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Antineoplastic Activity of Benzimidazo[1,2-*b*]-Isoquinolines, Indolo[2,3-*b*]Quinolines, and Pyridocarbazoles

Ronni L. Weinkauf,[1] Allan Y. Chen,[2] Chiang Yu,[2] Leroy Liu,[2] Louis Barrows[3] and Edmond J. LaVoie[1]*

[1]*Department of Pharmaceutical Chemistry, College of Pharmacy, Rutgers, The State University of New Jersey, Piscataway, NJ 08855, U.S.A.*

[2]*Department of Pharmacology, The University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School, Piscataway, NJ 08855, U.S.A.*

[3]*Department of Pharmacology and Toxicology, The University of Utah, Salt Lake City, UT 84112, U.S.A.*

Abstract—Substituted pyrido[3,4-*b*]carbazoles, pyrido[2,3-*b*]carbazoles, indolo[2,3-*b*]quinolines, and benzimidazo[1,2-*b*]-isoquinolines were synthesized and evaluated for biological activity. Several methylated derivatives of these heterocyclic compounds had similar activity to ellipticine as mammalian topoisomerase II inhibitors. Methylated derivatives of these heterocyclic compounds were also highly active *in vitro*, inhibiting the growth of several human tumor cell lines. These data demonstrate that the antineoplastic activity associated with ellipticine can be retained within a wide variety of analogous heterocyclics.

Introduction

Ellipticine (**1**), 5,11-dimethylpyrido[4,3-*b*]carbazole, is a naturally-occurring plant alkaloid which is known for its broad spectrum of antineoplastic activity.[1,2] Extensive structure–activity studies have been performed to examine the effect of substituents on the pyrido[4,3-*b*]carbazole ring. Earlier studies noted that the presence of a 5-methyl substituent on pyrido[4,3-*b*]carbazole was associated with antineoplastic activity. It was also shown that substitution of the carbazole heteroatom by either oxygen or sulfur resulted in the complete loss of activity.[3] Structure–activity data have suggested that two heterocyclic nitrogen atoms are required for activity. The absence of antitumor activity reported for 5,11-dimethylpyrido[3,4-*b*]carbazole had initially suggested that the location of the pyridinic heteroatom was critical for activity.[4] Subsequent structure–activity studies performed with indolo[2,3-*b*]quinolines, however, have indicated that the specific location of the pyridinic heteroatom, the N^2 of ellipticine, may not be critical.[5]

A series of heterocyclic compounds with similar methyl substitution to ellipticine was synthesized in the present study. Available structure–activity data suggested that the induction of mammalian topoisomerase II cleavage and cytotoxic activity would be associated with ellipticine derivatives in which the second nitrogen heteroatom alternated 2*n* atoms from the indolo nitrogen. In order to further evaluate this hypothesis, several compounds were evaluated for cytotoxic activity against human tumor cells and as inhibitors of mammalian topoisomerase II. Among the compounds evaluated were 5,11-dimethyl-10*H*-pyrido[3,4-*b*]carbazole (**2**), 5,11-dimethyl-10*H*-pyrido-[2,3-*b*]carbazole (**3**), 5,11-dimethyl-5*H*-indolo[2,3-*b*]quinoline (**4**), and 6,11-dimethylbenzimidazo[1,2-*b*]isoquinoline (**5**), Figure 1. Using the synthetic approach developed for the preparation of 6,11-dimethylbenzimidazo[1,2-*b*]isoquinoline, several additional derivatives were prepared and evaluated for biological activity. These included 11-methylbenzimidazo[1,2-*b*]isoquinoline (**6**), 2,3,6,11-tetramethylbenzimidazo[1,2-*b*]isoquinoline (**7**), 2,3-dichloro-6,11-dimethylbenzimidazo[1,2-*b*]isoquinoline (**8**) and 5,14-dimethylnaphth[2',3':4,5]imidazo[1,2-*b*]isoquinoline (**9**).

