Synthesis and Structure–Activity Relationship of a New Series of Potent Angiotensin II Receptor Antagonists: Pyrazolo[1,5-*a*]pyrimidine Derivatives

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We have already reported 7-oxo-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid derivatives, which are potent *in vitro* angiotensin II (AII) antagonists, but have no oral antihypertensive activity. Removal of the carboxylic acid and replacement of the heteroaromatic system afforded potent *in vitro* antagonists. Removal of the carbonyl oxygen and changing the position of the biphenyltetrazole substituent were critical to the display of oral activity. To improve the *in vitro* and oral activities, modifications were made of the substituents at the 3- and 5-positions of the pyrazolo[1,5-*a*]pyrimidine. Structure–activity studies showed the methyl substituent at the 3-position to be essential for potent *in vivo* activity. We present the design, syntheses, and biological data of a series of pyrazolo[1,5-*a*]pyrimidine derivatives, which are orally active AII receptor antagonists.

Key words angiotensin II antagonist; antihypertensive; pyrazolo[1,5-*a*]pyrimidine

The remarkable success achieved by angiotensin-converting enzyme inhibitors in the treatment of hypertension and congestive heart failure has generated considerable interest in the development of novel and selective pharmacological agents designed to intervene in the renin–angiotensin system (RAS). In the past several years there have been extraordinary advances in the development of potent nonpeptide angiotensin II (AII) receptor antagonists. Compounds such as losartan (Dup753, Cozaar®),[1] D-8731,[2] L-158809,[3] and A-81988[4] are examples of angiotensin II type 1 (AT_1) receptor selective antagonists (Fig. 1).[5]

In our previous report,[6] we described the discovery of novel nonpeptide AII receptor antagonist 7-oxo-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (**1**) and its analogues. These derivatives showed potent *in vitro* activity, but no marked decrease in blood pressure was observed in spontaneously hypertensive rats (SHRs) after their oral administration. To obtain potent orally active AII antagonists, we performed the three-step transformations illustrated in Fig. 2. First, we removed the 3-carboxylic acid and changed the heterocyclic system. Second, we designed a new heterocyclic system, pyrazolo[1,5-*a*]pyrimidine, considering the structures of the other existing orally active AII antagonists (such as A-81988 or D-8731) and the key features necessary for receptor binding of **5a** (Fig. 3). This compound showed oral antihypertensive activity in the SHR model. Finally, fine-tuning of the substituents on the heterocycle and spacer of the heterocycle and biphenyltetrazole provided highly potent and orally active AII antagonists. Here we report the details of our design and the structure–activity relationship (SAR) studies that led to the discovery of novel AII antagonists.

Chemistry A series of azolopyrimidine heterocycles of **3a**—**c** were readily accessible from condensation of ethyl 2-formylpentanate (**2**) and the corresponding aminoazole deriv-

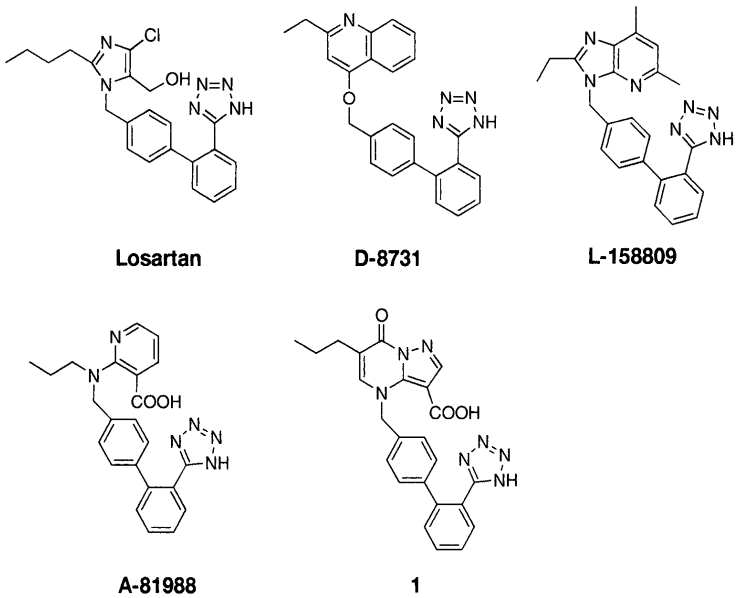

Fig. 1

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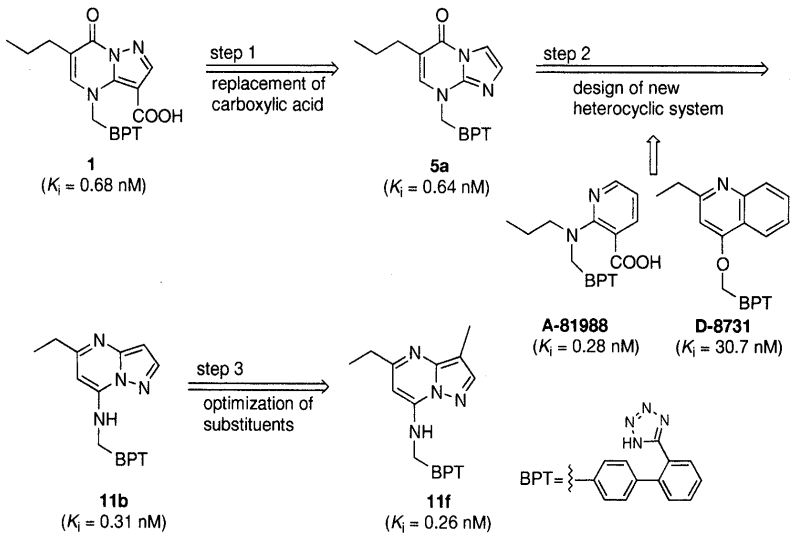


