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Synthesis and Structural Assignment of Some N-Substituted Imidazopyridine Derivatives

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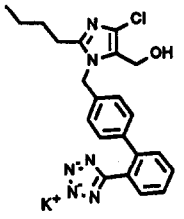
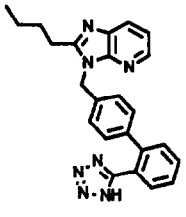
Abstract: A synthesis of all possible N-alkylated 2-n-butyl-imidazo[4,5]pyridine isomers is described as well as their structural assignment by ^{1}H NMR spectroscopy. One of these derivatives, 2-n-butyl-3-[2'-(1H-tetrazol-5-yl)-4-biphenylylmethyl]-3H-imidazo[4,5-b]pyridine **9** is a potent angiotensin II receptor antagonist.

Introduction

Drugs that inhibit the renin-angiotensin system (RAS) are effective in the treatment of hypertension in humans.[1] One of the possible modes of controlling the RAS is angiotensin II (AII) receptor antagonism.[2] Recently, a series of novel imidazoles has been described as potent, competitive, nonpeptide AII antagonists.[3] The search for an oral active compound led to the development of DuP 753 (see Figure 1),[4] which is currently undergoing clinical evaluation as a potential agent for the treatment of hypertension. In the course of our work on AII receptor antagonists a series of N-substituted imidazopyridines was synthesized, which led to the discovery of a further potent representative of this class, EMD 60 218 (see Figure 1).



DuP 753



EMD 60 218

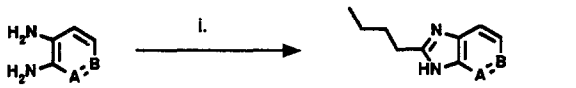
Fig. 1:

In the present study a short and flexible synthesis of all possible N-alkylated imidazopyridine isomers together with their structural characterization by NMR spectrocopy is described.

Results and Discussion

In the present investigation the attention is focussed on the contribution of the heterocyclic portion to the binding affinity of DuP 753 to the AII receptor. The imidazole part was substituted by an imidazopyridine ring in order to explore the role of the additional nitrogen atom. Since neither the ideal position of the nitrogen in the pyridine ring nor the best point of attachment of the biphenyl substituent was known with regard to the biological activity, it was decided to synthesize all possible isomers. The strategy was to synthesize the [4,5-b]- and [4,5-c]imidazopyridine nuclei according to Scheme 1 and then to introduce the biphenyl side chain in a second step. The synthesis led to a mixture of all three regioisomers which first had to be separated and characterized by NMR spectroscopy, before their AII antagonistic activity could be tested.

The key intermediates **4a** and **4b** were easily synthesized in good to excellent yields from 2,3-diaminopyridine **3a** or 3,4-diaminopyridine **3b** by a modified Phillips method.[5] The butyl chain was introduced directly by refluxing the aminopyridines with valeric acid in polyphosphoric acid (Scheme 1).



