Bulgarian Chemical Communications, Volume 48, Number 4 (pp. 725 – 730) 2016

Synthesis of 2-(substituted)-3*H*-benzimidazole-5-carboxylic acids and 2-(substituted)-3*H*-imidazo[4,5-b]pyridine-5-carboxylic acids: synthons for fluorescent Hx and *aza*-Hx amides

V.S. Satam[1], P.C. Patil[1], B. Babu[1], K.A. Brien[1], M. Gregory[1], M. Bowerman[1], J. Sweers[1], A. Mepham[1], M. Lee[1,2]*

[1]*Department of Chemistry, Hope College, Holland, Michigan, USA;*
[2]*Department of Chemistry, Georgia State University, Atlanta, Georgia, USA*

Received January 3, 2016; Revised March 4, 2016

The syntheses of fifteen fluorescent 2-(substituted)benzimidazole-5- (Hx) and 2-(substituted)imidazopyridine-5- (*aza*-Hx) carboxylic acids are reported. These are key moieties of Hx- and *aza*-Hx amides, which bind DNA at specific sequences in the minor groove. Condensation of methyl 3, 4-diaminobenzoate **10a** or methyl 5,6-diaminopyridine-2-carboxylate **10b** with the appropriate aryl- or heteroarylaldehyde **9** produced the desired Hx (**7a-k**) and *aza*-Hx esters (**8l-o**) in 31-88% and 18-70% yields, respectively. Hydrolysis of esters **7a-k** and **8l-o** gave the corresponding Hx (**5a-k**) and *aza*-Hx acids (**6l-o**) in 66-93% and 64-85% yields, respectively. Hx acids **5d**, **5e**, **5g**, and **5k**, and *aza*-Hx acids **6m-o** are novel compounds.

Keywords: polyamides; fluorescence; benzimidazole; imidazopyridine; DNA binding; sequence specificity

INTRODUCTION

Pyrrole (Py)- and imidazole (Im)-containing analogs of distamycin (**1**, Figure 1) are polyamides (PAs) that bind in the minor-groove of DNA in a stacked fashion at specific DNA sequences[1]. These PAs, such as **2** (Figure 1), can potentially be designed to target specific sequences and modulate the expression of genes, including those associated with cancer cell growth [2-7]. Recently, our group demonstrated the usefulness of PAs by reporting a new class of compounds called Hx amides [8]. These amides (**3**, Figure 1) contain the fluorescent 2-(4-methoxyphenyl)benzimidazole or Hx moiety at the *N*-terminus. Mimicking the fluorescent and DNA binding properties of Hoechst, a stacked Hx motif behaves as a Py-Py unit; thus, a stacked Hx/PP unit recognizes two A/T base pairs [8a] and a stacked Hx/II unit recognizes CC/GG [8b]. The important feature of Hx amides is their ability to fluoresce which enables tracking of these molecules in cells and in animals [9]. The success of Hx amides has led to the design and synthesis of *aza*-Hx amides **4** (Figure 1), which contains a fluorescent 2-(4-methoxyphenyl)-3*H*-imidazo[4,5-b]pyridine (*aza*-Hx) moiety [10]. Our group has recently reported that *aza*-Hx mimics a Py-Im unit; thus, when stacked with Im-Py the the stacked dimer binds preferentially to CG/GC. *Aza*-Hx amide **4** can also be tracked in cells by means of fluorescence [10].

In our pursuit of Hx and *aza*-Hx amides, we have synthesized a variety of analogs with the intention of affecting their DNA binding properties. Hx analogs that contain substituents such as 4-fluorophenyl, 4-(*N*,*N*-dimethyl)phenyl, 4-methoxy-3-nitrophenyl, pyridin-4-yl, indol-3-yl, or 7-(*N*,*N*-diethylamino) coumarin-3-yl in place of 4-methoxyphenyl were synthesized to mimic a Py-Py unit. However, replacing 4-methoxyphenyl in Hx with 6-methoxypyridin-2-yl, 6-methoxypyridin-3-yl, furan-2-yl, or benzofuran-2-yl could potentially mimic an Im-Py unit. Furthermore, replacing 4-methoxyphenyl in *aza*-Hx with 6-methoxypyridin-2-yl, 6-methoxypyridin-3-yl, or furan-2-yl could potentially provide analogs that mimic an Im-Im unit. The synthesis of Hx and *aza*-Hx amides is challenging due to the susceptibility of *N*-methylpyrrole-2-carbonyl chloride to undergo polymerization [11], the instability of the polyamide amines [6-10,12] and the lack of access to key Hx acids (**5a-k**) and *aza*-Hx acids (**6l-o**). Table 1 depicts fifteen Hx and *aza*-Hx acids synthesized in this study. Hx acids **5a** [13,14], **5b** [14,15], **5c** [14,16], **5h**[14,17] and **5j** [14,18] were previously reported and are commercially available. Hx acids **5f** and **5i** are commercially available [14], and *aza*-Hx acid **6l** was preliminarily reported by our group [10] but no experimental or characterization data was published. The synthesis and characterization data for the novel Hx and *aza*-Hx acids (**5d**, **5e**, **5g**, **5k**, and **6n-o**) are reported herein, along with *aza*-Hx acid **6l**.