Fig. 2

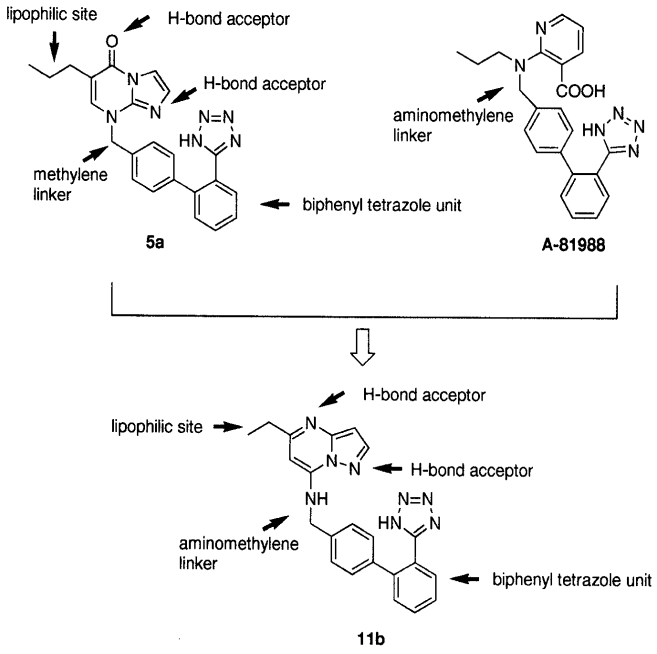


Fig. 3

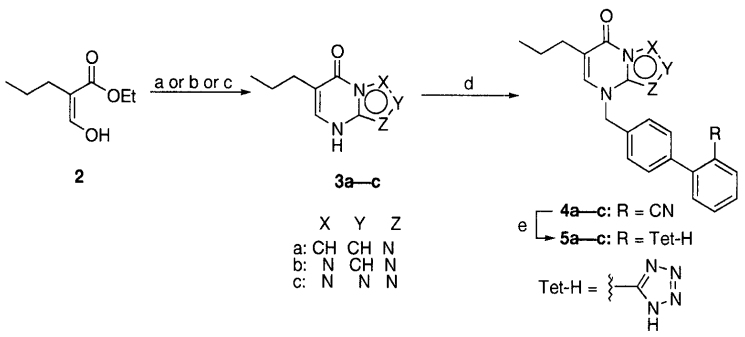
atives as shown in Chart 1. Alkylation of the resulting azolopyrimidine derivatives (**3a**—**c**) with 4-bromomethyl-2′-cyanobiphenyl[1] in *N*,*N*-dimethylformamide (DMF) using sodium hydride as base, followed by conversion of the cyano group to the tetrazole using trimethyltin azide gave **5a**—**c**. Chart 2 illustrates the general route to the pyrazolo[1,5-*a*]pyrimidine derivatives. 3-Aminopyrazole derivatives (**6a**—**h**) were cyclized with *β*-keto esters (**7a**—**d**) to afford the corresponding substituted pyrazolo[1,5-*a*]pyrimidin-7-(4*H*)-ones (**8a**—**m**), which were converted to the 7-chloro derivatives (**9a**—**m**) by treatment with phosphorous oxychloride.[7] 2-Cyano-4′-(aminomethyl)biphenyl[8] was allowed to react with 7-chloropyrazolo[1,5-*a*]pyrimidines (**9a**—**m**), and the resulting cyano derivatives (**10a**—**m**) were converted to the tetrazole derivatives (**11a**—**m**) using trimethyltin azide. Preparations of 5-heteroatom-substituted derivatives (**16**, **19a**—**d**) and the unsubstituted compound (**15**) are presented in Chart 3. Reaction of 5,7-dichloropyrazolo[1,5-*a*]pyrimidine[9] (**12**) with 2-cyano-4′-(aminomethyl)biphenyl gave **13**. Converting the cyano group to the tetrazole gave the 5-chloro derivative (**16**). Unsubstituted compound (**15**) was synthesized by reduction of **13** on Pd/C, followed by conversion of the cyano group to the tetrazole. 5-Heteroatom-substituted derivatives (**18a**—**d**) were obtained by reaction of the *tert*-butoxycarbonyl (Boc)-protected compound (**17**) with various nucleophiles. After deprotection of the Boc group, the tetrazole ring was formed with trimethyltin azide in refluxing xylene. Direct biphenylmethylation of **9b** and **9f** was performed by coupling with zinc reagent (**20**) in the presence of palladium catalyst as shown in Chart 4. The regioselective cross-coupling reaction of 5,7-dichloro derivative (**12**) with **20** was achieved using LiCl as an additive.[10] The coupling product (**23**) was treated with various nucleophiles, and the cyano derivatives were converted to the tetrazole derivatives (**25a**—**c**).

Results and Discussion

All of the compounds synthesized were evaluated as AII antagonists by testing their potency to displace [^{125}I]AII binding to COS cells transfected with a cDNA encoding a human AT_1 receptor. We also tested the inhibition of [^{125}I]AII binding in a rat liver membrane preparation (AT_1 receptors). The K_i values calculated from IC_{50} values in these assays are listed in Tables 1—3.

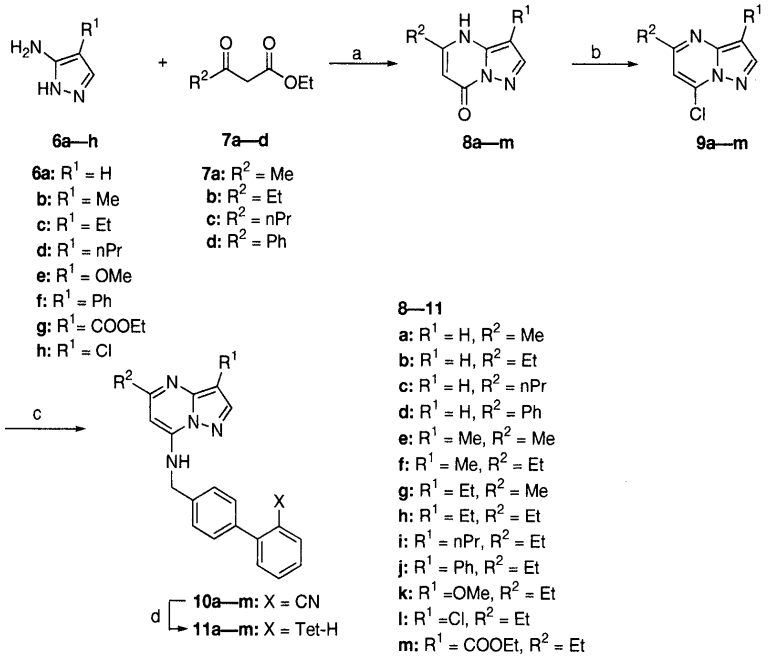
Oral activity was not found in the compound **1** series due to its low bioavailability. The presence of two acidic functional groups may have been the cause of the poor absorption,[11] so we first examined whether it was possible to remove the 3-carboxyl group in **1** and replace the heteroaromatic systems (step 1 in Fig. 2). In this step, we tried replacing the carboxylic acid with an aromatic nitrogen atom, because there were several examples of incorporation of various hydrogen bonding groups, such as carboxyl, carbonyl or aromatic nitrogen, in heterocyclic systems leading to equal enhancement of the binding activity.[12]

From the results shown in Table 1, imidazolo[1,5-*a*]pyrimidine (**5a**) showed affinity almost comparable to the parent carboxylic acid derivative (**1**). The number of nitrogen atoms in the heterocyclic system dramatically influenced the binding activity. The order of the binding activity of these com-



Reagents: (a) 2-aminoimidazole, piperidine, EtOH; (b) 3-aminotriazole, Dowtherm A; (c) 5-aminotetrazole, AcOH, EtOH, then PPA; (d) 4-bromomethyl-2'-cyanobiphenyl, NaH, DMF; (e) Me_3SnN_3, xylene

Chart 1



Reagents: (a) AcOH; (b) $POCl_3$, pyridine, DMAP, CH_3CN; (c) 2-cyano-4'-(aminomethyl)biphenyl, K_2CO_3, CH_3CN; (d) Me_3SnN_3, xylene

Chart 2

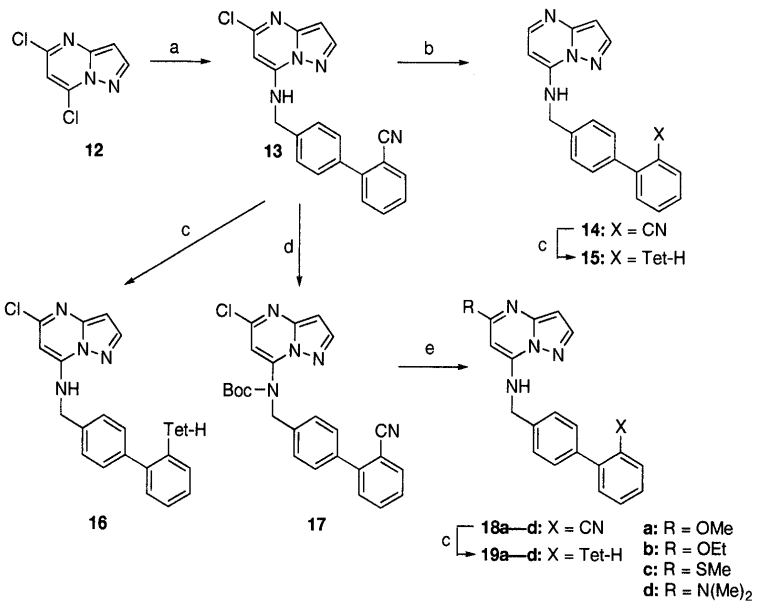
pounds (**5a**>**5b**>**5c**) was related to the hydrogen bonding ability of the 5-membered ring portion (imidazole>triazole >tetrazole).[13] These results suggest that this nitrogen plays an important role as a hydrogen bond acceptor when binding to the receptor. Although **5a** was potent *in vitro*, it lacked *in vivo* activity.

Next, we designed the pyrazolo[1,5-*a*]pyrimidine heterocycle, which was linked to the biphenyltetrazole moiety by an aminomethylene group such as **11b** (step 2 in Fig. 2). As outlined in Fig. 3, this structure was derived from incorporation of the essential features for receptor binding suggested as imidazolo[1,5-*a*]pyrimidine derivative **5a** and the published compounds, A-81988 or D-8731, which were reported as good orally active AII antagonists. In this heterocycle, the amide group of **1**, which was thought to be one of the causes of poor absorption, was removed.

Compound **11b** retained its potent binding affinity (IC_{50}=0.31 nM) and when orally administered to SHRs, caused a moderate decrease in blood pressure. We next focused on preparing analogs of **11b** for optimizing the *in vitro* and *in vivo* activities (step 3 in Fig. 2).

