (0.272 g, 2.16 mmol). Then the microwave-assisted reaction was performed at 70 W using a CEM Discover LabMate equipment in a closed vessel with the temperature monitored by a built-in infrared sensor for 2 min at 52 °C with cooling. The final product was then filtered through a glass funnel, and the filtrate was neutralized with sat. aq $NaHCO_3$ until pH 7. The organic layer was separated and dried (Na_2SO_4). The crude product was purified by preparative TLC using EtOAc–hexane (9:1) as eluent to give **6a** (80%) as a semi-solid; yield: 17 mg (80%); $[\alpha]_D^{23}$ +252 (*c* 1.0, MeOH).

^{1}H NMR (200 MHz, DMSO-d_6): δ = 10.20 (br s, 1 H), 7.85–8.00 (m, 1 H), 7.40–7.50 (m, 1 H), 7.08–7.26 (m, 2 H), 4.60–4.70 (m, 1 H), 4.40–4.55 (m, 1 H), 4.10–4.26 (m, 1 H), 3.85–3.95 (m, 1 H), 3.50–3.62 (m, 1 H), 2.78–2.95 (m, 1 H), 2.00–2.10 (m, 1 H).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 169.6, 165.0, 135.3, 131.2, 128.2, 125.4, 123.4, 120.5, 67.1, 54.7, 53.3, 33.8.

EI-MS: *m*/*z* = 233 [M$^+$].

(2*R*,11a*S*)-(8-Benzyloxy)-2-hydroxy-7-methoxy-1,2,3,10,11,11a-hexahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione (6b)
Yield: 73%; $[\alpha]_D^{23}$ –42 (*c* 0.5, MeOH).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 10.11 (br s, 1 H), 7.43 (s, 1 H), 7.32 (m, 5 H), 6.51 (s, 1 H), 5.01 (s, 2 H), 4.31 (m, 1 H), 4.05 (m, 1 H), 3.81 (s, 3 H), 3.60–3.65 (m, 2 H), 1.90–1.98 (m, 2 H), 1.21 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.1, 166.3, 152.8, 146.7, 138.1, 131.2, 129.9, 119.4, 112.7, 108.5, 80.1, 70.2, 68.9, 56.9, 55.3, 40.3, 38.2.

EI-MS: *m*/*z* = 368 [M$^+$].

(2*R*,11a*S*)-2-Hydroxy-7,8-dimethoxy-1,2,3,10,11,11a-hexahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione (6c)
Yield: 64%; $[\alpha]_D^{23}$ +138 (*c* 1.0, MeOH).

^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ = 8.98 (s, 1 H), 7.47 (s, 1 H), 6.63 (s, 1 H), 4.61 (d, *J* = 5.78 Hz, 1 H), 4.41 (m, 1 H), 4.17 (t, *J* = 4.08 Hz, 1 H), 4.08 (d, *J* = 6.78 Hz, 1 H), 3.84 (s, 3 H), 3.86 (s, 3 H), 3.45–3.60 (m, 1 H), 3.65–3.85 (m, 1 H), 1.93–2.98 (m, 1 H).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 170.8, 165.1, 152.5, 146.1, 131.7, 118.6, 112.2, 104.8, 67.8, 57.2, 56.8, 54.2, 34.2.

EI-MS: *m*/*z* = 292 [M$^+$].

(2*R*,11a*S*)- 2-Hydroxy-8-methyl-1,2,3,10,11,11a-hexahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione (6d)
Yield: 78%; $[\alpha]_D^{23}$ +189 (*c* 1.0, MeOH).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.31 (br s, 1 H), 7.75 (s, 1 H), 7.23 (d, *J* = 7.32 Hz, 1 H), 6.95 (d, *J* = 7.32 Hz, 1 H), 4.93 (d, *J* = 5.58 Hz, 1 H), 4.41 (m, 1 H), 4.16 (t, *J* = 8.08 Hz, 1 H), 3.74 (m, 1 H), 3.50–3.60 (m, 1 H), 2.71–2.82 (m, 1 H), 2.37 (s, 2 H), 1.97–2.07 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.1, 166.2, 143.8, 134.7, 1231.4, 128.0, 124.6, 118.6, 67.3, 57.9, 51.2, 34.6, 22.0.

EI-MS: *m*/*z* = 246 [M$^+$].

(2*R*,11a*S*)-8-Chloro-2-hydroxy-1,2,3,10,11,11a-hexahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione (6e)
Yield: 81%; $[\alpha]_D^{23}$ –88 (*c* 1.0, MeOH).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.51 (br s, 1 H), 7.78 (d, *J* = 4.89 Hz, 1 H), 7.09 (m, 2 H), 4.00–4.05 (m, 1 H), 3.65 (m, 1 H), 3.43 (m, 1 H), 3.01, (br s, 1 H), 2.61 (m, 1 H), 1.95 (m, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 170.3, 164.4, 137.5, 131.8, 130.9, 125.3, 124.9, 119.8, 56.3, 46.9, 25.8, 23.1.