* To whom all correspondence should be sent:
E-mail: mosesleenf@gmail.com

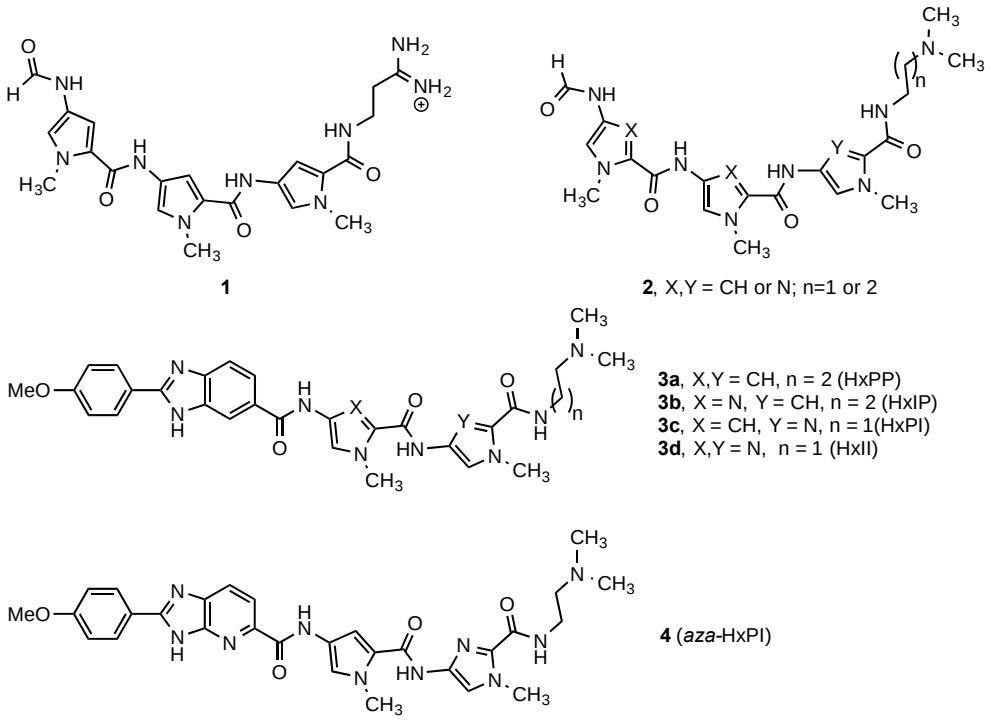
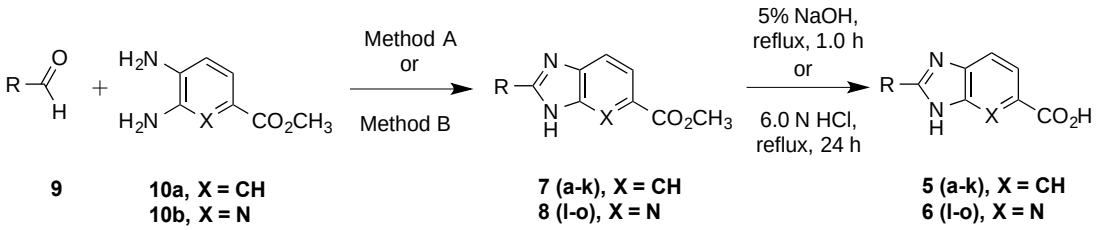


Fig. 1. Structures of distamycin **1**, *N*-formamido polyamide **2**, Hx amide **3,** and an *aza*-Hx amide **4 .**

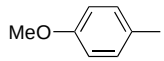
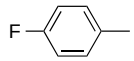
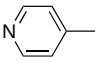
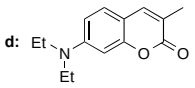
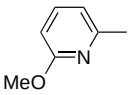
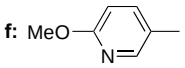
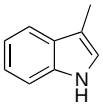
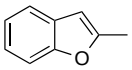
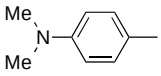
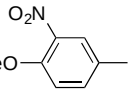
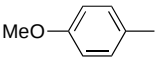
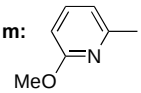
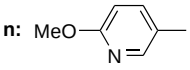


Scheme 1. Synthesis of Hx acids (**5a-k**) and *aza*-Hx acids (**6l-o**). Method A: nitrobenzene, 150-155 °C, 16 h; Method B: DMSO, 120-125 °C, 12 h.