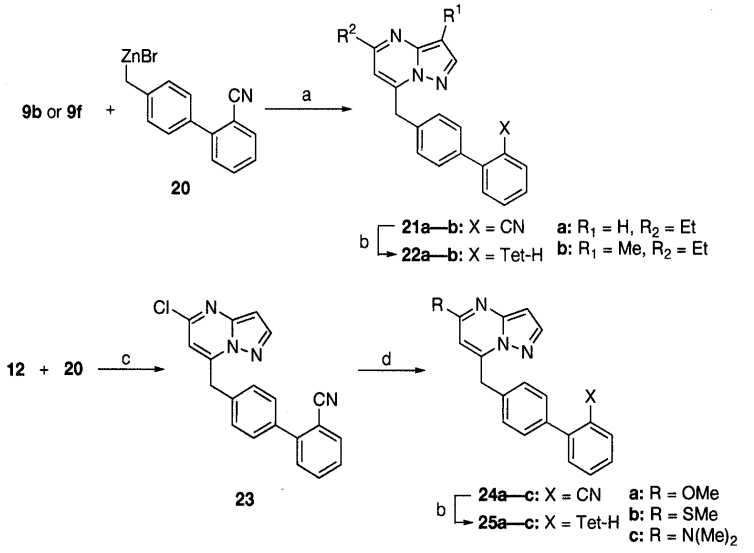
Several groups have reported the presence of two hydrophobic interactions between the AII receptor and the alkyl substituents on the heterocycle. One site is the C_5-position of 2,4-dihydro-3*H*-1,2,4-triazol-3-one receptor antagonist (**26** shown in Fig. 4), which corresponds to the 2-substituent of the imidazole ring in losartan, and the other site is the N_2-substituent of **26**.[8,12c—e] We superimposed the pyrazolo[1,5-*a*]pyrimidine (**11a**) and **26** in the same manner as that reported for the superimposition of D-8731 and Dup753 (Fig. 4).[2] As shown in Fig. 4, the first lipophilic moiety of the 5-position of **11a** corresponds to that of the 5-position of **26**. This superimposition indicated that the methyl group at the N_2-position of **26** corresponds to the hydrogen at the 3-position of **11a**. Thus our modification of the pyrazolo[1,5-*a*]pyrimidine derivatives focused on the 3- and 5-positions.

The SARs of the 3- and 5-positions of the pyrazolo[1,5-*a*]pyrimidines are summarized in Table 2. Introduction of methyl, ethyl or chloro groups into the 3-position enhanced binding activity (**11f**, **11h**, **11l** *vs.* **11b**). 3-Propyl or 3-



Reagents: (a) 2-cyano-4'-(aminomethyl)biphenyl, K_2CO_3, CH_3CN; (b) $HCOO^-NH_4^+$, triethylamine, 5%Pd/C, toluene; (c) Me_3SnN_3, xylene; (d) Boc_2O, DMAP, dioxane; (e) various nucleophiles, then CF_3COOH, CH_2Cl_2

Chart 3



Reagents: (a) $Pd(Ph_3P)_4$, DMF; (b) Me_3SnN_3, xylene; (c) LiCl, DMF; (d) various nucleophiles

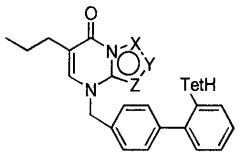
Chart 4

ethoxycarbonyl derivatives (**11i**, **11m**), had slightly less potency, whereas the 3-phenyl derivative (**11j**) showed a dramatic loss of the binding affinity.

Optimal activity at the 5-position occurred with the ethyl substituent (**11b**). The chloro, methyl and *n*-propyl compounds were less potent than ethyl derivative (**16**, **11a**, **11c** *vs.* **11b**). Introduction of larger groups such as phenyl and dimethylamino groups decreased the binding activity (**11d**, **19d**) and unsubstituted derivative (**15**) also decreased the binding activity. Electronic character of the 5-position was generally unrelated to the binding activity. Electron-donating groups, such as methoxy and ethoxy substituents, decreased the binding activity slightly, and the electron-withdrawing chloro substituent also decreased it.

We also examined the binding activity of a series of compounds with the biphenylmethyl moiety directly attached to the pyrazolo[1,5-*a*]pyrimidine heterocycle (Table 3). The 5-ethyl compound (**22a**) was one of the most potent AII antagonists of the pyrazolo[1,5-*a*]pyrimidine series. The 3-methyl-5-ethyl derivative (**22b**) showed similar potency to the aminomethylene linker counterpart (**11f**), but was less potent than **22a**. These results differed from those for aminomethylene linker derivatives (**11b** *vs.* **11f**), which indicates that this series of compounds bind to the AII receptor

Table 1. *In Vitro* AII Antagonistic Potencies of **5a—c**



Compd.	X	Y	Z	K_i (nM)[a]
5a	CH	CH	N	0.64
5b	N	CH	N	5.3
5c	N	N	N	690
1				0.68

a) K_i values were evaluated by testing their potency to displace [^{125}I]AII binding to COS cells transfected with a cDNA encoding a human AT_1 receptor.

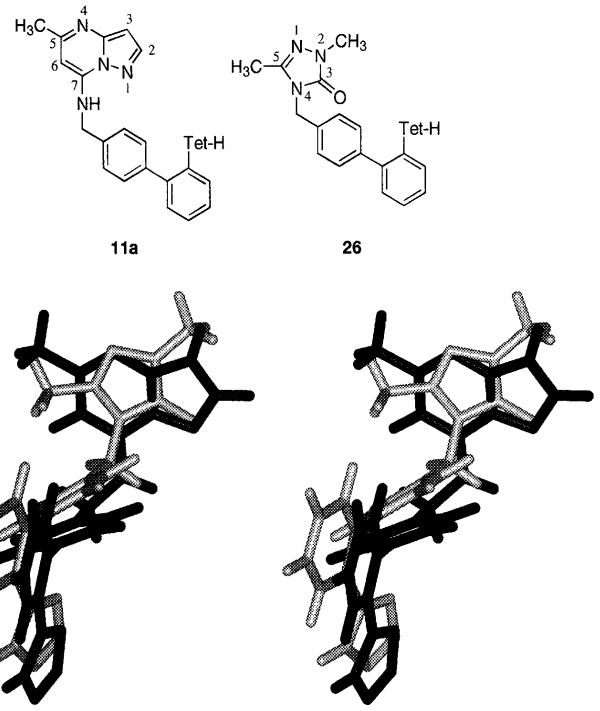
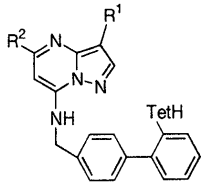


Fig. 4

in a different manner. The introduction of alkylhetero substituent groups at the 5-position generally led to adverse effects on receptor binding affinity (**25a—c**).

Selected compounds were given orally to SHR and the systolic blood pressure (SBP) was monitored. The changes of SBP after 7 h of oral dosing at 10 mg/kg are listed in Tables 2 and 3. The *in vivo* activities of these compounds did not always correlate well with the *in vitro* binding activities. Introduction of the 3-methyl substituent led to highly potent antihypertensive active compounds (**11e**, **11f**). The 5,7-dimethyl derivative (**11e**) is equipotent with losartan, and the 3-methyl-5-ethyl derivative (**11f**) showed the most potent *in vivo* activity in this study. While **11g—i**, and **16** were potent AII antagonists *in vitro*, they were extremely weak for decreasing blood pressure in this model. Because these compounds were potent AII antagonists in rat liver membranes, their low *in vivo* activity might be due to their low bioavailability. Direct biphenylmethyl substituted derivatives (**22a**, **22b**) showed antihypertensive activities but were less efficacious than losartan.

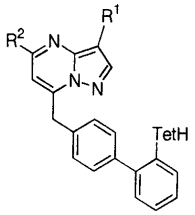
Table 2. *In Vitro* AII Antagonistic Potencies and *in Vivo* Antihypertensive Activities of 3- or 5-Substituted Pyrazolo[1,5-*a*]pyrimidine Analogs



Compd.	R^1	R^2	Human K_i (nM)[a]	Rat K_i (nM)[b]	*In vivo* (oral) change in SBP[c]
11b	H	Et	0.31	0.67	−26±4
11e	Me	Me	0.20	NT	−42±6
11f	Me	Et	0.26	0.29	−57±4
11g	Et	Me	0.73	1.9	Negative
11h	Et	Et	0.24	0.44	Negative
11i	*n*Pr	Et	1.3	6.1	Negative
11j	Ph	Et	1100	NT	NT
11k	OMe	Et	0.89	2.1	−19±6
11l	Cl	Et	0.17	NT	−37±6
11m	COOEt	Et	17	NT	NT
15	H	H	40	NT	NT
11a	H	Me	0.95	1.5	−43±9
11c	H	*n*Pr	0.65	1.4	−30±5
11d	H	Ph	100	NT	NT
16	H	Cl	2.6	5.1	Negative
19a	H	OMe	1.6	4.2	NT
19b	H	OEt	1.3	NT	NT
19c	H	SMe	2.3	8.0	NT
19d	H	NMe_2	22	NT	NT
Losartan			2.8	8.6	−44±4

a) K_i values were evaluated by testing their potency to displace [^{125}I]AII binding to COS cells transfected with a cDNA encoding a human AT_1 receptor. *b*) K_i values were evaluated by testing in a rat liver membrane preparation (AT_1 receptor). *c*) Effect of compounds on SBP 7 h after oral dosing at 10 mg/kg to SHRs. Data represent the mean±S.E. (n=4—6). NT=not tested.

