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SYNTHESIS OF NEW IMIDAZO[1,2-*b*]PYRIDAZINE ISOSTERES OF POTENT IMIDAZO[4,5-*b*]PYRIDINE ANGIOTENSIN II ANTAGONISTS[1]

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Abstract: The synthesis of a new class of angiotensin II receptor antagonists bearing a substituted imidazo[1,2-*b*]pyridazine moiety, and the evaluation of these compounds as isosteric replacements for potent imidazo[4,5-*b*]pyridine based antagonists is presented.

The linear octapeptide angiotensin II is a potent vasoconstrictor produced by the renin-angiotensin cascade which regulates blood pressure homeostasis, fluid volume and electrolyte balance in mammals. Angiotensin II (AII) interacts with specific cellular receptors causing vasoconstriction, aldosterone secretion, renal sodium retention and other biological effects.[2] Pharmacological blockade of the renin-angiotensin system with inhibitors of angiotensin converting enzyme (ACE) such as captopril and enalapril effectively lowers AII levels and is established therapy for the treatment of essential hypertension and congestive heart failure.[3] Recently, nonpeptidic and orally active AII receptor antagonists have emerged as alternative and potentially superior agents for lowering blood pressure in hypertensive patients.[4]

Our interest in a series of substituted 3-(2'-(tetrazol-5-yl)-biphenyl-4-yl)methyl-3H-imidazo[4,5-*b*] pyridines developed in these laboratories and exemplified by L-158,809 (**1**),[5] led to the concern that metabolic hydroxylation at the benzylic methylene group followed by cleavage of the heterocyclic moiety might inactivate these compounds. This paper describes the synthesis and biological activity of a new class of isosteric (biphenyl-4-methyl)imidazo[1,2-*b*]pyridazine AII antagonists (**2a-2d**) wherein the biphenylmethyl side chain is attached to the heterocyclic ring through a carbon-carbon bond.[6]

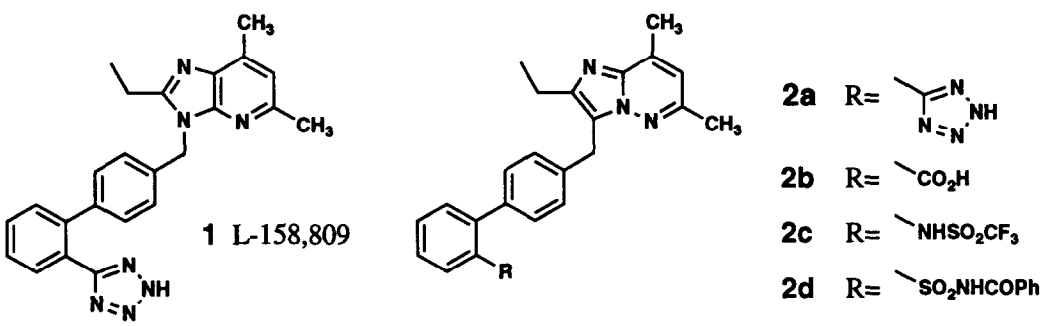
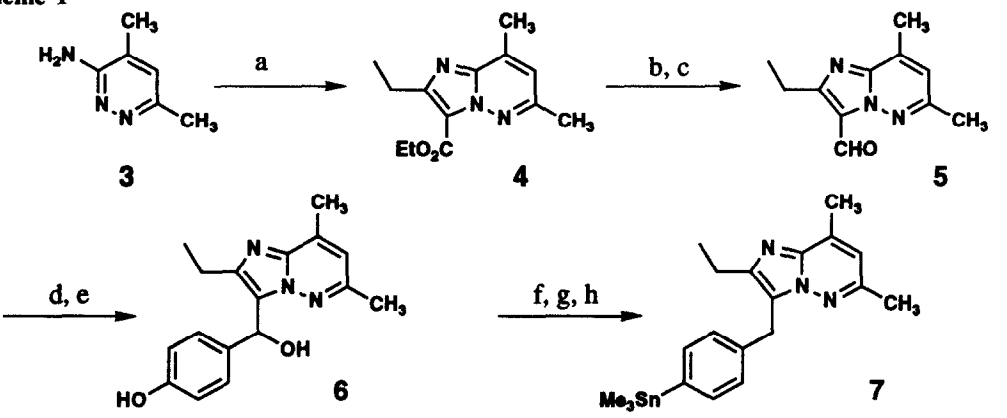


Figure 1.