RESULTS AND DISCUSSION

Hx acids (**5a-k**) and *aza*-Hx acids (**6l-o**) were prepared by hydrolysis of their corresponding esters **7a-k** and **8l-o**, respectively (Scheme1). Even though there are various methods for synthesizing benzimidazoles [19], the approach taken by our group is oxidative condensation of a substituted 1,2-diaminobenzene and a substituted benzaldehyde. In Method A, an appropriate aryl- or heteroarylaldehyde **9** (R groups are defined in Table 1) reacts with methyl 3,4-diaminobenzoate **10a** in nitrobenzene at 150-155 °C for 16 h to produce benzimidazole esters **7a-d** in modest to high yields (44-88%). However, using Method A, Hx esters **7e-7i**, were obtained in poor yields and methyl 5,6-diaminopyridine-2-carboxylate **10b** reacted with the aldehydes to generate diimino products. To overcome these challenges, we discovered that reaction of methyl 3,4-diaminobenzoate **10a** or methyl 5,6-diaminopyridine-2-carboxylate **10b** with an appropriate aryl- or heteroarylaldehyde **9** in DMSO at 120-125 °C proceeded smoothly in 12 h to give the desired products. Esters **7e-k** and **8l-o** were produced in low to good yields (18-84%). All the esters except compound **7d** were hydrolyzed using 5% aqueous sodium hydroxide at reflux to afford the corresponding carboxylic acids **5** and **6** in good to high yields (64-93%). The coumarin compound **7d** was hydrolyzed using 6.0 M hydrochloric acid - because the lactone framework was susceptible to hydrolysis under basic conditions to obtain Hx acid **5d** at a 79% yield. All the compounds were characterized by ^{1}H-NMR, IR spectroscopy, and mass spectrometry but only those for the novel compounds and acid **6l** are reported.

Table 1. Percent yields of Hx (**7**) and *aza*-Hx esters (**8**), as well as Hx (**5**) and *aza*-Hx acids (**6**) prepared in this study

R =	**7** (%)	**5** (%)	**R** =	**7** (%)	**5** (%)	**R** =	**7** (%)	**5** (%)
a: 	88	93	**b:** 	47	87	**c:** 	69	89
d: 	44	79	**e:** 	50	75	**f:** 	55	88
g: 	46	91	**h:** 	31	81	**i:** 	51	88
j: 	84	66	**k:** 	33	70			
R =	**8** (%)	**6** (%)	**R** =	**8** (%)	**6** (%)	**R** =	**8** (%)	**6** (%)
l: 	61	81	**m:** 	49	83	**n:** 	70	85
o: 	18	64						

EXPERIMENTAL

The solvents and reagents were purchased from Aldrich or Fisher and were used without further purification. The Melting points (Mp) were determined using a Mel-temp instrument and uncorrected. Infrared spectra were recorded on either a Midac FT-IR or Bruker Alpha-P spectrophotometer. ^{1}H-NMR spectra were obtained using a Bruker AVANCE III 400 MHz instrument with TMS as the internal standard. High-resolution mass spectra (HRMS) and low-resolution mass spectra (LRMS) were measured in the Mass Spectrometry Laboratory at the University of South Carolina, Columbia, USA.

*Method A:Synthesis of methyl 2-(substituted)-3H-benzimidazole-5-carboxylates (**7a-d**)*

Methyl 3,4-diaminobenzoate **10a** (3.0 mmol) and the appropriate aryl- or heteroarylaldehyde **9** (3.0 mmol) were dissolved in nitrobenzene (4.0 ml). The reaction mixture was heated at 150-155°C for 16 h. The reaction mixture was cooled to room temperature, the solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography. Compounds **7b** and **7d** precipitated upon cooling the reaction mixture. The products were filtered, washed with toluene followed by hexane and dried under vacuum at 45°C. The esters were directly hydrolyzed to obtain the corresponding carboxylic acids.**7a**: Pale brown solid (0.80 g); Mp 210-212°C.**7b**: White solid (0.37 g); Mp 196-200°C.**7c**: White solid (0.50 g); Mp 204-207°C.

Methyl 2-(7-(diethylamino)-2H-coumarin-3-yl)-3H-benzimidazole-5-carboxylate (**7d**): Yellow solid (0.35g, 44%); Mp >210°C; R_f 0.58 [ethyl acetate:hexane(5:5)]; IR (KBr): 3400, 2980, 2856, 1709, 1612, 1580, 1523, 1426, 1348, 1293, 1229, 1129, 777, 744, 689cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 11.41 (s br, 1H,), 8.95 (d, *J*=4.0 Hz, 1H), 8.35 (m, 1H), 8.00 (dd, *J*=4.0 Hz, 8.0 Hz, 1H), 7.50 (m, 2H), 6.70 (dd, *J*=4.0 Hz, 8.0 Hz, 1H), 6.57 (s, 1H), 3.95 (s, 3H), 3.48 (q, *J*=8.0 Hz, 4H), 1.26 (t, *J*=8.0 Hz, 6H); LRMS: (EI) *m/z* 391 (M^+, 100%).

*Method B: Synthesis of methyl 2-(substituted)-3H-benzimidazole-5-carboxylates (**7e-k**) and methyl 2-(substituted)-3H-imidazo[4,5-b]pyridine-5-carboxylates (**8l-o**)*

Methyl 3,4-diaminobenzoate **10a** or methyl 5,6-diaminopyridine-2-carboxylate **10b** (3.0 mmol) and the appropriate aryl- or heteroarylaldehyde **9** (3.0 mmol) were dissolved in DMSO (4.0 ml). The reaction mixture was heated at 120-125°C for 12 h. The removal of the solvent under reduced pressure was followed by purification of the residue by silica gel column chromatography yielding esters **7e-k** and **8l-o**, which were directly hydrolyzed to obtain the corresponding carboxylic acids. **7f**: White solid (0.69 g); Mp 198-202°C. **7h**: White solid (0.45 g);

Mp 129-131°C.**7i**: Yellow solid (0.45 g); Mp>210°C. **7j**: White solid (0.60 g); Mp 198-202°C.