Table 3. *In Vitro* AII Antagonistic Potencies and *in Vivo* Antihypertensive Activities of **22a**, **b** and **25a—c**



Compd.	R^1	R^2	Hunam K_i (nM)[a]	Rat K_i (nM)[b]	*In vivo* (oral) change in SBP[c]
22a	H	Et	0.29	0.74	−31±7
22b	Me	Et	0.41	0.73	−29±11
25a	H	OMe	4.3	8.0	NT
25b	H	SMe	3.3	10	NT
25c	H	NMe_2	14	NT	NT

a) K_i values were evaluated by testing their potency to displace [^{125}I]AII binding to COS cells transfected with a cDNA encoding a human AT_1 receptor. *b*) K_i values were evaluated by testing in a rat liver membrane preparation (AT_1 receptor). *c*) Effect of compounds on SBP 7 h after oral dosing at 10 mg/kg to SHRs. Data represent the mean±S.E. (n=4—6).

Conclusions

New orally active AII antagonists were explored with 7-oxo-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid derivatives as lead structures. The 3-carboxylic substituent can successfully replace the aromatic nitrogen atom with retention of *in vitro* activity. SAR of the series of com-

pounds **5a**—**c** revealed the role of this nitrogen as a hydrogen bond acceptor. Changing the 7-oxo-4,7-dihydropyrazolo[1,5-*a*]pyrimidine heterocycle to the pyrazolo[1,5-*a*]pyrimidine resulted in orally active antihypertensive compounds. Various substituents were introduced at the 3- and 5-positions in the pyrazolo[1,5-*a*]pyrimidine heterocycle based on knowledge of the existence of two lipophilic pockets in the AII receptor. The most active compound of this family, (5-ethyl-3-methylpyrazolo[1,5-*a*]pyrimidin-7-yl)-[2′-(1*H*-tetrazol-5-yl) biphenyl-4-ylmethyl]amine (**11f**), proved to be more active than losartan in SHRs after oral dosing.

Experimental

Molecular Modeling All calculations were performed with a Silicon Graphics Indigo^2 R4400 workstation. All molecular models were constructed with the molecular modeling software package SYBYL 6.01 and 6.10,[14] using molecular fragments and standard bond lengths and angles from the SYBYL structure library. Each structure was optimized by means of the molecular mechanics minimizer MAXIMIN2 and the standard TRIPOS force field by neglecting the electrostatic contribution. The conformations of **11a** and **26** in Fig. 4 were adopted in the gauche and helix-1 conformation, respectively, by referring to the literature.[2]

AII Receptor Binding Assay Using COS Cells A cDNA encoding human AT_1 receptor, donated by Dr. T. Inagami (Vanderbilt University, Nashville, TN), was inserted into the mammalian expression vector $psDNA_1$ (Invitrogen). COS-7 cells plated in 175-cm^2 flasks grew to 80% confluency after 3 d. The cells were then transfected with 40 μg DNA by 150 μl of lipofectin reagent (GIBCO). Two or three days after transfection, the binding assay was done as described previously.[15] In brief, cell suspensions (1.2×10^6 cell/ml), dispersed with 0.025% trypsin/1 mM EDTA, were incubated at 25 °C for 60 min in 0.2 ml of Hepes (20 ml)-buffered Hanks' solution containing 1 mg/ml phenylmethanesulfonyl fluoride (PMSF), 10 μg/ml aprotinin, 10 μg/ml leupeptin, 10 μg/ml pepstatin A, 250 μg/ml bacitracin, 10 μg/ml soybean trypsin inhibitor, and 0.1 mM amastatin 0.1 nM [^{125}I]AII (81.4 TBq/mmol, New England Nuclear) in the absence or presence of non-radioactive peptide or drugs. Each binding reaction was terminated by addition of 2.5 ml of ice-cold 50 mM Tris–HCl (pH 7.4), followed by rapid filtration through a GF/C glass fiber filter under reduced pressure. The filters were then quickly washed four more times with 2.5 ml of the Tris buffer, and the radioactivity retained on the filters was counted. Nonspecific binding, determined in the presence of 10^{-6} M nonradiolabeled AII, was 5—10% of the total binding. K_i values were calculated from the equation $K_i=IC_{50}/(1+[L]/K_d)$, where IC_{50}=the concentration causing 50% inhibition of specific [^{125}I]AII binding, [L]=[^{125}I]AII concentration and K_d=the dissociation constant for [^{125}I]AII (0.46 nM).

AII Receptor Binding Assay Using Rat Liver Membranes The rat liver membranes were prepared according to the method of Chiu *et al.*[16] The incubation mixture (0.1 ml) contained 50 mM Tris–HCl (pH 7.4), 0.1 mM amastatin, 1 mM α-PMSF, and membranes (0.03—0.05 mg of protein) with 0.2—0.3 nM [^{125}I]AII in the absence or presence of non-radioactive compounds. The equilibrium binding studies were carried out according to the procedure using COS cells.

Oral Antihypertensive Activity in SHR Male SHRs, 16—18 weeks old, were used for the oral dose–response study of the acute hypotensive effect. SBP was measured by the tail-cuff method reported by our laboratory[17] at 7 h after oral administration of the test drugs.

Chemical Synthesis Unless otherwise stated, all reactions were carried out under a nitrogen atmosphere. Tetrahydrofuran (THF), ether, xylene and DMF were dried over 4 Å molecular sieves. Flash chromatography was performed on silica gel (Merck Kieselgel: Art9385). Zinc dust, $Pd(Ph_3P)_4$, and *n*-butyllithium in *n*-hexane solution were purchased from Aldrich, Inc.

6-Propyl-8*H*-imidazo[1,2-*a*]pyrimidin-5-one (3a) To a solution of ethyl *n*-valerate (3.91 g, 30 mmol) and ethyl formate (4.80 g, 64.8 mmol) in THF (15 ml) at 25 °C was added dropwise a solution of potassium *tert*-butoxide (7.50 g, 66.8 mmol) in THF (50 ml) over a period of 45 min. The resulting mixture was stirred for 3 h at room temperature and the solvent was evaporated *in vacuo*. The residue was dissolved in water and washed twice with ether. The resulting aqueous layer was acidified with 12 N HCl to pH 2 and extracted with three 50 ml portions of ether, and the combined extracts were dried ($MgSO_4$), and the solvent was evaporated *in vacuo* to give 3.82 g of crude ethyl 2-formylpentanate **2** as a yellow oil. This oil (1.9 g, 12 mmol) was dissolved in EtOH (20 ml). 2-Aminoimidazole sulfate (1.1 g, 8.4 mmol) and piperidine (1.0 ml, 10.1 mmol) were added to this solution, the resulting mixture was stirred for 2 h at room temperature, and the solvent was evaporated *in vacuo*. The resulting residue was partitioned between EtOAc and water. The organic layer was separated, washed with water, dried ($MgSO_4$), and the solvent was evaporated *in vacuo*. The crude material was purified by flash chromatography (CH_2Cl_2 : EtOAc=1 : 10—CH_2Cl_2 : MeOH=10 : 1 as an eluent) to give **3a** (879 mg, 58%) as colorless prisms after recrystallization from EtOAc. mp 132—134 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.99 (3H, t, J=7.4 Hz), 1.67 (2H, m), 2.55 (2H, t, J=7.7 Hz), 7.18 (1H, d, J=2.0 Hz), 7.63 (1H, d, J=2.4 Hz), 7.73 (1H, s), 10.10 (1H, br). IR (Nujol): 3504, 3444, 1665 cm^{-1}. *Anal.* Calcd for $C_9H_{11}N_3O\cdot0.2H_2O$: C, 59.79; H, 6.36; N, 23.24. Found: C, 60.18; H, 6.38; N, 23.13.

6-Propyl-4*H*-[1,2,4]triazolo[1,5-*a*]pyrimidin-7-one (3b) A mixture of ethyl 2-formylpentanate **2** (4.45 g, 20.7 mmol) and 3-amino-1,2,4-triazole (1.65 g, 19.6 mmol) in Dowtherm A (20 ml) was stirred for 1 h at 200 °C and cooled to room temperature. The precipitated solids were collected and recrystallized from methanol to give **3b** (2.77 g, 79%) as colorless prisms. mp 247—248 °C. ^{1}H-NMR (DMSO-d_6) δ: 0.90 (3H, t, J=7.4 Hz), 1.55 (2H, m), 2.42 (2H, t, J=7.4 Hz), 7.91 (1H, s), 8.21 (1H, s). IR (Nujol): 3478, 3368, 1675 cm^{-1}. *Anal.* Calcd for $C_8H_{10}N_4O\cdot0.15H_2O$: C, 53.12; H, 5.74; N, 30.97. Found: C, 53.36; H, 5.71; N, 31.24.