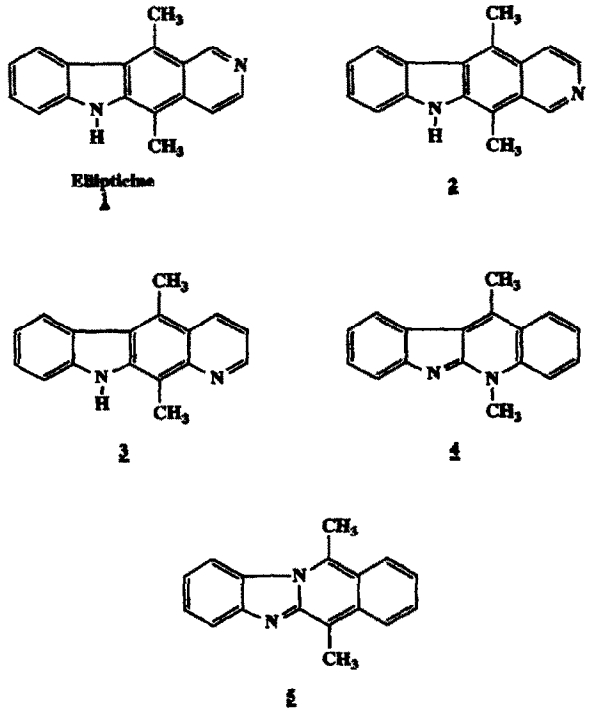


Figure 1. Ellipticine (**1**) and its isomeric pyridocarbazoles (**2** and **3**), indolo[2,3-b]quinoline (**4**), and benzimidazo[1,2-b]isoquinoline (**5**) analogs.

Chemistry

Methods for the preparation of compounds **2**, **3**, and **4** have been previously reported.[5–7] The synthetic method employed for the preparation of compounds **5–9** is outlined in Scheme I. Reaction of the appropriate phenylenediamine with α-(*o*-carboxyphenyl)-α-methylacetonitrile or α-(*o*-carboxyphenyl)acetonitrile produced good yields (53–83 %) of the desired 5*H*-benzimidazo[1,2-*b*]isoquinolin-11-ones (**5a–8a**) or 5-methyl-6*H*-naphth[2',3':4,5]imidazo[1,2-*b*]isoquinoline-11-one (**9a**). The N-5-SEM-protected derivatives of the 5*H*-benzimidazo[1,2-*b*]isoquinolin-11-ones were formed by reaction with 2-(trimethylsilyl)ethoxymethylchloride ether. Reaction of these SEM-protected benzimidazo[1,2-*b*]isoquinoline-11-ones with 2 equivalents of methyllithium afforded the desired 2-(*o*-acetyl-α-methylbenzyl)-1-SEM-benzimidazoles (**5b–8b**). Deprotection of the SEM group with 2 N HCl at 90 °C resulted in cyclization to the desired benzimidazo[1,2-*b*]isoquinolines (**5–8**). The preparation of naphth[2',3':4,5]imidazo[1,2-*b*]isoquinoline (**9**) was similarly accomplished by reacting **9a** with SEM-Cl in the presence of two equivalents of methyllithium to form 2-(*o*-acetyl -α- methylbenzyl)-1-[2-SEM]-naphth [2,3-*d*] imidazole (**9b**). Removal of the SEM group under acidic conditions resulted in cyclization to yield **9**.

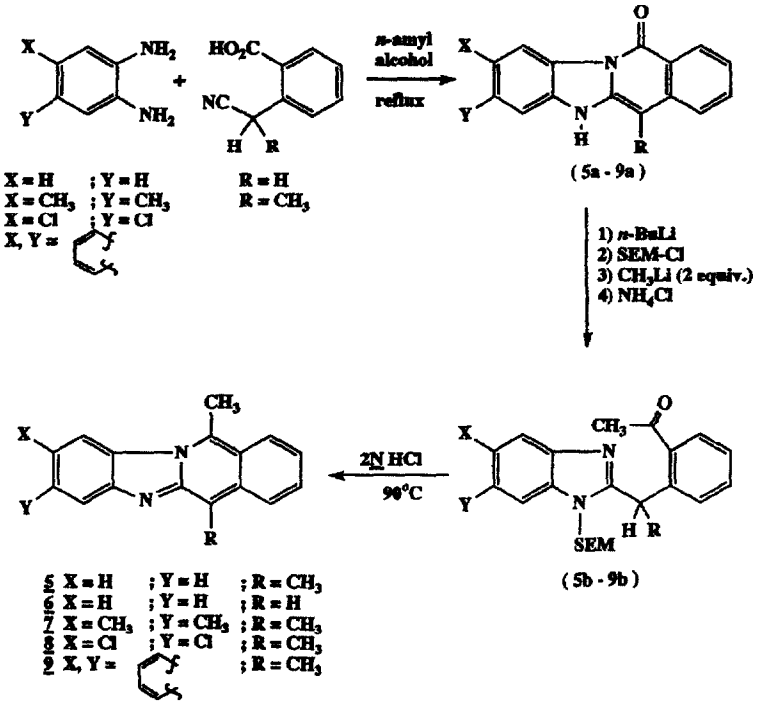
Pharmacology

DNA topoisomerase II was purified from calf thymus gland as previously detailed.[8] Plasmid YEPG was purified by the alkali lysis method followed by phenol deproteination and CsCl/ethidium isopycnic centrifugation.[9] End-labeling of the plasmid was accomplished as reported in the literature.[10] The cleavage assays were performed as previously outlined.[11]

The MTT-microtiter plate tetrazolium cytotoxicity assay (MTA) was used in this study to evaluate relative cytotoxicity.[12–14] Each dose of drug (as a solution in DMSO) was evaluated in four replicate plates. Each plate contained eight replicate control wells which were treated with DMSO only. The percent growth inhibition was determined for each set of quadruplicate wells by comparison of the average absorbance to that obtained for the control wells.