Methyl 2-(6-methoxypyridin-2-yl)-3H-benzimidazole-5-carboxylate(**7e**): White solid (0.43 g); Mp200-204°C; R_f 0.44 [ethyl acetate:hexane (4.5:5.5)]; IR (KBr): 3385, 3041, 2956, 2860, 1694, 1599, 1573, 1535, 1471, 1430, 1408, 1319, 1290, 1227, 1152, 1028, 883, 774, 665cm^{-1}; ^{1}H-NMR: ($CDCl_3$) δ 8.30 (s, 1H), 7.93 (d, *J*=8.0Hz, 1H), 7.90 (dd, *J*=4.0Hz, 8.0Hz, 1H), 7.62 (m, 1H), 7.57 (d, *J*=8.0Hz, 1H), 6.74 (d, *J*=8.0Hz, 1H), 3.89 (s, 3H), 3.85 (s, 3H); LRMS: (EI) *m/z* 283 (M^+, 100%).

Methyl 2-(indol-3-yl)-3H-benzimidazole-5-carboxylate (**7g**): Off-white solid (0.56 g, 46%); Mp 238-242°C; R_f 0.62 [methanol:chloroform (2:8)];IR (KBr): 3264, 3224, 3198, 3119, 2953, 2948, 1684, 1621, 1590, 1573, 1500, 1458, 1388, 1312, 1182, 1087, 1036, 880, 772, 692 cm^{-1};^{1}H-NMR (DMSO-d6): δ 12.86 (s, 1H), 11.75 (s, 1H), 8.49 (d, *J*=8.0Hz, 1H), 8.20 (s, 1H), 8.13 (s, 1H), 7.81 (d, *J*=8.0Hz, 1H), 7.62 (d, *J*=8.0Hz, 1H), 7.52 (d, *J*=4.0Hz, 1H), 7.23 (d, *J*=1.5Hz, 2H), 3.88 (s, 3H); LRMS: (EI) *m/z* 291 (M^+, 100%).

Methyl 2-(3-nitro-4-methoxyphenyl)-3H-benzimidazole-6-carboxylate (**7k**): White solid (0.30 g); Mp 185-189°C; R_f 0.27[ethyl acetate:hexane (1:1)]; IR (KBr): 1713, 1621, 1530, 1449, 1433, 1350, 1334, 1274, 1265, 1233, 1186, 1162, 1119, 1085, 1069, 1012, 973, 827 cm^{-1};^{1}H-NMR(DMSO-d_6): δ13.40 (s, 1H), 8.70 (d, *J*=2.0Hz, 1H), 8.47 (dd, *J*=4.0Hz, 8.0Hz, 1H), 8.18 (d, *J*=12.0Hz, 1H), 7.86 (d, *J*=8.0Hz, 1H), 7.70 (s, 1H), 7.61 (d, *J*=12.0Hz, 1H), 4.03 (s, 3H), 3.88 (s, 3H); LRMS: (EI) *m/z* 327 (M^+, 100%); HRMS: calc. for *m/z* $C_{16}H_{13}N_3O_5$327.0855, found 327.0860.

Methyl 2-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-5-carboxylate (**8l**): White solid (0.52 g); Mp 238-241°C; R_f 0.45 [ethyl acetate:hexane (4:6)]; IR (KBr): 3047, 3006, 2949, 1728, 1717, 1607, 1494, 1461, 1443, 1413, 1397, 1279, 1028, 947, 838, 788, 740, 641 cm^{-1}; ^{1}H-NMR (DMSO-d6): δ 13.87 (s, 1H), 8.20 (d, *J*=8.0Hz, 2H), 8.08 (d, *J*=8.0Hz, 1H), 7.97 (d, *J*=8.0Hz, 1H), 7.16 (d, *J*=8.0Hz, 2H), 3.90 (s, 3H), 3.86 (s, 3H); LRMS: (EI) *m/z* 283 (M^+, 100%).

Methyl 2-(6-methoxypyridin-2-yl)-3H-imidazo[4,5-b]pyridine-5-carboxylate (**8m)**:White solid (0.42 g); Mp 204-206°C; R_f 0.49 [methanol:chloroform (0.5:9.5)]; IR (KBr): 3040, 2920, 2856, 1719, 1571, 1473, 1394, 1272, 1220, 1122, 1027, 821, 763 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 10.81 (s, 1H), 8.15 (d, 1H), 8.00 (dd, *J*=4.0Hz, 8.0Hz, 1H), 7.75 (d, *J*=8.0Hz, 1H), 7.73 (d, *J*=8.0Hz, 1H), 6.88 (dd, *J*=4.0Hz, 8.0Hz, 1H), 4.01 (s, 3H), 3.99 (s, 3H); LRMS: (EI) *m/z* 284 (M^+, 40%).