6-Propyl-4*H*-tetrazolo[1,5-*a*]pyrimidin-7-one (3c) A mixture of ethyl 2-formylpentanate **2** (1.8 g, 8.6 mmol) and 5-aminotetrazole (723 mg, 8.5 mmol) in glacial acetic acid (2 ml) and absolute ethanol (8 ml) was heated under reflux for 50 h. The solvent was evaporated *in vacuo*, and the residue was treated with EtOAc, then filtered. The resulting solids were recrystallized from EtOAc to give enamine intermediate (219 mg) as a colorless powder. mp 247—248 °C. ^{1}H-NMR (DMSO-d_6) δ: 0.89 (3H, t, J=7.2 Hz), 1.23 (3H, t, J=7.0 Hz), 1.36 (2H, m), 2.30 (2H, t, J=7.2 Hz), 4.12 (2H, q, J=7.0 Hz), 7.84 (1H, d, J=12.6 Hz). IR (Nujol): 3146, 3076, 1687 cm^{-1}. *Anal.* Calcd for $C_9H_{15}N_5O_2$: C, 47.99; H, 6.71; N, 31.09. Found: C, 47.88; H, 6.65; N, 31.02. The above enamine intermediate (204 mg, 0.9 mmol) was dissolved in 2 ml of polyphosphoric acid (PPA) and the resulting solution was stirred at room temperature for 18 h. The mixture was poured into ice water, neutralized to pH 6—7 with NaOH. The solution was extracted with three 30 ml portions of $CHCl_3$, the combined extracts were dried ($MgSO_4$), and the solvent was evaporated *in vacuo*. The residue was recrystallized from EtOAc–*n*-hexane to give **3c** (14 mg, 1%) as colorless prisms. mp 108—110 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.04 (3H, t, J=7.2 Hz), 1.69 (2H, m), 2.57 (2H, t, J=7.2 Hz), 4.15 (1H, br), 8.32 (1H, s). *Anal.* Calcd for $C_7H_9N_5O\cdot0.1H_2O$: C, 46.46; H, 5.12; N, 38.70. Found: C, 46.43; H, 5.14; N, 38.97.

4′-[(5-Oxo-6-propyl-5*H*-imidazo[1,2-*a*]pyrimidin-8-yl)methyl]-biphenyl-2-carbonitrile (4a) A mixture of **3a** (532 mg, 3.0 mmol) and NaH (60% dispersion in mineral oil; 130 mg, 3.3 mmol) in DMF (4.5 ml) was stirred until evolution of hydrogen ceased. A solution of 4-bromomethyl-2′-cyanobiphenyl (817 mg, 3.0 mmol) in DMF (5 ml) was added and the mixture was stirred for 1 h at 0 °C. The resultant mixture was poured into ice water and extracted with three 30 ml portions of EtOAc. The combined extracts were washed with water (20 ml) and saturated brine (20 ml) and then dried ($MgSO_4$). The solvent was evaporated *in vacuo* and the residue was purified by flash chromatography (CH_2Cl_2 : CH_3CN=1 : 10 as an eluent) to give **4a** (589 mg, 26%; less polar product) as colorless needles. mp 135—136 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.95 (3H, t, J=7.4 Hz), 1.62 (2H, m), 2.49 (2H, t, J=7.4 Hz), 5.42 (2H, s), 7.22 (1H, d, J=1.8 Hz), 7.34 (1H, s), 7.38—7.82 (8H, m), 7.65 (1H, d, J=1.8 Hz). IR (Nujol): 2214, 1667 cm^{-1}. *Anal.* Calcd for $C_9H_{15}N_5O_2$: C, 74.98; H, 5.47; N, 15.21. Found: C, 74.84; H, 5.60; N, 15.07.

4′-[(5-Oxo-6-propyl-5*H*-[1,2,4]triazolo[1,5-*a*]pyrimidin-8-yl)methyl]-biphenyl-2-carbonitrile (**4b**): The title compound was prepared from **3b** and 4-bromomethyl-2′-cyanobiphenyl according to the procedure described in the preparation of **4a** as colorless prisms. mp 192—193 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.96 (3H, t, J=7.4 Hz), 1.64 (2H, m), 2.54 (2H, t, J=7.7 Hz), 5.41 (2H, s), 7.38 (1H, s), 7.41—7.86 (8H, m), 8.09 (1H, s). IR (Nujol): 2216, 1690, 1672 cm^{-1}. *Anal.* Calcd for $C_{22}H_{19}N_5O_2\cdot0.2H_2O$: C, 70.84; H, 5.24; N, 18.77. Found: C, 70.87; H, 5.23; N, 18.66.

4′-[(7-Oxo-6-propyl-7*H*-tetrazolo[1,5-*a*]pyrimidin-4-yl)methyl]biphenyl-2-carbonitrile (**4c**): The title compound was prepared from **3c** and 4-bromomethyl-2′-cyanobiphenyl according to the procedure described in the preparation of **4a** as a colorless amorphous powder. ^{1}H-NMR ($CDCl_3$) δ: 1.04 (3H, t, J=7.4 Hz), 1.69 (2H, m), 2.58 (2H, t, J=7.4 Hz), 5.49 (2H, s), 7.35—7.83 (8H, m), 8.24 (1H, s). IR ($CHCl_3$): 2222, 1682 cm^{-1}.

6-Propyl-8-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-8*H*-imidazo[1,2-*a*]pyrimidin-5-one (5a) A mixture of **4a** (520 mg, 1.4 mmol) and trimethyltin azide (350 mg, 1.7 mmol) in xylene (6 ml) was heated under

reflux for 48 h, and the solvent was evaporated *in vacuo*. The residue was stirred with 1 N HCl (1.5 ml) for 1 h at room temperature, neutralized to pH 8 with saturated aqueous $NaHCO_3$ and extracted with three 30 ml portions of CH_2Cl_2. The combined extracts were washed with water (20 ml) and saturated brine (20 ml) and dried ($MgSO_4$). The solvent was evaporated *in vacuo* and the residue was purified by flash chromatography (CH_2Cl_2 : CH_3CN = 1 : 10 as an eluent) to give **5a** (370 mg, 61%) as a pale yellow amorphous powder. ^{1}H-NMR ($CDCl_3$) δ: 0.94 (3H, t, J=7.4 Hz), 1.59 (2H, m), 2.46 (2H, t, J=7.4 Hz), 5.18 (2H, s), 6.93—8.00 (11H, m). IR ($CHCl_3$): 3398, 1674 cm^{-1}. *Anal.* Calcd for $C_{23}H_{21}N_7O \cdot 0.5C_2H_5OH$: C, 65.19; H, 5.70; N, 22.64. Found: C, 65.28; H, 5.58; N, 22.31.

6-Propyl-4-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-4*H*-[1,2,4]triazolo[1,5-*a*]pyrimidin-7-one (**5b**): The title compound was prepared from **4b** and trimethyltin azide according to the procedure described in the preparation of **5a** as a solid (57%). mp 194—196 °C. ^{1}H-NMR (DMSO-d_6) δ: 0.91 (3H, t, J=7.4 Hz), 1.56 (2H, m), 2.43 (2H, t, J=7.4 Hz), 5.36 (2H, s), 7.08 and 7.34 (4H, ABq, J=8.0 Hz), 7.42—7.78 (4H, m), 8.20 (1H, s), 8.24 (1H, s). IR (Nujol): 3436, 1676 cm^{-1}. *Anal.* Calcd for $C_{22}H_{20}N_8O \cdot 0.5C_2H_5OH \cdot 0.3CH_2Cl_2$: C, 60.71; H, 5.16; N, 24.31. Found: C, 60.55; H, 5.09; N, 24.26.

6-Propyl-4-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-4*H*-tetrazolo[1,5-*a*]pyrimidin-7-one (**5c**): The title compound was prepared from **4c** and trimethyltin azide according to the procedure described in the preparation of **5a** as a brown amorphous powder. ^{1}H-NMR ($CDCl_3$) δ: 1.04 (3H, t, J=7.4 Hz), 1.68 (2H, m), 2.57 (2H, t, J=7.4 Hz), 5.41 (2H, s), 7.07—8.13 (8H, m), 8.26 (1H, s). IR ($CHCl_3$): 3398, 1682 cm^{-1}. *Anal.* Calcd for $C_{22}H_{20}N_8O \cdot 1.9MeOH \cdot 0.1CH_2Cl_2$: C, 57.22; H, 5.59; N, 26.11. Found: C, 57.60; H, 5.29; N, 26.08.