EI-MS: *m*/*z* = 266 [M$^+$].

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References

(1) (a) Scriven, E. F. V.; Turnbull, R. *Chem. Rev.* **1988**, *88*, 297. (b) Brase, S.; Gil, C.; Knepper, K.; Zimmermann, V. *Angew. Chem. Int. Ed.* **2005**, *44*, 5188. (c) *Azides and Nitrenes: Reactivity and Utility*; Scriven, E. F. V., Ed.; Academic Press: New York, **1984**. (d) *The Chemistry of the Azido Group*; Patai, S., Ed.; Wiley: Chichester, **1971**.

(2) (a) Tiecco, M.; Testaferri, L.; Santi, C.; Tomassini, C.; Marini, F.; Bagnoli, L.; Temperini, A. *Angew. Chem. Int. Ed.* **2003**, *42*, 3131. (b) Sridhar, P. R.; Prabhu, K. R.; Chandrasekaran, S. *J. Org. Chem.* **2003**, *68*, 5261. (c) Hays, D. S.; Fu, G. C. *J. Org. Chem.* **1998**, *63*, 2796. (d) Goulaonic-Dubois, C.; Hesse, M. *Tetrahedron Lett.* **1995**, *36*, 7427. (e) Samano, M. C.; Robius, M. J. *Tetrahedron Lett.* **1991**, *32*, 6293. (f) Rolla, F. *J. Org. Chem.* **1982**, *47*, 4327. (g) Kondo, T.; Nakai, H.; Goto, T.