3a: A=N,B=CH
3b: A=CH,B=N

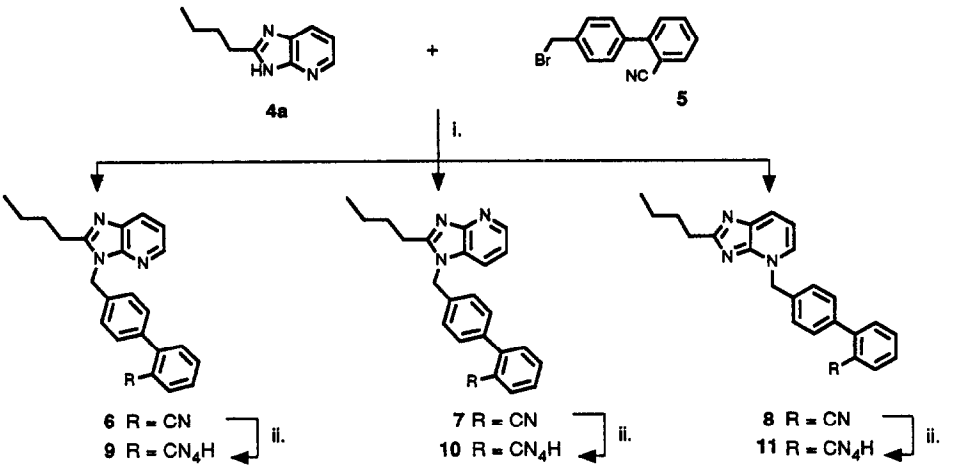
4a: A=N,B=CH
4b: A=CH,B=N

i. PPA, n-$C_4H_9CO_2H$, 160°C

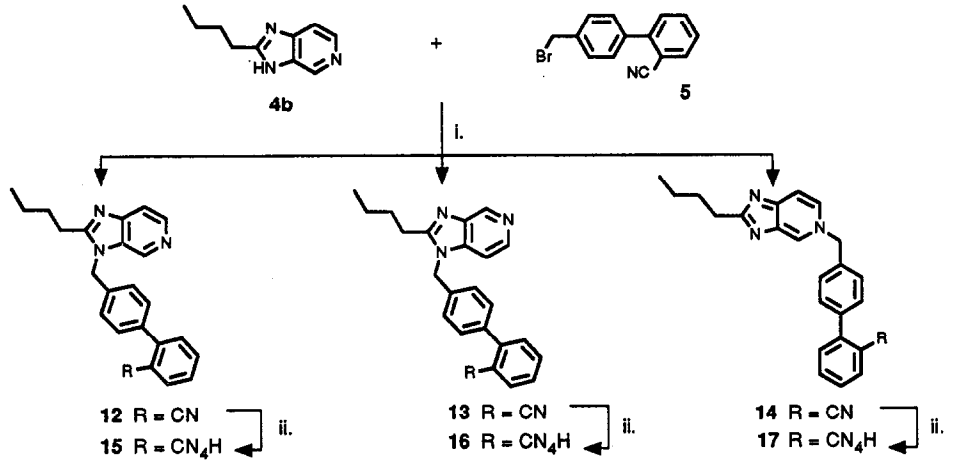
Scheme 1:

The resulting imidazo[4,5-b]pyridine **4a** was converted to **6**, **7** and **8** by alkylation of the monoanion of **4a** with 4'-(bromomethyl)-2-cyanobiphenyl **5**.[3,6] The reaction yielded a mixture of the three isomers which could easily be separated by column chromatography on silica gel. In the [4,5-b]imidazopyridine series the main product was the N-3 substituted isomer **6**, the precursor of EMD 60 218 (**9**). The 1(*H*)-tetrazoles **9**, **10** and **11** could be prepared in satisfactory yield by the thermal addition of Me_3SnN_3[7] to the nitriles **6**, **7** and **8**, respectively, in refluxing toluene followed by decomposition of the trimethyltin intermediates with anhydrous HCl (Scheme 2).

Following the same procedure as described in Scheme 2, deprotonation of imidazo[4,5-c]pyridine **4b** with sodium methoxide in DMF and trapping the anion with the bromomethyl compound **5** also resulted in the formation of all three isomers **12**, **13** and **14**, but in contrast to the outcome of the reaction of **4a** the N-5 alkylated product **14** was predominant. Condensation of the resulting nitriles with Me_3SnN_3[7] and subsequent acid hydolysis of the trimethyltin tetrazole adducts finally gave the compounds **15**, **16** and **17** (Scheme 3).



Scheme 2: i. NaOMe, DMF, RT ii. Me_3SnN_3, toluene, reflux; then HCl



Scheme 3: i. NaOMe, DMF, RT ii. Me_3SnN_3, toluene, reflux; then HCl

The NMR data, chemical shifts and coupling constants, are given in Table 1. The numbering of the proton resonances is as indicated in Figure 2.

Table 1: 1H Chemical shifts in ppm relative to internal TMS and coupling constants in Hz for compounds **6** - **17**.