Methyl 2-(6-methoxypyridin-3-yl)-3H-imidazo[4,5-b]pyridine-5-carboxylate (**8n**): White solid (0.64 g); Mp>260 °C; R_f 0.41 [ethyl acetate:hexane (4:6)]; IR (KBr): 3050, 2948, 2870, 1720, 1601, 1475, 1401, 1360, 1274, 1228, 1132, 1019, 832, 761, 666 cm^{-1};^{1}H-NMR(DMSO-d6): δ 13.93 (s, 1H); 9.09 (d, *J*=4.0Hz, 1H), 8.53 (dd, *J*=4.0Hz, 12.0Hz, 1H), 8.19 (d, *J*=8.0Hz, 1H), 8.05 (d, *J*=8.0Hz, 1H), 7.11 (d, *J*=12.0Hz, 1H), 4.02 (s, 3H), 3.97 (s, 3H); LRMS: (EI) *m/z* 284 (M^+, 100%).

Methyl 2-(furan-2-yl)-3H-imidazo[4,5-b]pyridine-5-carboxylate (**8o**):Light brown solid (0.10 g); Mp 204-207°C (dec); R_f0.5 [methanol:chloroform (2.5:7.5)];IR (KBr): 3040, 2981, 2926, 2883, 1763, 1716, 1603, 1574, 1519, 1504, 1489, 1475, 1412, 1391, 1276, 1107, 1017, 960, 884, 757, 745 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 10.12 (s br, 1H), 8.18 (d, *J*=12.0Hz, 1H), 8.12 (d, *J*=8.0Hz, 1H), 7.66 (d, *J*=2.0Hz, 1H), 7.36 (d, *J*=4.0Hz, 1H), 6.67 (dd, *J*=4.0Hz, 1H), 4.02 (s, 3H); LRMS: (EI) *m/z* 243 (M^+, 100%).

*Synthesis of 2-(substituted)-3H-benzo[d]imidazole-5-carboxylic acids (**5a-c, e-k**) and 2-(substituted)-3H-imidazo[4,5-b]pyridine-5-carboxylic acids(**6l-o**).*

The appropriate Hx ester (**7a-c**, 7**e-k**, and **8l-o**) (2.0 mmol) was added to an aqueous solution of sodium hydroxide (5%, 10 ml) and the reaction mixture was heated to reflux for 1.0 h. The reaction mixture was cooled to ambient temperature and acidified to pH of 3-4 with concentrated hydrochloric acid. The precipitate was filtered, washed with water and dried under vacuum at 50°C.**5a**: Tan solid (1.10 g); Mp 253°C [13,14]. **5b**: White solid (0.41 g); Mp 204-208°C [14,15]. **5c:** White solid (0.42 g); Mp >250°C [14,16]. **5f**: White solid (0.42 g); Mp >210°C [14]. **5h**: Off-white solid (0.44 g); Mp 245°C [14,17]. **5i**: White solid (0.42 g); Mp 201-205°C [14]. **5j**: Off-white solid (0.38 g); Mp 220-222°C [14,18].

2-(6-Methoxypyridin-2-yl)-3H-benzimidazole-5-carboxylic acid (**5e**): White solid (0.36 g); Mp 157-159°C; R_f 0.28 [ethyl acetate:hexane (4:6)]; IR (KBr): 3082, 2984, 2949, 1691, 1599, 1536, 1474, 1409, 1328, 1296, 1272, 1243, 1152, 1120, 1073, 1028, 769, 678, 617 cm^{-1}; ^{1}H-NMR (DMSO-d6): δ 13.00 (s br, 1H), 8.27 (s, 1H), 7.93 (m, 3H), 7.72 (s, 1H), 6.98 (d, *J*=4.0Hz, 1H), 4.10 (s, 3H); LRMS: (EI) *m/z* 269 (M^+, 100%); HRMS: calc. for *m/z* $C_{14}H_{11}N_3O_3$ 269.0800, found 269.0792.

2-(Indolyl-3-yl)-3H-benzimidazole-5-carboxylic acid (**5g**): Light orange solid (0.55 g); Mp 250-252°C(dec); R_f 0.25 [methanol:chloroform (2:8)];IR (KBr): 3275, 3184, 3113, 3065, 1630,

1587, 1557, 1499, 1446, 1373, 1312, 1226, 1178, 1086, 745, 678 cm^{-1};^{1}H-NMR (DMSO-d6): δ 12.72 (s, 1H), 11.73 (s, 1H), 8.51 (d, *J*=4.0Hz, 1H), 8.21 (s, 1H), 8.10 (s, 1H), 7.78 (d, *J*=8.0Hz, 1H), 7.49 (d, *J*=4.0Hz, 2H), 7.20 (m, 3H); LRMS: (EI) *m/z* 277 (M^+, 100%); HRMS: calc. for *m/z* $C_{16}H_{11}N_3O_2$ 277.0851, found 277.0854.