A synthetic strategy was designed to facilitate evaluation of analogs with differing acidic pharmacophoric groups at the C-2' position of the biphenyl. Thus, the synthesis proceeded by first assembling the imidazo[1,2-*b*] pyridazine ring, installation of a 4-trimethylstannylbenzyl group at C-3, followed by construction of the biphenyl element *via* a palladium catalyzed biaryl coupling reaction. Preparation of the

Scheme I[a]

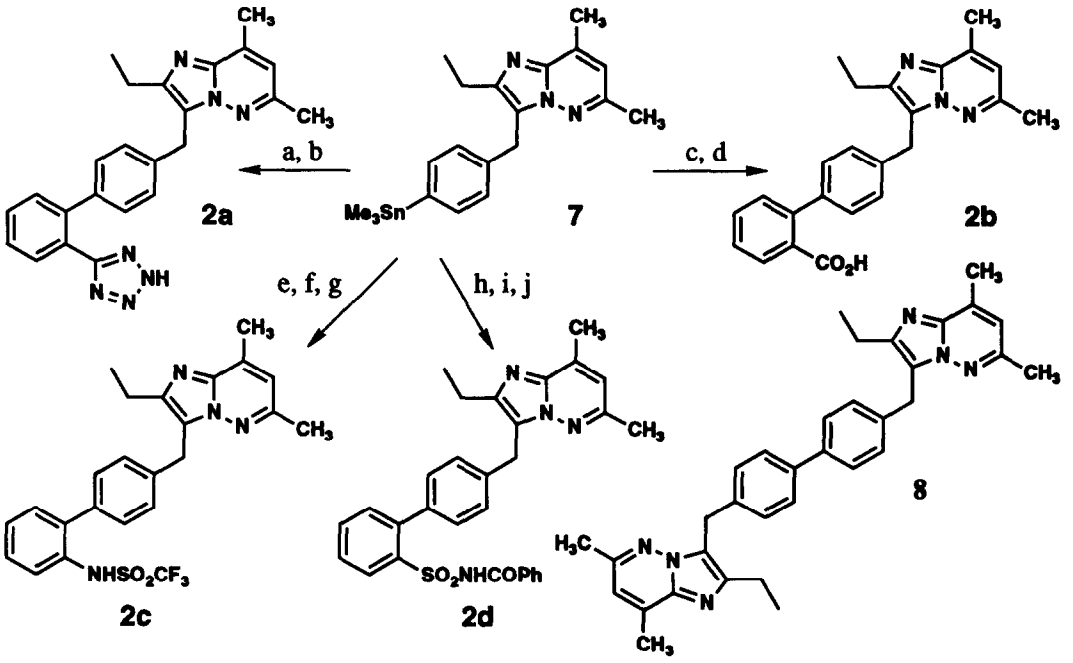


[a]Reagents: (a) ethyl α-chloropropionylacetate, $(i\text{-Pr})_2NEt$, CH_2Cl_2, 80°C, 12 h; (b) $LiAlH_4$, THF, 0°C, 1 h; (c) MnO_2, 4Å molecular sieves, CH_2Cl_2, 16 h; (d) Mg, 4-(t-BuMe$_2$SiO)C_6H_4Br, THF, 67°C, 1.5 h; product of step c, rt, 30 min; (e) $(n\text{-Bu})_4NF$, THF, rt, 3 h; (f) Me_2SiCl_2, NaI, CH_3CN, rt 10 min; (g) $(F_3CSO_2)_2O$, pyridine, rt, 1 h; (h) $Me_3SnSnMe_3$, $Pd(Ph_3)_4$, LiCl, dioxane, 60°C, 24 h.