General Method for the Synthesis of 4*H*-Pyrazolo[1,5-*a*]pyrimidin-7-one Derivatives (8). 5-Methyl-4*H*-pyrazolo[1,5-*a*]pyrimidin-7-one (8a) A mixture of 3-aminopyrazole (831 mg, 10 mmol) and ethyl acetoacetate (1.3 g, 10 mmol) in acetic acid (10 ml) was heated under reflux for 3 h and the solvent was evaporated *in vacuo*. The residue was treated with EtOAc and filtered. The resulting solids were recrystallized from EtOH to give **8a** (1.39 g) as colorless prisms (87%). mp 267—272 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.29 (3H, s), 5.57 (1H, s), 6.09 (1H, d, J=2.0 Hz), 7.82 (1H, d, J=2.0 Hz). IR (Nujol): 3150, 1700, 1630 cm^{-1}. *Anal.* Calcd for $C_7H_7N_3O$: C, 56.37; H, 4.73; N, 28.17. Found: C, 56.41; H, 4.82; N, 28.23.

Using this procedure, the following 4*H*-pyrazolo[1,5-*a*]pyrimidin-7-one derivatives were synthesized.

5-Ethyl-4*H*-pyrazolo[1,5-*a*]pyrimidin-7-one (**8b**): Colorless prisms (57%), mp 247—248 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.23 (3H, t, J=7.6 Hz), 2.58 (3H, q. J=7.6 Hz), 5.60 (1H, s), 6.11 (1H, d, J=2.0 Hz), 7.84 (1H, d, J=2.0 Hz), 12.23 (1H, br). IR (Nujol): 3292, 3154, 2734, 1685 cm^{-1}. *Anal.* Calcd for $C_8H_9N_3O$: C, 58.88; H, 5.56; N, 25.75. Found: C, 58.79; H, 5.61; N, 25.64.

5-Propyl-4*H*-pyrazolo[1,5-*a*]pyrimidin-7-one (**8c**): Colorless prisms (78%). mp 210—212 °C. ^{1}H-NMR (DMSO-d_6) δ: 0.93 (3H, t, J=7.2 Hz), 1.67 (2H, m), 2.50—2.67 (2H, m), 5.59 (1H, s), 6.11 (1H, d, J=2.0 Hz), 7.83 (1H, d, J=2.0 Hz), 12.22 (1H, br). IR (Nujol): 3150, 1700, 1630 cm^{-1}. *Anal.* Calcd for $C_9H_{10}N_3O$: C, 61.00; H, 6.26; N, 23.71. Found: C, 61.12; H, 6.30; N, 23.76.

5-Phenyl-4*H*-pyrazolo[1,5-*a*]pyrimidin-7-one (**8d**): Colorless needles (92%). mp 298—300 °C. ^{1}H-NMR (DMSO-d_6) δ: 6.07 (1H, s), 6.23 (1H, d, J=2.0 Hz), 7.59 (3H, m), 7.84 (2H, m), 7.91 (1H, d, J=2.0 Hz). IR (Nujol): 3140, 1665 cm^{-1}. *Anal.* Calcd for $C_{12}H_9N_3O$: C, 68.24; H, 4.30; N, 19.90. Found: C, 68.14; H, 4.52; N, 19.91.

3,5-Dimethyl-4*H*-pyrazolo[1,5-*a*]pyrimidin-7-one (**8e**): Colorless prisms (42%). mp 209—213 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.12 (3H, s), 2.31 (3H, s), 5.52 (1H, s), 7.68 (1H, s), 11.93 (1H, br). IR (Nujol): 1673 cm^{-1}. *Anal.* Calcd for $C_8H_9N_3O$: C, 58.88; H, 5.56; N, 25.75. Found: C, 58.64; H, 5.66; N, 25.75.

5-Ethyl-3-methyl-4*H*-pyrazolo[1,5-*a*]pyrimidin-7-one (**8f**): Colorless needles (14%). mp 303—305 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.23 (3H, t, J=7.6 Hz), 2.13 (3H, s), 2.60 (2H, q, J=7.6 Hz), 5.54 (1H, s), 7.69 (1H, s), 11.86 (1H, br). IR (Nujol): 3292, 3156, 1674 cm^{-1}. *Anal.* Calcd for $C_9H_{11}N_3O$: C, 61.00; H, 6.26; N, 23.71. Found: C, 60.70; H, 6.29; N, 23.63.

3-Ethyl-5-methyl-4*H*-pyrazolo[1,5-*a*]pyrimidin-7-one (**8g**): Colorless prisms (42%). mp >290 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.22 (3H, t, J=7.6 Hz), 2.33 (3H, s), 2.55 (2H, q, J=7.6 Hz), 5.55 (1H, s), 7.68 (1H, s). IR (Nujol): 1680, 1630 cm^{-1}. *Anal.* Calcd for $C_9H_{11}N_3O$: C, 61.00; H, 6.26; N, 23.71. Found: C, 60.87; H, 6.23; N, 23.59.

3,5-Diethyl-4*H*-pyrazolo[1,5-*a*]pyrimidin-7-one (**8h**): Colorless prisms (91%). mp >290 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.16 (3H, t, J=7.6 Hz), 1.28 (3H, t, J=7.6 Hz), 2.54 (2H, q, J=7.6 Hz), 2.68 (2H, q, J=7.6 Hz), 5.61 (1H, s), 7.67 (1H, s). IR (Nujol): 3169, 1669, 1632 cm^{-1}. *Anal.* Calcd for $C_{10}H_{13}N_3O$: C, 62.81; H, 6.85; N, 21.97. Found: C, 62.91; H, 6.89; N, 21.98.

5-Ethyl-3-propyl-4*H*-pyrazolo[1,5-*a*]pyrimidin-7-one (**8i**): Colorless prisms (19%). mp 270—275 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.83 (3H, t, J=7.0 Hz), 1.28 (3H, t, J=7.6 Hz), 1.54 (2H, m), 2.46 (2H, q, J=7.6 Hz), 2.70 (2H, q, J=7.6 Hz), 5.62 (1H, s), 7.65 (1H, s). IR (Nujol): 3171, 1679, 1633 cm^{-1}. *Anal.* Calcd for $C_{11}H_{15}N_3O \cdot 0.1H_2O$: C, 63.81; H, 7.40; N, 20.29. Found: C, 63.55; H, 7.35; N, 20.44.

5-Ethyl-3-phenyl-4*H*-pyrazolo[1,5-*a*]pyrimidin-7-one (**8j**): A colorless powder (95%). ^{1}H-NMR ($CDCl_3$+CD_3OD) δ: 1.31 (3H, t, J=7.6 Hz), 2.69 (2H, q, J=7.6 Hz), 5.69 (1H, s), 7.2—7.5 (5H, m), 7.90 (1H, s).

5-Ethyl-3-methoxy-4*H*-pyrazolo[1,5-*a*]pyrimidin-7-one (**8k**): An amorphous powder (34%). ^{1}H-NMR ($CDCl_3$) δ: 1.33 (3H, t, J=7.6 Hz), 2.76 (2H, q, J=7.6 Hz), 3.75 (3H, s), 5.68 (1H, s), 7.72 (1H, s). *Anal.* Calcd for $C_{14}H_{13}N_3O$: C, 70.28; H, 5.48; N, 17.56. Found: C, 70.01; H, 5.56; N, 17.31.

3-Chloro-5-ethyl-4*H*-pyrazolo[1,5-*a*]pyrimidin-7-one (**8l**): White prisms (60%). mp 286—288 °C. ^{1}H-NMR ($CDCl_3$+CD_3OD) δ: 1.33 (3H, t, J=7.6 Hz), 2.68 (2H, q, J=7.6 Hz), 5.72 (1H, s), 7.80 (1H, s). IR (Nujol): 1683, 1639 cm^{-1}. *Anal.* Calcd for $C_8H_8ClN_3O$: C, 48.62; H, 4.08; Cl, 17.94; N, 21.26. Found: C, 48.53; H, 4.11; Cl, 18.23; N, 21.28.

Ethyl 5-ethyl-7-oxo-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-3-carboxylate (**8m**): White prisms (89%). mp 177—178 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.22 (3H, t, J=7.4 Hz), 1.33 (3H, t, J=7.0 Hz), 2.75 (2H, q, J=7.4 Hz), 3.34 (1H, br), 4.32(2H, q, J=7.0 Hz), 5.86(1H, s), 8.18(1H, s). IR (Nujol): 3180, 1701, 1670 cm^{-1}. *Anal.* Calcd for $C_{11}H_{13}N_3O_3$: C, 56.16; H, 5.57; N, 17.85. Found: C, 56.15; H, 5.59; N, 17.83.