2-(3-Nitro-4-methoxyphenyl)-3H-benzimidazole-6-carboxylic acid (**5k**): Light yellow solid (0.20 g); Mp >250°C; R_f 0.20 [methanol:chloroform (0.5:9.5)]; IR (KBr): 1706, 1695, 1685, 1629, 1530, 1509, 1484, 1426, 1387, 1349, 1335, 1294, 1214, 1126, 1091, 1060, 984, 890 cm^{-1}; ^{1}H-NMR (DMSO-d6): δ 8.80 (s, 1H), 8.61 (d, *J*=12.0Hz, 1H), 8.20 (s, 1H), 7.87 (d, *J*=8.0 Hz, 1H), 7.68 (d, *J*=12.0Hz, 1H), 7.62 (d, *J*=8.0Hz, 1H), 4.03 (s, 3H); LRMS: (ES^+, TOF) *m/z* 314 ($M+H^+$, 100%); HRMS: calc. for *m/z* $C_{16}H_{13}N_3O_5$ 314.0777, found 314.0781.

2-(4-Methoxyphenyl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid(**6l**): White solid (0.38 g); Mp >250°C; R_f 0.4 [methanol:chloroform (0.5:9.5)]; IR (KBr): 3065, 2961, 2836, 1706, 1607, 1575, 1492, 1441, 1397, 1363, 1250, 1176, 1024, 829, 763, 692, 675 cm^{-1}; ^{1}H-NMR (DMSO-d6): δ 8.22 (d, *J*=8.0Hz, 2H), 8.05 (d, *J*=8.0Hz, 1H), 7.97 (d, *J*=8.0Hz, 1H), 7.15 (d, *J*=8.0Hz, 2H), 3.86 (s, 3H);LRMS: (ES^+, TOF) *m/z* 270 ($M+H^+$ 100%); HRMS: calc. for *m/z* $C_{14}H_{11}N_3O_3$ 270.0878, found 270.0870.

2-(6-Methoxypyridin-2-yl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid (**6m**): White solid (0.30 g); Mp >250°C (dec); R_f0.23 [methanol:chloroform (1:9)]; IR (KBr): 3200, 3050, 2982, 2943, 1763, 1714, 1603, 1573, 1557, 1504, 1475, 1463, 1412, 1366, 1351, 1321, 1305, 1269, 1204, 1097, 1074, 895, 762, 735, 669 cm^{-1}; ^{1}H-NMR (DMSO-d6): δ 8.17 (d, *J*=8.0Hz, 1H), 8.04 (d, *J*=12.0Hz, 1H), 7.99 (d, *J*=8.0Hz, 1H), 7.94 (t, *J*=8.0Hz, 1H), 7.02 (d, *J*=8.0Hz, 1H), 4.09 (s, 3H);LRMS: (EI) *m/z* 270 (M^+, 67%); HRMS: calc. for *m/z* $C_{13}H_{10}N_4O_3$ 270.0753, found 270.0757.

2-(6-Methoxypyridin-3-yl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid (**6n**): White solid (0.40g); Mp 251-253°C; R_f 0.38 [methanol:chloroform (0.5:9.5)]; IR (KBr): 3050, 2946, 1602, 1466, 1373, 1283, 1019, 767, 664 cm^{-1}; ^{1}H-NMR (DMSO-d6, two drops D_2O): δ 8.95 (s, 1H), 8.42 (d, *J*=8.0Hz, 1H), 7.97 (d, *J*=8.0Hz, 1H), 7.91 (d, *J*=8.0Hz, 1H), 7.02 (d, *J*=8.0Hz, 1H), 3.92 (s, 3H); LRMS: (EI)*m/z* 270 (M^+ 100%); HRMS calc. for *m/z* $C_{13}H_{10}N_4O_3$ 270.0753, found 270.0754.

2-(Furan-2-yl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid (**6o**): Light brown solid (0.24 g); Mp 245-247°C (dec); R_f 0.12 [methanol:chloroform (2.5:7.5)]; IR (KBr): 3250, 3110, 3069, 1702, 1620, 1523, 1471, 1399, 1294, 1254, 1230, 1172, 1081, 1022, 890, 797, 699, 679, 634 cm^{-1}; ^{1}H-NMR (CD_3OD): δ 8.05 (d, *J*=8.0Hz, 1H), 7.97 (d, *J*=8.0Hz, 1H), 7.77 (d, *J*=2.0Hz, 1H), 7.30 (d, *J*=4.0Hz, 1H), 6.65 (dd, *J*=4.0Hz, 1H); LRMS: (EI) *m/z* 229 (M^+ 100%); HRMS: calc. for *m/z* $C_{12}H_7N_3O_3$ 229.0487, found 229.0483.

2-(7-(Diethylamino)-2H-coumarin-3-yl)-benzoimidazole-5-carboxylic acid (**5d**):Hx ester**7d** (782 mg, 2.0 mmol) was added to a solution of hydrochloric acid (6.0 M, 15 ml) and the reaction mixture was heated to reflux for 24 h. The reaction mixture was cooled to 10-15°C and neutralized using 10% aqueous sodium hydroxide solution. The precipitate obtained was filtered, washed with water and dried. The crude product was purified by silica gel column chromatography using 10% methanol in chloroform as the eluent system to afford the desired Hx acid **5d** as a yellow solid (597 mg); Mp >210°C; R_f 0.52 [methanol:chloroform (2:8)]; IR (KBr): 3294, 2970, 2860, 1701, 1619, 1586, 1526, 1432, 1353, 1295, 1233, 1182, 1134, 1073, 848, 799, 744 cm^{-1};^{1}H-NMR (DMSO-d6): δ 12.70 (s, 1H), 8.98 (s, 2H), 8.25 (s, 1H), 7.84 (d, *J*=12.0Hz, 1H), 7.75 (d, *J*=8.0Hz, 1H), 7.68 (d, *J*=8.0Hz, 1H), 6.85 (dd, *J*=4.0Hz, 8.0Hz, 1H), 6.70 (s, 1H), 3.52 (q, *J*=8.0Hz, 4H), 1.18 (t, *J*=8.0Hz, 6H); LRMS: (ES^+, TOF) *m/z* 378 ($M+H^+$, 100%); HRMS: calc. for *m/z* $C_{21}H_{19}N_3O_4$ 378.1454, found 378.1447.