requisite organostannane is illustrated in Scheme I. Reaction of 3-amino-4,6-dimethylpyridazine[7] with ethyl α-chloropropionylacetate in the presence of diisopropylethylamine afforded a 73% yield of ester **4**. Lithium aluminum hydride reduction of **4** and reoxidation of the alcohol provided the aldehyde **5** (75% overall). Condensation of aldehyde **5** with the Grignard reagent prepared from the *tert*-butyldimethylsilylether of 4-bromophenol followed by silylether hydrolysis gave phenol **6** (82% from **5**). Next, the benzylic hydroxyl group of **6** was conveniently deoxygenated with *in situ* generated diiododimethylsilane[8] (90%), and the resulting phenol was converted to an aryl triflate. Palladium(0) catalyzed cross coupling of this triflate with hexamethylditin[9] afforded after 24 hours a 47% yield of the desired arylstannane. Longer reaction times failed to improve this yield, however unreacted triflate (44%) was readily recovered upon flash column chromatography[10] (84% yield based upon recovered triflate).

The cross coupling of organostannane **7** with aryl halides bearing appropriate substituents for further elaboration into the targeted acidic functional groups were next investigated. Palladium(II) catalyzed coupling reactions[11] effected the biphenyl bond coupling, and the resulting intermediates were then converted to the title compounds **2a-2d** as shown in Scheme II. Thus, stannane **7** coupled with 2-bromobenzonitrile in the presence of 5 mol% bis(triphenylphosphine)palladium(II) chloride (83%) and the resulting nitrile was converted to the tetrazole **2a**[12] with trimethyltinazide in 75% yield. Under similar conditions, **7** was coupled with *tert*-butyl 2-iodobenzoate (73%) and subsequent *tert*-butyl ester hydrolysis (86%) afforded acid **2b**.[13] Coupling of **7** with 1-bromo-2-nitrobenzene (78%), followed by nitro group reduction (95%) and trifluorosulfonylation (66%) gave

Scheme II[a]



[a]Reagents: (a) 2-bromobenzonitrile, $(PPh_3)_2PdCl_2$, DMF, 100°C, 12 h; (b) Me_3SnN_3, toluene, 120°C, 20 h; (c) *tert*-butyl 2-iodobenzoate, $(PPh_3)_2PdCl_2$, DMF, 100°C, 12 h; (d) CF_3CO_2H, anisole, CH_2Cl_2, rt, 14 h; (e) 1-bromo-2-nitrobenzene, $(PPh_3)_2PdCl_2$, DMF, 80°C, 12 h; (f) H_2 (50 psig), 10% Pd/C, EtOH, 30 min; (g) $(CF_3SO_2)_2O$, 2,6-di-*tert*-butyl-4-methylpyridine, CH_2Cl_2, 0°C, 1 h; (h) N-*tert*-butyl-2-bromobenzenesulfonamide, $(PPh_3)_2PdCl_2$, DMF, 50°C, 12 h; (i) CF_3CO_2H, CH_2Cl_2, rt, 8 h; (j) $PhCO_2H$, CDI, THF, 80°C, 2 h; product of step i, DBU, THF, 80°C, 3 h.

the triflamide **2c**.[14] In the final example, the coupling of stannane **7** with N-*tert*-butyl-2-bromobenzenesulfonamide consistently provided only 28-32% of the desired biphenyl, attended by substantial quantities (38%) of the symmetrical 4,4'-biphenyl **8**, even when the coupling reaction was conducted in the presence of three equivalents of the arylbromide. Nonetheless, this coupling reaction proved sufficient to permit removal of the N-*tert*-butyl group with trifluoroacetic acid (95%), and subsequent acylation of the resultant primary sufonamide with N-benzoylimidazole (derived from 1,1'-carbonyldiimidazole and benzoic acid, 76%) to afford the desired N-benzoylsulfonamide **2d**.[15,16]

Table I. Data for compounds **2a-2d**.