7-Chloro derivatives (**9**) were synthesized by the literature method[7] and crude products were passed through short silica gel column chromatography and used without further purification. ^{1}H-NMR spectrum data are listed in

Table 4. ^{1}H-NMR Spectral Data for 7-Chloro pyrazolo[1,5-*a*]pyrimidines **9**

Compd.	Solvent	Chemical shift (δ)
9a	CD_3Cl	2.61 (3H, s), 6.67 (1H, d, J=2.3 Hz), 6.86 (1H, s), 8, 17 (1H, d, J=2.3 Hz)
9b	CD_3Cl	1.32 (3H, t, J=7.6 Hz), 2.87 (2H, q, J=7.6 Hz), 6.69 (1H, d, J=2.4 Hz), 6.87 (1H, s), 8.17 (1H, d, J=2.4 Hz)
9c	CD_3Cl	1.02 (3H, t, J=7.4 Hz), 1.82 (2H, m), 2.81 (2H, m), 6.69 (1H, d, J=2.4 Hz), 6.86 (1H, s), 8.17 (1H, d, J=2.4 Hz)
9d	CD_3Cl	6.84 (1H, d, J=2.4 Hz), 7.45 (1H, s), 7.52—7.56 (3H, m), 8.06—8.11 (2H, m), 8.23 (1H, d, J=2.4 Hz)
9e	CD_3Cl	2.37 (3H, s), 2.61 (3H, s), 6.79 (1H, s), 8.02 (1H, s)
9f	CD_3Cl	1.36 (3H, t, J=7.6 Hz), 2.38 (3H, s), 2.86 (2H, q, J=7.6 Hz), 6.80 (1H, s), 8.01 (1H, s)
9g	CD_3Cl	1.33 (3H, t, J=7.6 Hz), 2.60 (3H, s), 2.83 (2H, q, J=7.6 Hz), 6.79 (1H, s), 8.03 (1H, s)
9h	CD_3Cl	1.33 (3H, t, J=7.6 Hz), 1.35 (3H, t, J=7.6 Hz), 2.84 (2H, q, J=7.6 Hz), 2.86 (2H, q, J=7.6 Hz), 6.80 (1H, s), 8.02 (1H, s)
9i	CD_3Cl	0.99 (3H, t, J=7.2 Hz), 1.35 (3H, t, J=7.6 Hz), 1.74 (2H, m), 2.78 (2H, t, J=7.6 Hz), 2.85 (2H, q, J=7.6 Hz), 6.80 (1H, s), 8.02 (1H, s)
9j	CD_3Cl	1.42 (3H, t, J=7.5 Hz), 2.94 (2H, q, J=7.5 Hz), 6.90 (1H, s), 7.25—8.11 (5H, m)
9k	CD_3Cl	1.42 (3H, t, J=7.5 Hz), 2.94 (2H, q, J=7.5 Hz), 6.90 (1H, s), 7.25—8.11 (5H, m)
9l	CD_3Cl	1.38 (3H, t, J=7.4 Hz), 2.92 (2H, t, J=7.4 Hz), 6.92 (1H, s), 8.15 (1H, s)
9m	CD_3Cl	1.41 (3H, t, J=7.6 Hz), 1.43 (3H, t, J=7.2 Hz), 3.00 (2H, q, J=7.6 Hz), 4.42 (2H, q, J=7.2 Hz), 7.05 (1H, s), 8.59 (1H, s)

Table 4.

General Method for the Synthesis of 4′-[(Pyrazolo[1,5-*a*]pyrimidin-7-yl)aminomethyl]biphenyl-2-carbonitrile Derivatives (10). 4′-[(5-Methylpyrazolo[1,5-*a*]pyrimidin-7-yl)aminomethyl]biphenyl-2-carbonitrile (10a) A mixture of **9a** (168 mg, 1 mmol), 2-cyano-4′-(aminomethyl)-biphenyl (208 mg, 1 mmol) and potassium carbonate (276 mg, 2.0 mg) in acetonitrile (10 ml) was stirred for 16 h at room temperature and the solvent was evaporated *in vacuo*. The resultant mixture was poured into ice water and extracted with three 30 ml portions of EtOAc. The combined extracts were washed with water (20 ml) and saturated brine (20 ml) and then dried ($MgSO_4$). The solvent was evaporated *in vacuo* and the residue was purified by flash chromatography (CH_2Cl_2 : CH_3CN=10 : 1 as an eluent) to give **10a** as an amorphous powder (77%). ^{1}H-NMR ($CDCl_3$): 2.50 (3H, s), 4.67 (2H, m), 5.87 (1H, s), 6.42 (1H, d, *J*=2.2 Hz), 6.74 (1H, m), 7.42—7.81 (8H, m), 7.97 (1H, d, *J*=2.2 Hz). IR (Nujol): 3450, 2350, 1680 cm^{-1}. *Anal.* Calcd for $C_{21}H_{17}N_5$: C, 74.32; H, 5.05; N, 20.64. Found: C, 74.44; H, 5.10; N, 20.72.

Using this procedure, the following 4′-[(pyrazolo[1,5-*a*]pyrimidin-7-yl)aminomethyl]biphenyl-2-carbonitrile derivatives were synthesized.

4′-[(5-Ethylpyrazolo[1,5-*a*]pyrimidin-7-yl)aminomethyl]biphenyl-2-carbonitrile (**10b**): Colorless needles (81%). mp 136—137 °C. ^{1}H-NMR ($CDCl_3$) *δ*: 1.31 (3H, t, *J*=7.4 Hz), 2.75 (2H, q, *J*=7.4 Hz), 4.68 (2H, d, *J*=6.0 Hz), 5.88 (1H, s), 6.42 (1H, d, *J*=2.4 Hz), 6.76 (1H, br), 7.40—7.84 (8H, m), 7.98 (1H, d, *J*=2.4 Hz). IR (Nujol): 3382, 2222 cm^{-1}. *Anal.* Calcd for $C_{22}H_{19}N_5$: C, 74.77; H, 5.42; N, 19.82. Found: C, 74.83; H, 5.48; N, 19.71.

4′-[(5-Propylpyrazolo[1,5-*a*]pyrimidin-7-yl)aminomethyl]biphenyl-2-carbonitrile (**10c**): Amorphous (99%). ^{1}H-NMR ($CDCl_3$) *δ*: 0.98 (3H, t, *J*=7.4 Hz), 1.77 (2H, m), 2.69 (2H, m), 4.68 (2H, m), 5.87 (1H, s), 6.44 (1H, d, *J*=2.4 Hz), 6.70 (1H, m), 7.44—7.81 (8H, m), 7.98 (1H, d, *J*=2.4 Hz). IR (Nujol): 3375, 3250, 2220, 1620 cm^{-1}. *Anal.* Calcd for $C_{23}H_{21}N_5$: C, 75.18; H, 5.76; N, 19.06. Found: C, 75.23; H, 5.64; N, 19.03.

4′-[(5-Phenylpyrazolo[1,5-*a*]pyrimidin-7-yl)aminomethyl]biphenyl-2-carbonitrile (**10d**): An amorphous powder. ^{1}H-NMR ($CDCl_3$) *δ*: 4.78(2H, d, *J*=5.8 Hz), 6.41 (1H, s), 6.60 (1H, d, *J*=2.2 Hz), 6.83 (1H, br), 7.43—7.80 (7H, m), 7.96—8.02 (6H, m), 8.04 (1H, d, *J*=2.2 Hz). *Anal.* Calcd for $C_{26}H_{19}N_5$: C, 77.79; H, 4.77; N, 17.44. Found: C, 77.52; H, 4.88; N, 17.23.

4′-[(3,5-Dimethylpyrazolo[1,5-*a*]pyrimidin-7-yl)aminomethyl]biphenyl-2-carbonitrile (**10e**): Colorless needles (78%). mp 163—164.5 °C. ^{1}H-NMR ($CDCl_3$) *δ*: 2.34 (3H, s), 2.52 (3H, s), 4.65 (2H, d, *J*=5.8 Hz), 5.82 (1H, s), 6.66 (1H, t, *J*=5.8 Hz), 7.40—7.88 (9H, m). IR (Nujol): 2216, 1620 cm^{-1}. *Anal.* Calcd for $C_{22}H_{19}N_5$: C, 74.77; H, 5.42; N, 19.82. Found: C, 74.93; H, 5.49; N, 19.71.

4′-[(5-Ethyl-3-methylpyrazolo[1,5-*a*]pyrimidin-7-yl)aminomethyl]-biphenyl-2-carbonitrile (**10f**): Pale yellow prisms (58%). ^{1}H-NMR ($CDCl_3$) *δ*: 1.31 (3H, t, *J*=7.6 Hz), 3.35 (3H, s), 2.77 (2H, q, *J*=7.6 Hz), 4.67 (2H, d, *J*=6.2 Hz), 5.83 (1H, s), 6.63 (1H, t, *J*=6.2 Hz), 7.40—7.81 (8H, m), 7.82 (1H, s). IR (Nujol): 3384, 2212 cm^{-1}. *Anal.* Calcd for $C_{23}H_{21}N_5$: C, 75.18; H, 5.76; N, 19.06. Found: C, 75.37; H, 5.92; N, 19.08.