Results and Discussion

Table 1 summarizes the topoisomerase II inhibitory activity and cytotoxicity of ellipticine and several related compounds. In comparing the relative cytotoxic activity of the *N*-isomeric heterocyclic analogs (**2–5**) in HCT-116 cells, it is evident that several of these isomers have similar potency to ellipticine, **1**. Compounds **2** and **3** were somewhat less effective in inhibiting 9-KB cell growth than ellipticine. While **2** was less cytotoxic than ellipticine, it did possess reasonable cytotoxicity. These data conflict with the hypothesis that cytotoxic ellipticine analogs require that the second nitrogen heteroatom be at a position 2*n* atoms away from the indolo nitrogen. In the assays performed with both HCT-116 and 9-KB cells, it is evident that **4** exhibits greater cytotoxic activity than ellipticine. Each of the *N*-isomeric heterocyclic analogs of ellipticine (**2–5**) were active as inhibitors of topoisomerase II. In comparing their relative potency as inhibitors of topoisomerase, these analogs exhibited approximately 5 to 10-fold greater potency than ellipticine. These data indicate a significant enhancement of the structural variations possible with retention of activity among derivatives of ellipticine. The structure–activity relationship associated with dimethylbenzimidazo[1,2-*b*]isoquinoline analogs



Scheme I. Preparation of benzimidazo[1,2-b]isoquinolines, **5–8**, and 5,14-dimethylnaphtho[2',3':4,5]imidazo[1,2-b]isoquinoline, **9**.

related to compound **5** was also investigated. Four distinct analogs, compounds **6–9**, were synthesized. These agents were all substantially less active than ellipticine both as inhibitors of mammalian topoisomerase II as well as inhibitors of tumor cell growth. In the structure–activity studies performed with ellipticine, it was shown that the C-5 methyl group was necessary for activity.[2] The diminished cytotoxic activity observed for **6** as well as its relatively weak activity as an inhibitor of topoisomerase II suggest that a similar structure–activity relationship to that observed with ellipticine analogs exists among the benzimidazo[1,2-*b*]isoquinolines. Of the compounds evaluated, 2,3-dichloro-6,11-dimethylbenzimidazo[1,2-*b*]-isoquinoline (**8**) was the least potent inhibitor of topoisomerase II and had very weak activity in inhibiting 9-KB and HCT-116 cell growth. These results are also consistent with the diminished efficacy observed for similarly substituted chlorinated ellipticine analogs in inhibiting tumor cell growth.[15] The presence of additional methyl groups on ellipticine has also been associated with diminished antineoplastic activity.[16] While 2,3,6,11-tetramethylbenzimidazo[1,2-*b*]isoquinoline (**7**) and 5,14-dimethylnaphth[2',3':4,5]imidazo[1,2-*b*]isoquinoline (**9**) had appreciable activity as inhibitors of topoisomerase, neither derivative exhibited greater cytotoxic activity than ellipticine to HCT-116 or 9-KB cells. These data further support the premise that several of the structural requirements for antineoplastic activity among ellipticine derivatives are likely to apply to these benzimidazo[1,2-*b*]-isoquinoline derivatives. As indicated from Table 1, compounds **7** and **9** did have comparable activity to ellipticine as inhibitors of topoisomerase II. The results from NCI Development Therapeutic Program screening against 60 human tumor cell lines have indicated that both of these compounds generally exhibit IC_{50} values which are below 10μM. Thus, the relative potency of these agents as inhibitors of topoisomerase II appears consistent with their overall cytotoxic potential.

The ability of the *N*-isomeric analogs of ellipticine (**2–5**) to exhibit relatively potent inhibitory activity against topoisomerase II as well as similar cytotoxic activity in HCT-116 cells clearly indicate that the antineoplastic activity associated with ellipticine can be retained within a wide variety of analogous heterocyclic derivatives. Structure–activity studies on ellipticine have demonstrated that the presence of either a 9-hydroxy or 9-methoxy substituent results in enhanced cytotoxic activity *in vitro*.[2] There have also been reports that substitution at the C-1 of ellipticine with an [(*N,N*-dialkylamino)alkyl]amino moiety significantly enhances activity.[17] In view of these results, studies are in progress to examine the biological properties of similarly substituted derivatives of these heterocyclic analogs.