Entry	L-Number	IC_{50}		FAB-Mass Spectrum (MH^+)	
		AT_1(nM)	AT_2(μM)	Calc'd *m/z*:	Found *m/z*:
2a	L-161,719	5.7	>10	410.2093	410.2076
2b	L-161,718	83	>10	386.1869	386.1871
2c	L-162,278	1.7	>10	489.1572	489.1597
2d	L-163,144	0.8	>10	525.1960	525.1963

The angiotensin II binding affinities (IC_{50}'s)[17] for AT_1 and AT_2 receptor subtypes, and mass spectral data for the title compounds are presented in Table I. The imidazo[1,2-*b*]pyridazines **2a-2d** displayed potent AT_1 selective AII antagonist activity. In conscious normotensive rats, a 1.0 mg/kg iv bolus administration of tetrazole **2a** provided a greater than 90% maximal inhibition of blood pressure response to 0.1μg/kg iv AII challenges, and the duration of the inhibitory effect (>30% inhibition) exceeded six hours. Thus, imidazo[1,2-*b*] pyridazines **2a-2d** are shown to be effective bioisosteres for the corresponding imidazo[4,5-*b*]pyridine-containing angiotensin II antagonists.

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References and Notes

1. Presented in part at the Thirteenth International Congress of Heterocyclic Chemistry, August 11-16, 1991, Oregon State University, Corvallis, Oregon.
2. Peach, M.J. *Physiol. Rev.* **1977**, *57*, 313.
3. Vallotton, M.B. *Trends Pharmacol. Sci.* **1987**, *8*, 69.
4. Chiu, A.T.; McCall, D.E.; Price, W.A.; Wong, P.C.; Carini, D.J.; Duncia, J.V.; Johnson, A.L.; Wexler, R.R.; Yoo, S.E.; Timmermans, P.B.M.W.M. *J. Pharmacol. Ther.* **1990**, *252*, 711.
5. Mantlo, N.B.; Chakravarty, P.K.; Ondeyka, D.L.; Siegl, P.K.S.; Chang, R.S.; Lotti, V.J.; Faust, K.A.; Chen, T.-B.; Schorn, T.W.; Sweet, C.S.; Emmert, S.E.; Patchett, A.A.; Greenlee, W.J. *J. Med. Chem.* **1991**, *34*, 2919.
6. Allen, E.E.; Chakravarty, P.K.; Greenlee, W.J.; MacCoss, M.; Patchett, A.A.; Walsh, T.F. European Patent Appl. 0,490,587, June 17, 1992.
7. Becker, H.G.O.; Bötcher, H. *Tetrahedron*, **1968**, *24*, 2687.
8. Wiggins, J.M. *Synth. Commun.* **1988**, *18*, 741.
9. Wulff, W.D.; Peterson, G.A.; Bauta, W.E.; Chan, K.-S.; Faron, K.L.; Gilbertson, S.R.; Kaesler, R.W.; Yang, D.C.; Murray, C.K. *J. Org. Chem.* **1986**, *51*, 277. Echavarren, A.M.; Stille, J.K. *J. Am. Chem. Soc.* **1987**, *109*, 5478.
10. Still, W.C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
11. Milstein, D.; Stille, J.K. *J. Am. Chem. Soc.* **1979**, *101*, 4992.
12. NMR Data for **2a**: ^{1}H-NMR (400 MHz, CD_3OD, ppm) δ 1.23 (t, *J*=7.6 Hz, 3H), 2.51 (s, 3H), 2.57 (s, 3H), 2.80 (q, *J*=7.6 Hz, 2H), 4.34 (s, 2H), 6.99 (s, 1H), 7.00 (d, *J*=8.0 Hz, 2H), 7.15 (d, *J*=8.0 Hz, 2H), 7.48-7.51 (m, 2H), 7.59-7.62 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$, ppm) δ 14.52, 16.34, 20.06, 21.60, 27.71, 118.87, 122.55, 123.89, 127.75, 128.13(2C), 129.04(2C), 130.57, 130.79, 130.91, 134.56, 137.23, 137.53, 137.73, 141.20, 143.44, 152.00, 155.95.