Acknowledgements: *The authors thank the NSF (CHE 0809162) for supporting this project.*

REFERENCES

1.(a) S. N. Mitra, M. C. Wahl, M. Sundaralingam, *Acta Crystallogr. Sect. D*, **55**, 602 (1999); (b) J. G. Pelton, D. E. Wemmer, *Proc. Natl. Acad. Sci*., **86**, 5723 (1989); (c) J. G. Pelton, D. E Wemmer, *J. Am. Chem. Soc*., **112**, 1393 (1990).

2.(a) C. J. Chou, M. E. Farkas, S. M. Tsai, D. Alvarez, P. B. Dervan, J. M. Gottesfeld, *Mol. Cancer Ther*., **7**, 769 (2008); (b) B. H. Geierstanger, M. Mrksich, P. B. Dervan, D. E. Wemmer, *Nat. Struct. Biol*., **3**, 321 (1996); (c) D. M. Chenoweth, P. B. Dervan, *Proc. Natl. Acad. Sci*., **106**, 13175 (2009).

3.(a) D. Hochhauser, M. Kotecha, C. O'Hare, P. J. Morris, J. M. Hartley, Z. Taherbhai, D. Harris, C. Forni, R. Mantovani, M. Lee, J. A. Hartley, *Mol. Cancer Ther*., **6**, 346 (2007); (b) T. J. Dwyer, B. H. Geierstanger, Y. Bathini, J. W. Lown, D. E. Wemmer, *J. Am. Chem. Soc*., **114**, 5911 (1992).

4.(a) K. Shinohara, T. Bando, H. Sugiyama, *Anticancer Drugs*,**21**, 228 (2010); (b) M. Minoshima, T. Bando, K. Shinohara, H. Sugiyama, *Nucl. Acids Symp. Ser*., **53**, 69 (2009); (c) S. Borman, *Chem. Eng. News*, **88**, 50 (2010).