Experimental

General procedure for the preparation of 5H-benzimidazo[1,2-b]isoquinolin-11-ones and 5-methyl-6H-naphth[2',3':4,5]imidazo[1,2-b]isoquinolin-11-one

o-Phenylenediamine (360 mg, 3.31 mmol) and α-(*o*-carboxyphenyl)-α-methylacetonitrile (580 mg, 3.31 mmol) were refluxed in *n*-amyl alcohol (15 mL) for 8 h. At this time a Dean–Stark trap was attached to allow for the continuous removal of water, and the reaction mixture was heated at reflux for an additional 10 h. The reaction mixture was cooled to room temperature, and the precipitate was collected and washed with cold methanol to afford 551 mg of **5a** as a yellow fluffy precipitate in 67 % yield. mp 271 °C (dec.). UV: 222, 244, 340, 410, 430 nm (log ε = 4.26, 4.27, 4.09, 3.51, 3.43). IR (KBr): 3149, 1667, 1620, 1580, 1544, 1477, 1456, 1349, 1318, 1241, 1185, 1154, 1026, 754, 739, 708, 682 cm^{-1}. ^1H NMR (DMSO): 11.66 (s, 1H, NH), 8.65 (d, 1H, J = 7.8 Hz), 8.39 (d, 1H, J = 8.0 Hz), 7.75–7.71 (m, 2H), 7.43–7.17 (m, 4H), 2.43 (s, 3H).

Table 1. Effect of ellipticine analogs on the inhibition of the growth of HCT-116 and 9-KB cells and mammalian topoisomerase II

Compound	Cytotoxic Activity HCT-116 (IC_{50}; μM)	Cytotoxic Activity 9-KB (IC_{50}; μM)	Inhibition of Topoisomerase II Relative Activity[a]
1	6.3	11	1.0
2	8.5	40	5.0
3	7.4	64	10.0
4	0.8	2.2	5.0
5	6.2	14	10.0
6	53	75	0.2
7	30	23	2.0
8	>150	>150	0.1
9	33	26	1.0

[a]Relative activity to induce topoisomerase-mediated DNA cleavage is based on the relative potency of these compounds to cause 90 % of topoisomerase-mediated cleavage of linear 8.4-kb YEPG DNA. The potency of elipticine to stimulate topoisomerase-mediated DNA cleavage in these assay is taken as 1.0.

^{13}C NMR: 158.70 (q), 139.19 (q), 138.12 (q), 133.95 (q), 132.22, 128.54 (q), 127.53, 126.27, 121.63, 121.59, 120.17, 118.22 (q), 116.17, 109.32, 83.94 (q), 10.84. MS: 248 (M^+, 70), 246 (100), 233 (65), 218 (36), 190 (8), 151 (4), 77 (6).

*5H-Benzimidazo[1,2-b]isoquinolin-11-one (**6a**).* 604 mg or 83 % yield. mp 291 °C (dec.) UV: 248, 332, 398, 418 nm (log ε = 4.11, 4.14, 3.57, 3.52). ^{1}H NMR (DMSO): 11.88 (s, NH), 8.65 (d, 1H, *J* = 8.2 Hz), 8.31 (d, 1H, *J* = 8.2 Hz), 7.70–7.57 (m, 2H), 7.48–7.30 (m, 2H), 7.29–7.18 (m, 2H), 6.39 (s, 1H). ^{13}C NMR: 159.46 (q), 141.79 (q), 139.05 (q), 133.53 (q), 132.24, 128.19 (q), 127.23, 126.36, 125.07, 121.75, 120.33, 117.73 (q), 116.09, 109.49, 78.79. HRMS: calculated for $C_{15}H_{10}N_2O$: 234.0794; found: 234.0795. MS: 234 (M^+, 100), 205 (12). Analysis: calculated for $C_{15}H_{10}N_2O$: C, 76.91; H, 4.30; N, 11.96; found: C, 76.98; H, 4.35; N, 12.02.

*2,3,6-Trimethyl-5H-benzimidazo[1,2-b]isoquinolin-11-one (**7a**).* 754 mg or 75 % yield. mp > 230 °C (dec.). UV: 212, 230, 250, 272, 340, 420, 438 nm (log ε = 4.40, 4.50, 4.57, 4.44, 4.48, 3.96, 3.91). IR (KBr): 3189, 1672, 1615, 1580, 1544, 1487, 1349, 1308, 1256, 1215, 1180, 1149, 1077, 1026, 995, 872, 851, 744, 677 cm^{-1}. ^{1}H NMR (DMSO): 11.45 (s, NH), 8.44 (s, 1H), 8.35 (d, 1H, *J* = 8.1 Hz), 7.71–7.68 (m, 2H), 7.33–7.24 (m, 1H), 7.14 (s, 1H), 2.41 (s, 3H, 6-C*H*$_3$), 2.35 (s, 2-C*H*$_3$, 3-C*H*$_3$). ^{13}C NMR: 158.42 (q), 139.39 (q), 137.97 (q), 134.49 (q), 132.11 (q), 131.98, 127.98 (q), 127.47, 126.71 (q), 121.50, 121.29, 118.04 (q), 116.89, 110.07, 83.80 (q), 20.23, 19.98, 10.84. Analysis: calculated for $C_{18}H_{16}N_2O$: C, 78.24; H, 5.84; N, 10.14; found: C, 78.17; H, 5.81; N, 10.08.