13. NMR Data for **2b**: ^{1}H-NMR (400 MHz, CD_3OD, ppm) δ 1.23 (t, *J*=7.6 Hz, 3H), 2.51 (s, 3H), 2.57 (s, 3H), 2.80 (q, *J*=7.6 Hz, 2H), 4.34 (s, 2H), 6.99 (s, 1H), 7.00 (d, *J*=8.0 Hz, 2H), 7.15 (d, *J*=8.0 Hz, 2H), 7.48-7.51 (m, 2H), 7.59-7.62 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$, ppm) δ 14.36, 16.43, 20.36, 21.56, 27.92, 118.23, 123.07, 126.92, 127.92(2C), 128.67(2C), 129.49, 130.24, 130.33, 130.45, 133.64, 134.92, 137.21, 139.94, 141.21, 143.75, 151.46, 172.27.
14. NMR Data for **2c**: ^{1}H-NMR (400 MHz, CD_3OD, ppm) δ 1.26 (t, *J*=7.6 Hz, 3H), 2.49 (s, 3H), 2.55 (s, 3H), 2.82 (q, *J*=7.6 Hz, 2H), 4.39 (s, 2H), 4.91 (s, 1H), 6.91 (s, 1H), 7.27-7.35 (m, 8H); ^{13}C-NMR (100 MHz, $CDCl_3$, ppm) δ 14.63, 16.43, 21.21, 21.58, 28.25, 117.63, 117.96, 122.47, 122.52, 126.58, 128.71, 129.03(2C), 129.16(2C), 130.83, 131.89, 135.09, 135.12, 135.39, 137.93, 139.09, 144.76, 151.07.
15. NMR Data for **2d**: ^{1}H-NMR (400 MHz, CD_3OD, ppm) δ 1.32 (t, *J*=7.6 Hz, 3H), 2.57 (s, 3H), 2.62 (s, 3H), 2.89 (q, *J*=7.6 Hz, 2H), 4.42 (s, 2H), 7.18-7.22 (m, 5H), 7.24-7.27 (m, 3H), 7.42-7.44 (m, 2H), 7.50-7.63 (m, 3H), 8.23 (dd, *J*=8.0, 1.2 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$, ppm) δ 14.39, 17.54, 21.63, 21.70, 27.59, 127.60, 127.74(2C), 127.96(2C), 128.03, 128.14, 128.23, 128.65, 128.72(2C), 129.28, 129.35, 129.44(2C), 130.62, 130.68, 131.04, 132.39, 133.42, 133.53, 133.60, 136.78, 140.50, 163.83.
16. Naylor, E.M.; Chakravarty, P.K.; Costello, C.A.; Chang, R.S.L.; Chen, T.-B.; Faust, K.A.; Lotti, V.J.; Kivlighn, S.D.; Zingaro, G.J.; Siegl, P.K.S.; Patchett, A.A.; Greenlee, W.J. *Book of Abstracts*, 205th National Meeting of the American Chemical Society, Division of Medicinal Chemistry, Denver, CO 1993; American Chemical Society· Washington, DC, 1993; Abstract 114.
17. Binding affinities expressed as IC_{50}'s for the compounds in Table I were determined by their ability to displace the specific binding ligand ^{125}I-Sar^1,Ile^8-AII from rabbit aortic membrane (AT_1) and rat brain membrane (AT_2) receptors as described in: Chang, R.S.L.; Siegl, P.K.S.; Clineschmidt, B.V.; Mantlo, N.B.; Chakravarty, P.K.; Greenlee, W.J.; Patchett. A.A.; Lotti, V.J. *J. Pharmacol. Exp. Ther.* **1992**, *262*, 133 with the exception that the 0.2% BSA component was omitted.

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