Compound	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**
H1	8.315	8.363	8.265	8.294	8.334	8.425	8.871	8.897	8.997	8.843	8.865	8.905
H2	7.270	7.201	7.153	7.248	7.176	7.326	8.303	8.304	8.199	8.288	8.278	8.154
H3	8.019	7.962	8.065	7.990	7.908	8.217	7.598	7.620	7.621	7.581	7.579	7.575
H4	7.923	7.923	7.926	7.617	7.570	7.608	7.926	7.927	7.939	7.606	7.595	7.545
H5	7.566	7.571	7.570	7.509	7.414	7.478	7.570	7.570	7.577	7.472	7.462	7.361
H6	7.765	7.765	7.765	7.594	7.459	7.538	7.767	7.767	7.771	7.537	7.513	7.375
H7	7.576	7.575	7.579	7.450	7.339	7.405	7.584	7.580	7.600	7.406	7.379	7.292
H8	7.540	7.552	7.590	7.076	7.068	7.086	7.564	7.560	7.617	7.080	7.073	7.241
H9	7.314	7.255	7.566	7.046	6.980	7.361	7.294	7.255	7.570	7.046	6.997	7.122
H10	5.616	5.637	5.910	5.504	5.502	5.856	5.696	5.638	5.744	5.580	5.512	5.613
H11	2.879	2.912	2.862	2.813	2.868	2.910	2.930	2.899	2.861	2.881	2.850	2.834
H12	1.702	1.734	1.795	1.678	1.722	1.793	1.742	1.732	1.782	1.721	1.713	1.757
H13	1.351	1.376	1.385	1.344	1.375	1.379	1.374	1.367	1.363	1.366	1.362	1.343
H14	0.850	0.873	0.918	0.856	0.881	0.918	0.874	0.865	0.906	0.876	0.869	0.901
J(1,2)	4.8	4.8	6.3	4.8	4.7	6.3	<1	<1	1.5	n.m.	<1	1.6
J(1,3)	1.4	1.6	<1	1.3	1.4	0.0	0.0	0.0	0.0	n.m.	0.0	0.0
J(2,3)	7.9	8.0	7.5	8.0	8.0	7.7	5.5	5.5	6.8	5.2	5.5	6.7
J(4,5)	7.3	7.6	7.6	7.5	7.5	7.4	7.8	7.8	7.8	7.4	7.5	7.5
J(4,6)	1.1	1.2	1.1	1.3	1.4	0.8	1.1	1.3	1.1	1.0	1.4	1.6
J(5,6)	7.7	7.7	7.7	7.5	7.4	7.5	7.7	7.7	7.7	7.5	7.5	7.5
J(5,7)	n.m.	n.m.	n.m.	0.9	1.2	1.2	n.m.	n.m.	n.m.	0.9	1.2	1.7
J(6,7)	7.7	7.7	7.7	7.8	7.5	7.5	7.7	7.7	7.7	7.8	7.7	7.4
J(8,9)	8.2	8.2	8.4	8.3	8.2	8.2	8.2	8.3	8.5	8.3	8.2	8.2
J(11,12)	7.6	7.5	7.6	7.6	7.6	7.6	7.5	7.5	7.5	7.6	7.5	7.5
J(12,13)	7.5	7.6	7.5	7.5	7.6	7.5	7.5	7.5	7.5	7.5	7.5	7.5
J(13,14)	7.4	7.4	7.4	7.4	7.4	7.4	7.4	7.4	7.4	7.4	7.4	7.4

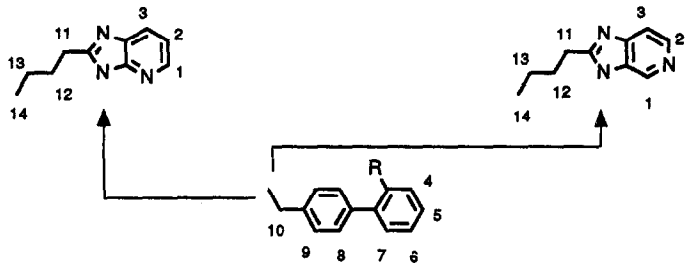


Fig. 2: Numbering system for NMR data. The numbering is independent of the position of the biphenyl substituent on the heterocyclic ring (compounds **7 - 11** and **13 - 17**).

The assignment of the aliphatic protons of the butyl side chain was straightforward from a comparison of chemical shifts, intensities, and multiplicities of the signals. The resonances of the pyridine protons were also unambiguously assigned from the characteristic chemical shifts and coupling constants. The protons of the 1,4-disubstituted ring of the biphenyl substituent gave rise to an AA'BB' spin system which is easily recognized. The remaining four one-proton signals in the aromatic region, two doublets and two triplets with large ortho-couplings of 7-8 Hz and further fine structure caused by longe-range couplings, belong to the protons of the 1,2-disubstituted phenyl ring. These assignments could be confirmed by further 2D experiments. The expanded aromatic region of the COSY spectrum of compound **6** in Fig. 3 shows the correlation between the heterocyclic protons H1 to H3, between H8 and H9, and the assignment of the sequence H7-H6-H5-H4 of the 1,2-disubstituted phenyl ring. The relative assignment of H8 and H9 and the assignment of the doublet at δ=7.923 to either H4 or H7 is based on the observation of NOE's. The ROESY spectrum of compound **16** in Fig. 4 may serve as an example how these assignments were clarified through NOE cross peaks between H10/H9 and H8/H7. The proton next to the substituent (nitrile or tetrazole) always occurred at lowest field in agreement with calculations based on substituent effects.