5.(a) P. B. Dervan, B. S. Edelson, *Curr. Opin. Struc. Biol.*, **13**, 284 (2003); (b) M. A. Marques, R. M. Doss, A. R. Urbach, P. B. Dervan, *Helv. Chim. Acta*, 85, 4485 (2002); (c) P. B. Dervan, *Bioorg. Med. Chem.*, **9**, 2215 (2001).
6.(a) X.-L. Yang, R. B. Hubbard IV, M. Lee, Z.-H. Tao, H. Sugiyama, A. H.-J. Wang, *Nucl. Acids Res*., **27**, 4183 (1999); (b) E. R. Lacy, K. K. Cox, W. D. Wilson, M. Lee, *Nucl. Acids Res.*, **30**, 1834 (2002); (c) E. R. Lacy, B. Nguyen, M. Le, K. K. Cox, C. O'hare, J. A. Hartley, M. Lee, W. D. Wilson, *Nucl. Acids Res.*, **32**, 2000 (2004); (d) V. C. Rucker, S. Foister, C. Melander, P. B. Dervan, *J. Am. Chem. Soc.*,**125**, 1195 (2003); (e) X.-L. Yang, C. Kaenzig, M. Lee, A. H.-J. Wang, *Eur. J. Biochem*., **263**, 646 (1999).
7.(a) K. L. Buchmueller, A. M. Staples, C. M. Howard, S. M. Horick, P. B. Uthe, N. M. Le, K. K. Cox, B. Nguyen, K. A. O. Pacheco, W. D. Wilson, M. Lee, *J. Am. Chem. Soc.*, **127**, 742 (2005); (b) K. L. Buchmueller, S. L. Bailey, D. A. Matthews, Z. T. Taherbhai, J. K. Register, Z. S. Davis, C. D. Bruce, C. O'Hare, J. A. Hartley, M. Lee, *Biochemisry*, **45**, 13551 (2006); (c) B. Babu, Y. Liu, A. Plaunt, C. Riddering, R. Ogilvie, L. Westrate, R. Davis, A. Ferguson, H. Mackay, T. Rice, S. Chavda, D. Wilson, S. Lin, K. Kiakos, J. A. Hartley, M. Lee, *Biochem. Biophys. Res. Commun*., **404**, 848 (2011); (d) V. Satam, B. Babu, A. Porte, M. Savagian, Y. Liu, M. Lee, J. Ramos, W. D. Wilson, S. Lin, K. Kiakos, J. A. Hartley, M. Lee, *Bioorg. Med. Chem. Lett*., **22**, 5898 (2012).
8.(a) S. Chavda, Y. Liu, B. Babu, R. Davis, A. Sielaff, J. Ruprich, L. Westrate, C. Tronrud, A. Ferguson, A. Franks, S. Tzou, C. Adkins, T. Rice, H. Mackay, J. Kluza, S. A. Tahir, S. Lin, K. Kiakos, C. D. Bruce, W. D. Wilson, J. A. Hartley, M. Lee, *Biochemistry*,**50**, 3127 (2011); (b) V. Satam, P. Patil, B. Babu, M. Gregory, M. Bowerman, M. Savagian, M. Lee, S. Tzou, K. Olson, Y. Liu, J. Ramos, W. D. Wilson, J. P. Bingham, K. Kiakos, J. A. Hartley, M. Lee, *Bioorg. Med. Chem. Lett.*, **23**, 1699 (2013).
9.(a) K. Kiakos, J. Ruprich, R. Davis, A. Sielaff, L. Westrate, C. Tronrud, A. Ferguson, T. Brown, H. Mackay, M. Lee, Y. Liu, D. Wilson, D. Hochhauser, J. A. Hartley, *Proc. Am. Assoc. Cancer Res*., abstract 3521 (2010); (b) K. Kiakos, L. Pett, V. Satam, P. Patil, D. Hochhauser, M. Lee, J. A. Hartley, *Chem. & Biol*., **22**, 862 (2015).
10.V. Satam, B. Babu, P. Patil, K. A. Brien, K. Olson, M. Savagian, M. Lee, A. Mepham, L. B. Jobe, J. P. Bingham, L. Pett, S. Wang, M. Ferrara, C. D. Bruce, W. D. Wilson, M. Lee, J. A. Hartley, K. Kiakos, *Bioorg. Med. Chem. Lett*., **25**, 3681 (2015).
11.M. Thomas, U. Varshney, S. Bhattacharya, *Eur. J. Org. Chem*., 3604 (2002).
12.H. Mackay, T. Brown, M. Lee, in: Synthetic and Biophysical Studies of DNA binding Compounds, M. Lee, L. Strekowski (eds), Transworld Research Network, India, 2007, p. 67.
13.C. Cong, H. Wang, Y. Hu, C. Liu, S. Ma, X. Li, J. Cao, S. Ma, *Eur. J. Med. Chem.*, **46**, 3105 (2011).
14.These compounds are commercially available according to a SciFinder search on December 26, 2015.
15.L. Yurttas, Y. Ozkay, H. Karaca, Y. Tunali, Z. A. Kaplancıkli, *Lett. Drug Design & Discovery*, **10**, 486 (2013).
16.R. Wubulikasimu, Y. Yang, F. Xue, X. Luo, D. Shao, Y. Li, R. Gao, W. Ye, *Bull. Korean Chem. Soc.*, **34**, 2297 (2013).
17.H. Göker, E. Tebrizli, U. Abbasoglu, *Famaco*, **51**, 53 (1996).
18.S. Manoharan, S. Anandan, *Dyes & Pigments*, **105**, 223 (2014).
19.Y. Kim, M. R. Kumar,N. Park, Y. Heo, S. Lee, *J. Org. Chem*., **76**, 9577 (2011), and references given therein.

СИНТЕЗА НА 2-(ЗАМЕСТЕН)-3*H*-БЕНЗИМИДАЗОЛ-5-КАРБОКСИЛНА КИСЕЛИНА И 2-(ЗАМЕСТЕН)-3*H*-ИМИДАЗО[4,5-b]ПИРИДИН-5-КАРБОКСИЛНИ КИСЕЛИНИ: СИНТОНИ ЗА ФЛУОРЕСЦЕНТНИ Нх И *aza*-Нх АМИДИ

В.С. Сатам[1], П.К. Патил[1], Б. Бабу[1], К.А. Брайън[1], М. Грегори[1], М. Бауъмен[1], Дж. Суирз[1], А. Мефам[1], М. Лии[1,2]*

[1]*Департамент по химия, Хоуп Колидж, Холанд, Мичиган, САЩ*
[2]*Департамент по химия, Щатски университет в Джорджия, Атланта, Джорджия, САЩ*

Постъпила на 3 януари, 2016 г.; коригирана на 4 март, 2016 г.

(Резюме)

Съобщава се за синтезите на 15 флуоресцентни 2-(заместен)бензимидазол-5-(Нх) и 2-(заместен) имидазопиридин-5-(*aza*-Нх) карбоксилни киселини. Ключови са половините на Нх- и *aza*-Нх амидите, които свързват ДНК в специфични секвенции. Кондензацията на метил 3, 4-диаминобензоат **10a** или метил 5,6-диаминопиридин-2-карбоксилат **10b** с подходящи арил- или хетероарил-алдехиди **9** дава желаните Нх (**7a-k**) и *aza*-Нх естери (**8l-o**) с добиви съответно 31-88% и 18-70%. Хидролизата на естерите **7a-k** и **8l-o** дава съответните Нх (**5a-k**) и *aza*-Нх киселиини (**6l-o**) с добиви съответно от 66-93% и 64-85%. Нх - киселините **5d**, **5e**, **5g** и **5k,** както и *aza*-Нх киселините **6m-o** са нови съединения.