Tetrahedron **1973**, *29*, 1801. (h) Corey, E. J.; Nicolaou, K. C.; Balanson, R. D.; Machide, Y. *Synthesis* **1975**, 590.
(3) (a) Rao, H. S. P.; Siva, P. *Synth. Commun.* **1994**, *24*, 549. (b) Alverez, S. G.; Fisher, G. B.; Singavam, B. *Tetrahedron Lett.* **1995**, *36*, 2567.
(4) Molina, P.; Diaz, I.; Tarraga, A. *Tetrahedron* **1995**, *51*, 5617.
(5) Ramesha, A. R.; Bhat, S.; Chandrasekaran, S. *J. Org. Chem.* **1995**, *60*, 7682.
(6) (a) Capperucci, A.; Degl'Innocenti, A.; Fumicello, M.; Mauriello, G.; Scafato, P.; Spagnolo, P. *J. Org. Chem.* **1995**, *60*, 2254. (b) Kamal, A.; Reddy, B. S. P.; Reddy, B. S. N. *Tetrahedron Lett.* **1996**, *37*, 6803.
(7) Huang, Y.; Zhang, Y.; Wang, Y. *Tetrahedron Lett.* **1997**, *38*, 1065.
(8) (a) Benati, L.; Bencivenni, G.; Leardini, R.; Minozzi, M.; Nanni, D.; Scialpi, R.; Spagnolo, P.; Zanardi, G. *J. Org. Chem.* **2006**, *71*, 434. (b) Benati, L.; Bencivenni, G.; Leardini, R.; Minozzi, M.; Nanni, D.; Scialpi, R.; Spagnolo, P.; Zanardi, G. *J. Org. Chem.* **2006**, *71*, 5822; and references cited therein.
(9) (a) Pogorelica, I.; Filipan-Litvica, M.; Merkasa, S.; Ljubica, G.; Cepaneca, I.; Litvic, M. *J. Mol. Catal. A: Chem.* **2007**, *274*, 202. (b) Molvinger, K.; Lopez, M.; Court, J. *Tetrahedron Lett.* **1999**, *40*, 8375. (c) Molvinger, K.; Lopez, M.; Court, J. *J. Mol. Catal. A: Chem.* **1999**, *150*, 267. (d) Santos, L. S.; Pilli, R. A. *Synthesis* **2002**, 87. (e) Khurana, J. M.; Kukreja, G. *Synth. Commun.* **2002**, *32*, 1265. (f) Osby, J. O.; Ganem, B. *Tetrahedron Lett.* **1985**, *26*, 6413. (g) Nose, A.; Kudo, T. *Chem. Pharm. Bull.* **1989**, *37*, 816.
(10) (a) Kamal, A.; Ramana, K. V.; Rao, M. V. *J. Org. Chem.* **2001**, *66*, 997. (b) Kamal, A.; Damayanthi, Y.; Reddy, B. S. N.; Lakshminarayana, B.; Reddy, B. S. P. *Chem. Commun.* **1997**, 1015. (c) Kamal, A.; Shankaraiah, N.; Markandeya, N.; Reddy, K. L.; Reddy, Ch. S. *Tetrahedron Lett.* **2008**, *49*, 1465. (d) Kamal, A.; Reddy, G. S. K.; Reddy, K. L. *Tetrahedron Lett.* **2001**, *42*, 6969. (e) Kamal, A.; Reddy, G. S. K.; Reddy, K. L.; Raghavan, S. *Tetrahedron Lett.* **2002**, *43*, 2103.
(11) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259; and references cited therein.
(12) (a) Kappe, C. O. *Angew. Chem. Int. Ed.* **2004**, *43*, 6250. (b) Lidstrom, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225.
(13) Bartoli, G.; Antonio, G. D.; Giovannini, R.; G iuli, S.; Lanari, S.; Paoletti, M.; Marcantoni, E. *J. Org. Chem.* **2008**, *73*, 1919.
(14) Thurston, D. E. In *Molecular Aspects of Anticancer Drug DNA Interactions*; Neidle, D.; Waring, M. J., Eds.; Macmillan: London, **1993**, 54–88.
(15) (a) Kaneko, T.; Wong, H.; Doyle, T. W. *J. Antibiotics* **1984**, *37*, 300. (b) Jones, G. B.; Davey, C. L.; Jenkins, T. C.; Kamal, A.; Kneale, G.; Neidle, S.; Webster, G. D.; Thurston, D. E. *Anticancer Drug Des.* **1990**, *5*, 249. (c) Kaneko, T.; Wong, H.; Doyle, T. W. *Tetrahedron Lett.* **1983**, *24*, 5165.
(16) Kamal, A.; Howard, P. W.; Reddy, B. S. N.; Reddy, B. S. P.; Thurston, D. E. *Tetrahedron* **1997**, *53*, 3223.
(17) (a) Thurston, D. E.; Bose, D. S. *Chem. Rev.* **1994**, *94*, 433. (b) Kamal, A.; Rao, M. V.; Reddy, B. S. N. *Chem. Heterocycl. Comp.* **1998**, 1588. (c) Kamal, A.; Rao, N. V. *Chem. Commun.* **1996**, 385.
(18) Blackburn, B. K.; Lee, A.; Baier, M.; Kohl, B.; Olivero, A. G.; Matamoros, R.; Robarge, K. D.; McDowell, R. S. *J. Med. Chem.* **1997**, *40*, 717.
(19) Wright, W. B.; Brabander, H. J.; Greenblatt, E. N.; Day, I. P.; Hardy, R. A. *J. Med. Chem.* **1978**, *21*, 1087.
(20) Di Martino, G.; Massa, S.; Corelli, F.; Pantaleoni, G.; Fanini, D.; Palumbo, G. *Eur. J. Med. Chem.* **1983**, *18*, 347.
(21) Karp, G. M.; Manfredi, M. C.; Guaciaro, M. A.; Ortlip, C. L.; Marc, P.; Szamosi, I. T. *J. Agric. Food Chem.* **1997**, *45*, 493.
(22) Antonow, D.; Jenkins, T. C.; Howarda, P. W.; Thurston, D. E. *Bioorg. Med. Chem.* **2007**, *15*, 3041.
(23) (a) Schlessinger, H. I.; Brown, H. C.; Finholt, A. E.; Gilbreath, J. E.; Hoestra, H. R.; Hyde, E. K. *J. Am. Chem. Soc.* **1953**, *75*, 215. (b) Brown, C. A. *J. Org. Chem.* **1970**, *35*, 1900. (c) Hoffer, L. J. E.; Schultz, J.; Panson, R. D.; Anderson, R. B. *Inorg. Chem.* **1964**, *3*, 1783. (d) Seltzman, H. H.; Berrang, B. *Tetrahedron Lett.* **1993**, *34*, 3083.
(24) Kamal, A.; Ramana, K. V.; Ankati, H. B.; Ramana, A. V. *Tetrahedron Lett.* **2002**, *43*, 6861.
(25) Amin, A. H.; Mehta, D. R. *Nature* **1959**, *183*, 1317.
(26) Al-Shamma, A.; Drake, S.; Flynn, D. L.; Mitscher, L. A.; Park, Y. H.; Rao, G. S. R.; Simpson, A.; Swape, J. K.; Veysoglu, T.; Wu, S. T. S. *J. Nat. Prod.* **1981**, *44*, 745.
(27) Grange, J. M.; Snell, N. J. *J. Ethnopharmacol.* **1996**, *49*, 5091.
(28) Kamal, A.; Reddy, K. L.; Devaiah, V.; Shankaraiah, N.; Reddy, G. S. K.; Raghavan, S. *J. Comb. Chem.* **2007**, *9*, 29.
(29) Kamal, A.; Reddy, K. L.; Devaiah, V.; Reddy, G. S. K. *Tetrahedron Lett.* **2003**, *44*, 4741.
(30) (a) Gronnow, M. J.; White, R. J.; Clark, J. H.; Macquarrie, D. J. *Org. Process Res. Dev.* **2005**, *9*, 516. (b) Ondruschka, B.; Bonrath, W.; Stuerga, D. In *Microwaves in Organic Synthesis*, 2nd ed.; Loupy, A., Ed.; Wiley-VCH: Weinheim, **2006**, Chap. 2, 62.
(31) Kavala, V.; Naik, S.; Patel, B. K. *J. Org. Chem.* **2005**, *70*, 4267.