*2,3-Dichloro-6-methyl-5H-benzimidazo[1,2-b]isoquinolin-11-one (**8a**).* 468 mg or 53 % yield. mp > 274 °C (dec.). UV: 210, 214, 252, 342, 422, 438 nm (log ε = 4.10, 4.08, 4.27, 4.08, 3.71, 3.70). IR (KBr): 3128, 1677, 1605, 1580, 1544, 1487, 1349, 1303, 1241, 1200, 1180, 1154, 1097, 1026, 954, 867, 749, 682 cm^{-1}. ^{1}H NMR (DMSO): 11.93 (s, 1H, NH), 8.71 (s, 1H), 8.38 (d, 1H, *J* = 8.0 Hz), 7.79–7.74 (m, 2H), 7.49 (s, 1H), 7.40–7.36 (m, 1H), 2.41 (s, 3H). HRMS: calculated for $C_{16}H_{10}N_2OCl_2$: 316.0172; found: 316.0161. MS: 318 (M^++2, 4), 316 (M^+, 7), 286 (5), 241 (5), 219 (100), 205 (30), 181 (1), 120 (8), 97 (4), 69 (13), 57 (40).

*5-Methyl-6H-naphth[2',3':4,5]imidazo[1,2-b]isoquinolin-14-one (**9a**).* 511 mg or 56 % yield. mp > 250 °C (dec.). UV: 216, 244, 316, 336, 352, 424, 448 nm (log ε = 4.19, 4.39, 4.22, 3.99, 4.05, 3.74, 3.75). IR (KBr): 3221, 1677, 1610, 1580, 1544, 1467, 1328, 1241, 1180, 1082, 1026, 974, 877, 846, 739, 677 cm^{-1}. ^{1}H NMR (DMSO): 11.60 (s, 1H, NH), 9.07 (s, 1H), 8.41 (d, 1H, *J* = 8.0 Hz), 8.07 (d, 1H, *J* = 7.6 Hz), 7.98 (d, 1H, *J* = 7.8 Hz), 7.78–7.69 (m, 2H), 7.62 (s, 1H), 7.56–7.33 (m, 3H), 2.43 (s, 3H). ^{13}C NMR: 159.15 (q), 139.67 (q), 138.44 (q), 133.80 (q), 132.74, 132.17 (q), 129.63 (q), 128.64, 128.52 (q), 127.64, 126.78, 125.98, 123.80, 122.27, 121.80, 119.19 (q), 113.25, 103.52, 84.79 (q), 10.86. Analysis: calculated for $C_{20}H_{14}N_2O$: C, 80.52; H, 4.73; N, 9.39; found: C, 80.39; H, 4.69; N, 9.40.

General procedure for the preparation of 2-(o-acetyl-α-methylbenzyl)-1-SEM-benzimidazoles and 2-(o-acetyl-α-methylbenzyl)-1-[2-(trimethylsilyl)ethoxymethyl]naphth-[2,3-d]imidazole

5a (166 mg, 0.67 mmol) in dry THF (15 mL) was cooled to –78 °C under nitrogen and treated with *n*-butyllithium (0.50 mL, 0.80 mmol). After 30 min at –78 °C, the reaction was quenched with 2-(trimethylsilyl)ethoxymethyl chloride (148 μL, 132.8 mg, 0.80 mmol). The reaction mixture was allowed to warm to room temperature, and after 1 h was treated with water (4 mL). The layers were separated, and the aqueous layer was washed with methylene chloride (2 × 20 mL). The THF and methylene chloride layers were combined, dried ($MgSO_4$), and concentrated to afford 254 mg of 5-SEM-5*H*-benzimidazo[1,2-*b*]isoquinolin-11-one. The SEM derivative (140.7 mg, 0.567 mmol) in dry THF (20 mL) was cooled to –78 °C under nitrogen and methyllithium (0.81 mL, 1.135 mmol) was added. The reaction mixture stirred at –78 °C for 3 h, at which time saturated ammonium chloride (4 mL) was added. The reaction mixture was warmed to room temperature, and the THF was removed *in vacuo*. The residue was diluted with water (30 mL), and extracted with methylene chloride (2 × 50 mL). The combined organic layers were dried ($MgSO_4$), and concentrated to afford an oil which was chromatographed on silica gel. The desired ketone was eluted as an oil with CH_2Cl_2 to provide 252 mg of **5b** in 100 % yield for the two step reaction. Compound **5b** had UV: 222, 248, 278, 286, 448 nm. IR: 1682, 1615, 1600, 1574, 1513, 1462, 1415, 1359, 1251, 1087, 944, 862, 836 cm^{-1}. ^{1}H NMR: 7.86–7.81 (m, 1H), 7.72–7.67 (m, 1H), 7.43–7.38 (m, 1H), 7.31–7.22 (m, 5H), 5.48 (q, 1H, *J* = 7.0 Hz), 5.33 (ABq, 2H, *J* = 11.2 Hz, *J* = 14.4 Hz) 3.22 (m, 2H), 2.66 (s, 3H), 1.79 (d, 3H, *J* = 7.0 Hz), 0.69 (m, 2H), –0.12 (s, 9H). ^{13}C NMR: 202.95 (q), 157.99 (q), 143.46 (q), 142.90 (q), 136.99 (q), 136.04 (q), 132.66, 129.67, 129.62, 127.04, 123.25, 122.66, 120.04, 110.36, 73.05, 66.32, 33.67, 30.48, 22.45, 18.19, –1.01. HRMS: calculated for $C_{23}H_{30}N_2O_2Si$: 394.2078; found: 394.2080. MS: 394 (M^+, 8), 321 (17), 276 (6), 263 (7), 247 (23), 191 (10), 146 (7), 103 (6), 73 (100).