The appearance of the ^{1}H NMR spectra, the intensities of the signals, their chemical shifts and coupling constants, were very similar and it was therefore not possible to determine to which N-atom of the heterocyclic ring the biphenyl substituent was attached. The problem could, however, be solved in an elegant and unambiguous fashion by observing NOE effects between protons of the biphenyl substituent, the heterocyclic ring system, and the butyl side chain.

For molecules of this type it proved advantageous to record ROESY spectra. Figure 4 also provides an example of the general approach: The position of the substituent on the heterocyclic ring is established by noting the NOE cross peaks connecting the methylene group of the substituent (H10) with H11 of the side chain and with the heterocyclic proton H3. Other NOE correlations (given in brackets) support previous assignments. Small cross peaks from H10 to H8 as well as H12 are probably caused by spin diffusion.

The distinction of the three possible isomers of one set of derivatives can therefore be made by simply looking at the NOE's originating at the methylene group of the biphenyl substituent which occurs at δ≅ 5.6

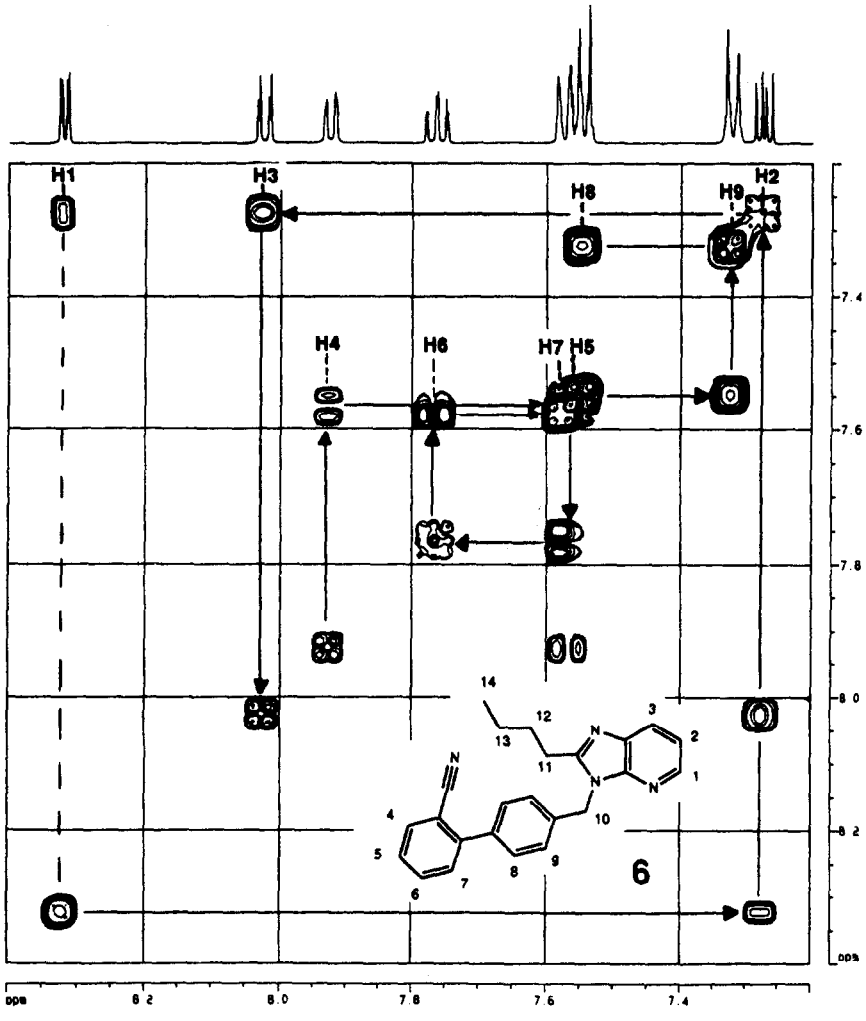


Fig. 3: Aromatic region of the COSY spectrum of compound **6**

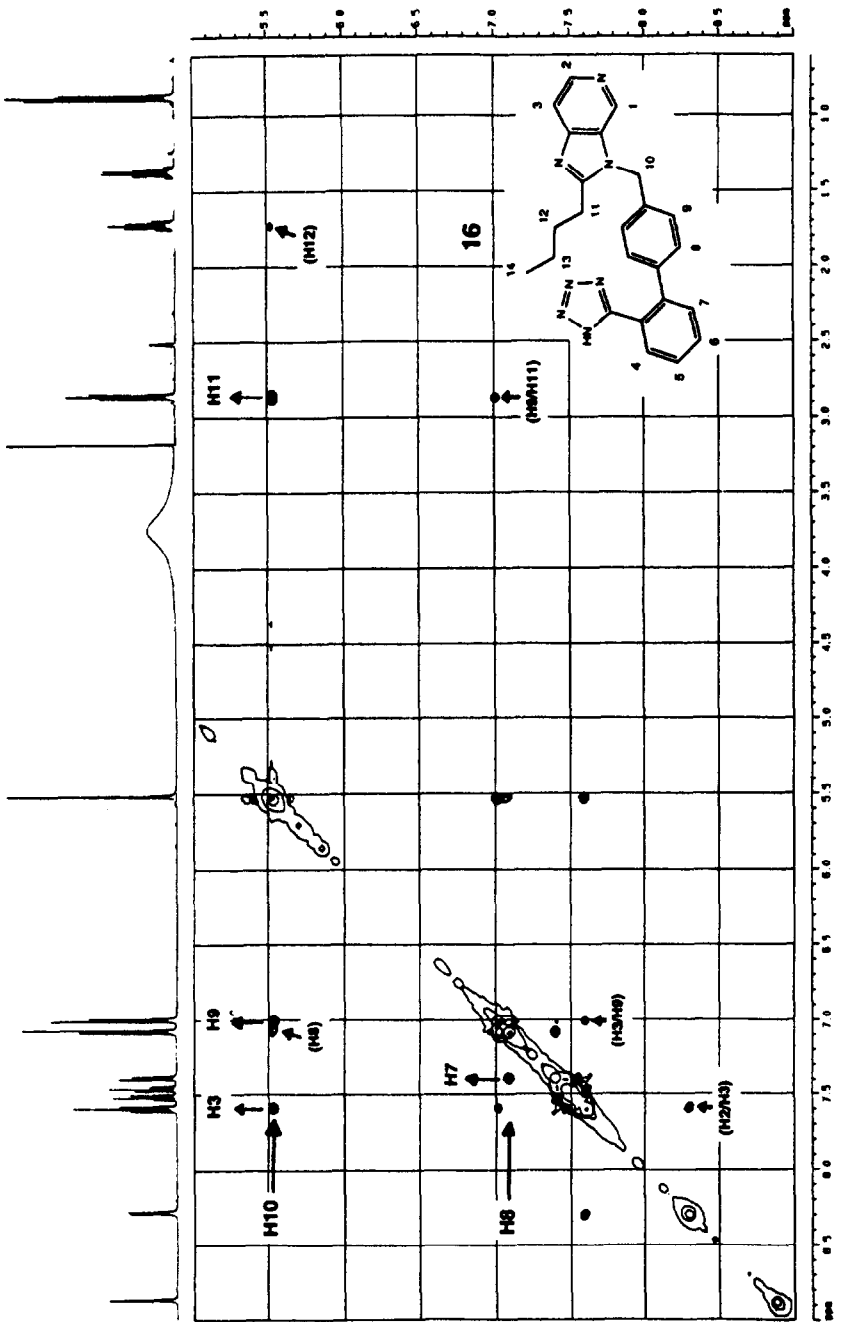


Fig. 4: Part of the 2D ROESY spectrum of compound **16**

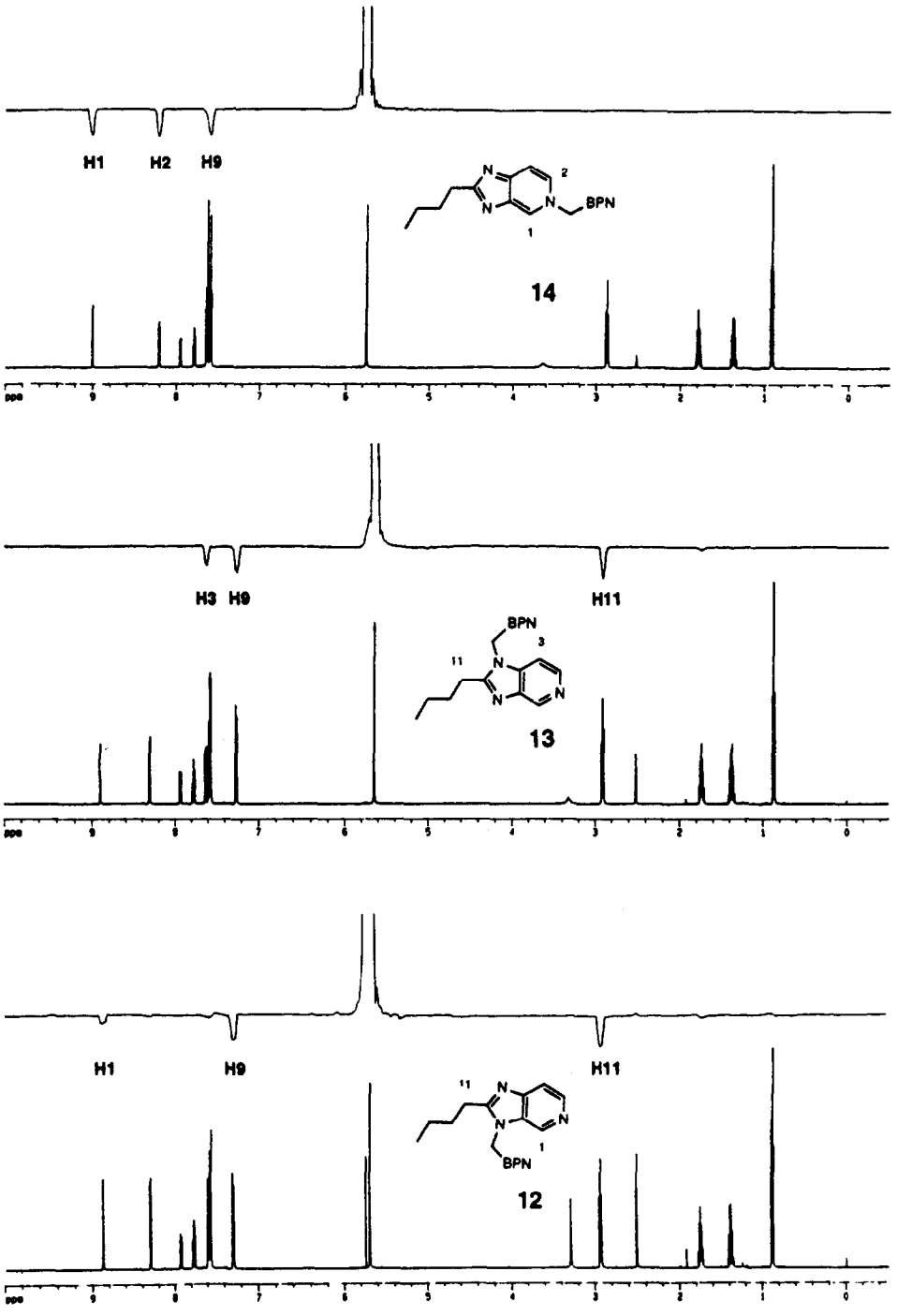


Fig. 5: Cross section of the 2D ROESY spectra of compounds **12**, **13**, and **14** through the H10 protons; BPN = biphenyl-2-carbonitrile

- 5.9. This is demonstrated in Figure 5, which shows the cross section through the methylene signal of the biphenyl substituent in the 2D ROESY spectra for the three isomers **12**, **13** and **14** and the relevant assignments.

The binding affinities to the AII receptor and their antagonistic activities of all six 1(*H*)-tetrazole isomers together with more potent derivatives will be discussed elsewhere.

Acknowledgements: We thank M. Gruber and G. Michel of our laboratory for preliminary experiments and H. Hölzel and Mrs. B. Jäger for recording the NMR spectra.