*2-(o-Acetylbenzyl)-1-[2-(trimethylsilyl)ethoxymethyl]-benzimidazole (**6b**).* 123 mg (38 % for the two steps). UV: 212, 244, 276, 284 nm (log ε = 4.66, 4.25, 3.93, 3.97). IR: 1682, 1462, 1359, 1251, 1215, 1092, 944, 862, 836 cm^{-1}. ^{1}H NMR: 7.80–7.67 (m, 2H), 7.47–7.22 (m, 6H), 5.55 (s, 2H), 4.66 (s, 2H), 3.47 (t, 2H, *J* = 8.2 Hz), 2.55 (s, 3H), 0.85 (t, 2H, *J* = 8.2 Hz), –0.06 (s, 9H). ^{13}C NMR: 202.37 (q), 154.63 (q), 143.06 (q), 137.67 (q), 136.80 (q), 135.92 (q), 132.53, 132.11, 130.18, 127.56, 123.08, 122.61, 119.95, 110.08, 73.24, 66.73, 32.43, 29.74, 18.31, –0.96. HRMS: calculated for $C_{22}H_{28}N_2O_2Si$: 380.1921; found: 380.1910. MS: 380 (M^+, 4), 307 (14), 249 (2), 233 (12), 221 (12), 191 (5), 147 (14), 91 (8), 73 (100).

*2-(o-Acetyl-α-methylbenzyl)-5,6-dimethyl-1-[2-(trimethylsilyl)ethoxymethyl]-benzimidazole (**7b**).* 388 mg or 64 % yield for the two step reaction. UV: 210, 246, 286, 294 nm (log ε = 4.65, 4.12, 3.93, 3.94). IR: 1682, 1513,

1467, 1359, 1251, 1221, 1205, 1087, 862, 836 cm^{-1}. ^1H NMR: 7.70–7.65 (m, 1H), 7.59 (s, 1H), 7.28–7.26 (m, 3H), 7.17 (s, 1H), 5.23 (q, 1H, J = 6.9 Hz), 5.26 (AB quartet, 2H, J = 10.9 Hz, J = 15.1 Hz), 3.29–3.14 (m, 2H), 2.66 (s, 3H), 2.37 (s, 6H), 1.77 (d, 3H), 0.76–0.65 (m, 2H), –0.11 (s, 9H). ^{13}C NMR: 202.93 (q), 157.09 (q), 143.72 (q), 141.46 (q), 137.01 (q), 134.55 (q), 132.57, 132.22 (q), 131.33 (q), 129.65, 129.51, 126.93, 120.17, 110.69, 73.01, 66.18, 33.65, 30.46, 22.43, 20.93, 20.72, 18.20, –1.01. HRMS: calculated for $C_{25}H_{34}N_2O_2Si$: 422.2391; found: 422.2399. MS: 422 (M^+, 15), 349 (17), 291 (32), 277 (58), 191 (10), 146 (6), 91 (9), 73 (100).

*2-(o-Acetyl-α-methylbenzyl)-5,6-dichloro-1-[2-(trimethylsilyl)ethoxymethyl]benzimidazole (**8b**).* 134.1 mg (53 % for the two steps). UV: 218, 292, 300 nm (log ε = 4.71, 3.96, 3.98). IR: 1682, 1451, 1405, 1359, 1251, 1205, 1092, 862, 836 cm^{-1}. ^1H NMR: 7.86 (s, 1H), 7.74–7.69 (m, 1H), 7.51 (s, 1H), 7.36–7.22 (m, 3H), 5.47 (q, 1H, J = 6.9 Hz), 5.30 (s, 2H), 3.26–3.10 (m, 2H), 2.65 (s, 3H), 1.73 (d, 3H, J = 6.9 Hz), 0.75–0.65 (m, 2H), –0.12 (s, 9H). ^{13}C NMR: 202.87 (q), 160.02 (q), 142.87 (q), 142.35 (q), 136.75 (q), 135.19 (q), 132.84, 129.87, 129.48, 127.32, 127.20 (q), 126.70 (q), 121.22, 112.07, 73.43, 66.60, 33.64, 30.39, 22.29, 18.19, –1.04. HRMS: calculated for $C_{23}H_{28}N_2O_2Si$: 462.1299; found: 462.1276. MS: 462 (M^+, 4), 389 (11), 345 (3), 315 (10), 191 (7), 146 (6), 103 (8), 73 (100).

*2-(o-Acetyl-α-methylbenzyl)-1-[2-(trimethylsilyl)ethoxymethyl]naphth[2,3-*d*]imidazole (**9b**).* 283 mg or 48 % yield for the two step reaction. UV: 246, 318 nm (log ε = 4.79, 3.88). IR: 1686, 1521, 1447, 1402, 1372, 1357, 1262, 1253, 1205, 1086, 859, 837 cm^{-1}. ^1H NMR: 8.28 (s, 1H), 8.03–7.89 (m, 2H), 7.80 (s, 1H), 7.76–7.70 (m, 1H), 7.43–7.27 (m, 5H), 5.56 (q, 1H, J = 6.9 Hz), 5.42 (AB quartet, 1H, J = 11.2 Hz, J = 15.5 Hz), 3.35–3.21 (m, 2H), 2.68 (s, 3H), 1.84 (d, 3H, J = 6.9 Hz), 0.79–0.69 (m, 2H), –0.11 (s, 9H). ^{13}C NMR: 202.89 (q), 162.06 (q), 143.09 (q), 136.96 (q), 136.71 (q), 132.78, 131.05 (q), 130.80 (q), 129.79, 129.60, 128.97, 127.94, 127.21, 124.85, 123.95, 116.92, 106.17, 73.31, 66.38, 34.04, 30.44, 22.33, 18.28, –1.00. HRMS: calculated for $C_{27}H_{32}N_2O_2Si$: 444.2235; found: 444.2243. MS: 444 (M^+, 8), 371 (15), 326 (10), 297 (6), 269 (14), 73 (100).

*General procedure for the preparation of benzimidazo-[1,2-*b*]isoquinolines and naphth[2',3':4,5]imidazo-[1,2-*b*]isoquinoline*

The methyl ketone, **5b**, (91.0 mg, 0.231 mmol) was heated in 2N HCl (13 mL) and absolute ethanol (2 mL) at 90 °C for 2 h. The reaction mixture was cooled, and concentrated *in vacuo* to approximately 1/2 the original volume. The aqueous solution was diluted with water (30 mL), basified to pH 10 with aqueous sodium hydroxide, and the product was extracted with CH_2Cl_2 (3 × 50 mL). The organic layers were combined, dried (Na_2SO_4), and concentrated to afford 61.3 mg of product which was pure but contained some water. Vigorous drying under vacuum afforded 55.4 mg of **5** in 97 % yield. mp 150–153 °C. UV: 210, 272, 296, 306, 346, 444, 468 nm (log ε = 4.35, 4.62, 4.24, 4.20, 3.25, 3.42, 3.46). IR: 1626, 1615, 1585, 1482, 1462, 1405, 1359, 1328, 1236, 1005, 759, 733, 622 cm^{-1}. ^1H NMR: 8.22 (d, 1H, J = 8.5 Hz), 7.97 (d, 1H, J = 7.9 Hz), 7.87–7.78 (m, 2H), 7.55 (ddd, 1H, J = 1.1 Hz, J = 7.1 Hz, J = 8.2 Hz), 7.33–7.10 (m, 3H), 3.23 (s, 11-CH_3), 2.95 (s, 6-CH_3). ^{13}C NMR: 146.95 (q), 135.33 (q), 131.31 (q), 130.04 (q), 127.64, 127.32 (q), 126.74, 124.80, 124.14, 123.94, 122.36 (q), 119.41, 119.30, 118.63 (q), 116.97, 17.19, 13.48. HRMS: calculated for $C_{17}H_{14}N_2$: 246.1158; found: 246.1148. MS: 246 (M^+, 100), 231 (23), 137 (4), 109 (4), 92 (7), 81 (13), 69 (24), 57 (11).