Experimental

General. NMR spectra were performed on a Bruker AM 500 spectrometer from ca. 0.05m solutions in DMSO-d_6 (99.95%^{2}D, E.Merck, Darmstadt) with internal TMS as reference. Abbrevations: s = singlet, d = doublet, t = triplet, qi = quintet and s = sextet.
1D spectra were recorded with a spectral width (SW) of 10000Hz and a digital resolution of 0.61Hz with the following parameters: number of data points (TD) = 32K, acquisition time (AQ) = 1.64s, number of scans (NS) = 32, pulse length (PW) = 6μs (flip angle 50°) and a relaxation delay (RD) = 1s. The data were processed with standard Bruker software employing a resolution enhancement of 0.3Hz.
2D COSY spectra were performed with a standard pulse programme[8,9] (relevant parameters: SW = 6400Hz, AQ = 0.16s, TD = 1024pts., RD = 1.2s, NS = 32, number of FID's (NE) = 512). Data were multiplied with a pure sinebell window function in both directions and zero-filled to give a 2K × 2K matrix after Fourier-transformation with a digital resolution of 3Hz/pt.
2D ROESY spectra were also obtained with a standard pulse programme[10] with a spectral width of ca. 5000Hz and the following parameters: TD = 512, AQ = 0.5s, NS = 48, RD = 1.5s, NE = 128 and mixing time (P2) = 200ms. The data were Fourier-transformed after zero-filling and multiplication with a $\sin^2$ window function in both domains to yield a 512 × 512 matrix with a digital resolution of ca. 10Hz.
IR spectra were obtained using a Perkin Elmer 397, Bruker IFS 48, Bruker IFS 66, Bruker IFS 88 spectrometer.
The melting points are uncorrected and were obtained in open capillaries on a Mettler FP 61 melting point apparatus.
Solvents and reagents were commercially available and used after distillation. All reactions were performed under nitrogen atmosphere. Solvents were removed by means of a rotary evaporator.
Chromatography was performed using 0.063-0.002 mm silica gel (E.Merck, Darmstadt, Si60). Analytical thin-layer chromatography was performed on Si60, F254 silica gel plates using phosphomolybdic acid for visualization.
2-n-Butyl-imidazo[4,5-b]pyridine (4a). 21.8 g (200 mmol) 2,3-Diaminopyridine (**3a**), 21.6 g (200 mmol) valeric acid and 600 g polyphosphoric acid were combined and refluxed for 3 hours. The reaction was poured into ice water and then the pH was adjusted to 8 with NaOH and the aqueous layer extracted with ethyl acetate. The organic layers ere dried (Na_2SO_4) and the solvent was removed in vacuo to yield 30.1 g (98%) of a colourless solid. **4a**: mp 103°C; IR (KBr) 2964, 1410 cm^{-1}; ^{1}H NMR δ 0.920 (3H, t), 1.367 (2H, sx), 1.781 (2H, qi), 2.852 (2H, t), 7.874 (1H, d), 8.154 (1H, dd), 8.250 (1H, d); anal. calcd. for $C_{10}H_{13}N_3$ (175.24): C, 68.54; H, 7.48; N, 23.98; found C, 68.50; H, 7.46; N, 24.30.
2-n-Butyl-imidazo[4,5-c]pyridine (4b). Following the procedure of **4a** 1.09 g (10 mmol) 3,4-diaminopyridine (**3b**) was treated with 1.02 g (10 mmol) valeric acid and 40 g polyphosphoric acid for 3 h at 160°C. Purification of the desired imidazopyridine by chromatography on silica gel with methylene chloride--methanol (90:10) afforded 1.70 g (97%) as a colourless viscous oil. **4b**: oil; IR (capillary) 1623 cm^{-1}; ^{1}H NMR δ 0.916 (3H, t), 1.359 (2H, sx), 1.771 (2H, qi), 2.865 (2H, t), 7.494 (1H, d), 8.247 (1H, d), 8.814 (3H, t).
4'-(2-n-Butyl-3*H*-imidazo[4,5-b]pyridin-3-ylmethyl)-biphenyl-2-carbonitrile (6), 4'-(2-n-Butyl-1*H*--imidazo[4,5-b]pyridin-1-ylmethyl)-biphenyl-2-carbonitrile (7) and 4'-(2-n-Butyl-4*H*-imidazo[4,5-b]-pyridin-4-ylmethyl)-biphenyl-2-carbonitrile (8). 5.0 g (28.5 mmol) 2-n-butyl-imidazo[4,5-b]pyridine (**4a**) was added to a stirred solution of sodium methoxide in 100 ml methanol (0.65 g Na, 28.5 mmol) at 25°C. The solvent was removed in vacuo, and the residue dissolved in 100 ml DMF. A solution of 7.75 g (28.5 mmol) 4'-(bromomethyl)-2-cyanobiphenyl (**5**) in 40 ml DMF was added dropwise at 0°C and the so-