*11-Methylbenzimidazo[1,2-*b*]isoquinoline (**6**).* 73 mg of 11-methylbenzimidazo[1,2-*b*]isoquinoline in 99 % yield. UV: 210, 272, 294, 302, 344, 442, 466 nm (log ε = 4.29, 4.50, 4.16, 4.12, 3.41, 3.24, 3.30). IR: 1677, 1641, 1595, 1503, 1487, 1456, 1385, 1313, 1098, 976, 861 cm^{-1}. ^1H NMR: 8.18 (d, 1H, J = 8.4 Hz), 7.79 (d, 1H, J = 8.4 Hz), 7.69 (s, 1H), 7.55–7.45 (m, 2H), 7.26–7.09 (m, 4H), 3.23 (s, 2H). HRMS: calculated for $C_{16}H_{12}N_2$: 232.1002; found: 232.1004. MS: 232 (M^+, 100), 217 (10), 204 (12), 166 (6), 147 (17), 127 (6), 105 (9), 91 (23), 77 (27).

*2,3,6,11-Tetramethylbenzimidazo[1,2-*b*]isoquinoline (**7**).* 126 mg in 93 % yield. mp 175–178 °C. UV: 208, 226, 276, 300, 312, 352, 448, 472 nm (log ε = 4.27, 4.30, 4.71, 4.45, 4.42, 3.42, 3.57, 3.55). IR: 1733, 1590, 1487, 1472, 1359, 1333, 1215, 1005, 908 cm^{-1}. ^1H NMR: 8.13 (s, 1H), 8.01–7.90 (m, 2H), 7.83 (s, 1H), 7.39–7.17 (m, 2H), 3.42 (s, 3H), 3.06 (s, 3H), 2.50 (s, 3H), 2.49 (s, 3H). ^{13}C NMR: 145.87 (q), 136.33 (q), 134.87 (q), 130.94 (q), 128.65 (q), 128.55 (q), 127.30, 124.89, 124.27, 123.73, 122.06 (q), 119.35, 118.57 (q), 116.87 (q), 116.79, 21.35, 21.20, 17.28, 13.54. HRMS: calculated for $C_{19}H_{18}N_2$: 274.1471; found: 274.1469. MS: 274 (M^+, 100), 259 (31), 129 (7) 95 (5), 81 (10), 69 (23), 57 (12).

*2,3-Dichloro-6,11-dimethylbenzimidazo[1,2-*b*]isoquinoline (**8**).* 85 mg or 93 % yield. mp 230–231 °C. UV: 220, 278, 308, 348, 446, 470, 502 nm (log ε = 4.63, 5.03, 4.52, 3.75, 3.79, 3.89, 3.71). IR: 1733, 1583, 1484, 1458, 1438, 1344, 1225, 1106, 1008, 971, 863, 769, 733, 718, 671 cm^{-1}. ^1H NMR: 8.44 (s, 1H), 8.06 (s, 1H), 8.02 (d, 1H, J = 9.2 Hz), 7.94 (d, 1H, J = 9.0), 7.48–7.26 (m, 2H), 3.39 (s, 3H), 3.03 (s, 3H). ^{13}C NMR: 128.49, 124.90, 124.84, 124.36, 122.61 (q), 120.05, 117.96, 117.87 (q), 17.30, 13.50. HRMS: calculated for $C_{17}H_{12}N_2Cl_2$: 314.0380; found: 314.0375. MS: 314 (M^+, 7), 299 (3), 137 (7), 97 (19), 81 (46), 69 (100), 57 (63).

*5,14-Dimethyl-6H-naphth[2',3':4,5]imidazo[1,2-*b*]isoquinoline (**9**).* 57 mg in 86 % yield. mp 184–185 °C. UV: 216, 256, 296, 340, 362, 510, 544 nm (log ε = 4.40, 4.35, 4.84, 4.15, 4.02, 3.41, 3.43). IR: 1623, 1592, 1499, 1483, 1462, 1408, 1343, 1271, 1240, 1229, 1214, 1007, 909, 856 cm^{-1}. ^1H NMR: 8.51 (s, 1H), 8.25 (s, 1H), 7.93–7.72 (m, 4H), 7.46–7.10 (m, 4H), 3.31 (s, 3H), 2.92 (s, 3H). ^{13}C NMR: 151.03 (q), 145.57 (q), 137.67 (q), 133.09 (q), 132.64 (q), 131.73 (q), 130.56 (q), 129.02, 128.69, 127.60, 125.65, 125.34, 124.01, 123.70, 123.23, 118.30 (q), 116.10 (q), 114.64, 113.99, 17.41, 13.48.

HRMS: calculated for $C_{21}H_{16}N_2$: 296.1315; found: 296.1310. MS: 296 (M^+, 13), 218 (21), 144 (6), 109 (8), 98 (25), 83 (29), 71 (42).

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