lution stirred overnight at 25°C. The solvent was removed in vacuo, and the residue partitioned between ethyl acetate and water. The aqueous layer was extracted twice with ethyl acetate. The organic layers were combined and dried over anhydrous Na_2SO_4, and the solvent was evaporated in vacuo. Medium pressure chromatography in methylene chloride-methanol (98:2) over silica gel yielded a faster eluting isomer **6** (5.9 g, 56%), a medium eluting isomer **7** (2.8 g, 27%) and a slower eluting isomer **8** (1.14 g, 11%).
6: mp 96°C; IR (KBr) 2960, 2220, 1605, 1425 cm^{-1}; anal. calcd. for $C_{24}H_{22}N_4$ (366.47): C, 78.66; H, 6.05; N, 15.29; found: C, 78.80; H, 6.16; N, 15.20.
7 mp 107°C; IR (KBr) 2927, 2225, 1615, 1404 cm^{-1}; anal. calcd. for $C_{24}H_{22}N_4$ (366.47): C, 78.66; H, 6.05; N, 15.29; found: C, 78.50; H, 6.31; N, 15.40.
8 viscous oil; IR (capillary) 2956, 2220, 1628, 1457 cm^{-1}.
4'-(2-n-Butyl-3*H*-imidazo[4,5-c]pyridin-3-ylmethyl)-biphenyl-2-carbonitrile (12), 4'-(2-n-Butyl-1*H*-imidazo[4,5-c]pyridin-1-ylmethyl)-biphenyl-2-carbonitrile (13) and 4'-(2-n-Butyl-5*H*-imidazo-[4,5-c]pyridin-5-ylmethyl)-biphenyl-2-carbonitrile (14). Using 5.2 g (30 mmol) 2-n-butyl-imidazo-[4,5-c]pyridine (**4b**), 0.7 g (30 mmol) Na and 8.1 g (30 mmol) 4'-(bromomethyl)-2-cyanobiphenyl in DMF and employing the same procedure as described above, a faster eluting isomer **12** (0.5 g, 4.5%), a medium eluting isomer **13** (0.7 g, 6%) and a slower eluting isomer **14** (8.5 g, 77%) were prepared.
12: oil; IR(capillary) 2210, 1605 cm^{-1}; anal. calcd. for $C_{24}H_{22}N_4x1H_20$ (384.49): C, 74.97; H, 6.29; N, 14.57; found: C,75.30; H, 6.24; N, 14.50.
13 mp 115°C; IR(KBr) 2210, 1609 cm^{-1}; anal. calcd. for $C_{24}H_{22}N_4$ (366.47): C, 78.66; H, 6.05; N, 15.29; found: C, 78.60; H, 6.29; N, 15.30.
14 mp 130°C; IR(KBr) 2220, 1624 cm^{-1}; anal. calcd. for $C_{24}H_{22}N_4$ (366.47): C, 78.66; H, 6.05; N, 15.29; found: C, 78.40; H, 6.33; N, 15.02.
2-n-Butyl-3-[2'-(1*H*-tetrazol-5-yl)-4-biphenylylmethyl]-3*H*-imidazo[4,5-b]pyridine (9). A solution of 9.0 g (24.6 mmol) **6** and 6.1 g (29.4 mmol) trimethyltin azide in 200 ml toluene was refluxed for 118 h. The mixture was allowed to cool to room temperature and evaporated. The residue was dissolved in etheral hydrogen chloride (200 ml) and stirred for 1.5 hours. Evaporation gave a crystalline mass that was purified by medium pressure chromatography on silica gel, eluting with methylene chloride-methanol (90:10) to give **9** (7.00g, 69,5%) as a colourless solid: mp 182°C; IR (KBr): 3409(H_20), 1600, 1507, 1469, 1408 cm^{-1}; anal. calcd. for $C_{24}H_{23}N_7x2H_20$ (455.53): C, 64.70; H, 6.11; N, 22.01; found: C, 64.54; H, 6.05; N, 21.90.
The following title compounds **10**, **11**, **15**, **16** and **17** were prepared from **7**, **8**, **12**, **13** and **14**, respectively, by the procedure described for the preparation of **9**:
2-n-Butyl-1-[2'-(1*H*-tetrazol-5-yl)-4-biphenylylmethyl]-1*H*-imidazo[4,5-b] pyridine (10). mp 125°C.
2-n-Butyl-4-[2'-(1*H*-tetrazol-5-yl)-4-biphenylylmethyl]-4*H*-imidazo[4,5-b]pyridine (11). mp 198°C; anal. calcd. for $C_{24}H_{23}N_7$ (409.50): C, 70.40; H, 5.66; N, 23.94; found: C, 70.30; H, 5.70; N, 23.90.
2-n-Butyl-3-[2'-(1*H*-tetrazol-5-yl)-4-biphenylylmethyl]-3*H*-imidazo[4,5-c]pyridine (15). mp 153°C.
2-n-Butyl-1-[2'-(1*H*-tetrazol-5-yl)-4-biphenylylmethyl]-1*H*-imidazo[4,5-c]pyridine (16). mp 147°C.
2-n-Butyl-5-[2'-(1*H*-tetrazol-5-yl)-4-biphenylylmethyl]-5*H*-imidazo[4,5-c]pyridine (17). mp 138°C.

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