4′-[(3-Ethyl-5-methylpyrazolo[1,5-*a*]pyrimidin-7-yl)aminomethyl]-biphenyl-2-carbonitrile (**10g**): Colorless needles (66%). mp 120—121 °C. ^{1}H-NMR ($CDCl_3$) *δ*: 1.32 (3H, t, *J*=7.6 Hz), 2.51 (3H, s), 2.71 (2H, q, *J*=7.6 Hz), 4.66 (2H, d, *J*=6.0 Hz), 5.82 (1H, s), 6.65 (1H, t, *J*=6.0 Hz), 7.41—7.52 (3H, m), 7.48, 7.57 (2H×2, ABq, *J*=8.4 Hz), 7.62—7.80 (1H, m), 7.85 (1H, s). IR (Nujol): 2220, 1623 cm^{-1}. *Anal.* Calcd for $C_{23}H_{21}N_5$: C, 75.18; H, 5.76; N, 19.06. Found: C, 75.31; H, 5.92; N, 19.07.

4′-[(3,5-Diethylpyrazolo[1,5-*a*]pyrimidin-7-yl)aminomethyl]biphenyl-2-carbonitrile (**10h**): Colorless prisms (75%). mp 110—112 °C. ^{1}H-NMR ($CDCl_3$) *δ*: 1.30 (3H, t, *J*=7.6 Hz), 1.32 (3H, t, *J*=7.6 Hz), 2.76 (2H, q, *J*=7.6 Hz), 2.81 (2H, q, *J*=7.6 Hz), 4.67 (2H, d, *J*=6.0 Hz), 5.83 (1H, s), 6.64 (1H, t, *J*=6.0 Hz), 7.41—7.60 (6H, m), 7.62—7.70 (1H, m), 7.75—7.80 (1H, m), 7.85 (1H, s). IR (Nujol): 3216, 2220, 1621 cm^{-1}. *Anal.* Calcd for $C_{24}H_{23}N_5$: C, 75.56; H, 6.08; N, 18.36. Found: C, 75.64; H, 6.13; N, 18.35

4′-[(5-Ethyl-3-propylpyrazolo[1,5-*a*]pyrimidin-7-yl)aminomethyl]-biphenyl-2-carbonitrile (**10i**): A colorless amorphous powder (51%). ^{1}H-NMR ($CDCl_3$) *δ*: 1.00 (3H, t, *J*=7.4 Hz), 1.30 (3H, t, *J*=7.6 Hz), 1.73 (2H, m), 2.75 (2H, t, *J*=7.2 Hz), 2.75 (2H, q, *J*=7.6 Hz), 4.66 (2H, d, *J*=6.0 Hz), 5.82 (1H, s), 6.64 (1H, t, *J*=6.0 Hz), 7.41—7.60 (6H, m), 7.61—7.70 (1H, m), 7.75—7.80 (1H, m), 7.83 (1H, s).

4′-[(5-Ethyl-3-phenylpyrazolo[1,5-*a*]pyrimidin-7-yl)aminomethyl]-biphenyl-2-carbonitrile (**10j**): A colorless amorphous powder (86%). ^{1}H-NMR ($CDCl_3$) *δ*: 1.36 (3H, t, *J*=7.5 Hz), 2.82 (2H, q, *J*=7.5 Hz), 4.68 (2H, d, *J*=5.8 Hz), 5.92 (1H, s), 6.72 (1H, t, *J*=5.8 Hz), 7.21—8.13 (13H, m).

4′-[(5-Ethyl-3-methoxypyrazolo[1,5-*a*]pyrimidin-7-yl)aminomethyl]-biphenyl-2-carbonitrile (**10k**): A colorless amorphous powder (75%). ^{1}H-NMR ($CDCl_3$) *δ*: 1.30 (3H, t, *J*=7.7 Hz), 2.76 (2H, q, *J*=7.7 Hz), 4.00 (3H, s), 4.67 (2H, d, *J*=6.0 Hz), 5.82 (1H, s), 6.62 (1H, t, *J*=6.0 Hz), 7.40—7.80 (8H, m), 7.70 (1H, s).

4′-[(3-Chloro-5-ethylpyrazolo[1,5-*a*]pyrimidin-7-yl)aminomethyl]-biphenyl-2-carbonitrile (**10l**): Yellow crystals (87%). mp 186.5—187.5 °C. ^{1}H-NMR ($CDCl_3$) *δ*: 1.32 (3H, t, *J*=7.4 Hz), 2.81 (2H, q, *J*=7.4 Hz), 4.68 (2H, d, *J*=5.8 Hz), 6.68 (1H, t, *J*=5.8 Hz), 7.26 (1H, s), 7.42—7.80 (8H, m), 7.92 (1H, s). IR (Nujol): 3388, 2212, 1617 cm^{-1}. *Anal.* Calcd for $C_{22}H_{18}ClN_5$: C, 68.13; H, 4.68; Cl, 9.14; N, 18.06. Found: C, 68.04; H, 4.78; Cl, 9.39; N, 17.81.

Ethyl 7-[(2′-Cyanobiphenyl-4-yl)methylamino]-5-ethylpyrazolo[1,5-*a*]-pyrimidine-3-carboxylate (**10m**): A colorless powder (67%). mp 155—156 °C. ^{1}H-NMR ($CDCl_3$) *δ*: 1.34 (3H, t, *J*=7.6 Hz), 1.41 (3H, t, *J*=7.2 Hz), 2.87 (2H, q, *J*=7.6 Hz), 4.40 (2H, q, *J*=7.2 Hz), 4.68 (2H, d, *J*=5.8 Hz), 6.05 (1H, s), 6.76 (1H, t, *J*=5.8 Hz), 7.42—7.84 (8H, m), 8.41 (1H, s). IR (Nujol): 3352, 2218, 1695 cm^{-1}. *Anal.* Calcd for $C_{25}H_{23}N_5O_2 \cdot 0.3H_2O$: C, 69.69; H, 5.52; N, 16.25. Found: C, 69.70; H, 5.76; N, 15.98.

The Pyrazolo[1,5-*a*]pyrimidin-7-yl-[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl-methyl]amine derivatives (**11**, **15**, **16**, **19**, **22**, **25**) were synthesized according to the procedure described for **5a** from corresponding cyano derivatives. Physical data are listed in Tables 5 and 6.

4′-[(5-Chloropyrazolo[1,5-*a*]pyrimidin-7-yl)aminomethyl]biphenyl-2-carbonitrile (13) The title compound was prepared from **12** and 2-cyano-4′-(aminomethyl)biphenyl according to the procedure described in the preparation of **10a** as colorless prisms. mp 152—153 °C. ^{1}H-NMR ($CDCl_3$) *δ*: 4.66 (2H, d, *J*=6.0 Hz), 6.00 (1H, s), 6.47 (1H, d, *J*=2.2 Hz), 6.94 (1H, t, *J*=6.0 Hz), 7.42—7.81 (8H, m), 7.99 (1H, d, *J*=2.2 Hz). IR (Nujol): 3435, 2223, 1608 cm^{-1}. *Anal.* Calcd for $C_{20}H_{14}ClN_5 \cdot 0.1H_2O$: C, 66.43; H, 3.96; Cl, 9.80; N, 19.37. Found: C, 66.45; H, 4.12; Cl, 9.87; N, 19.28.

4′-[(Pyrazolo[1,5-*a*]pyrimidin-7-yl)aminomethyl]biphenyl-2-carbonitrile (14) A mixture of **13** (210 mg, 0.58 mmol), ammonium formate (55 mg, 0.87 mmol) and 5% palladium on carbon (60 mg) in toluene (2 ml) was heated under reflux for 4 h and the mixture was filtered. The filtrate was evaporated *in vacuo* to give **14** (160 mg) as white crystals (85%). mp 171—172 °C. ^{1}H-NMR ($CDCl_3$) *δ*: 4.70 (2H, d, *J*=5.8 Hz), 5.98 (1H, d, *J*=5.2 Hz), 6.55 (1H, d, *J*=2.2 Hz), 6.87 (1H, br), 7.46—7.80 (8H, m), 8.03 (1H, d, *J*=2.2 Hz), 8.24 (1H, d, *J*=5.2 Hz). IR (Nujol): 3343, 2222, 1621, 1588 cm^{-1}. *Anal.* Calcd for $C_{20}H_{15}N_5 \cdot 0.4H_2O$: C, 72.23; H, 4.79; N, 21.06. Found: C, 72.34; H, 4.76; N, 20.76.

***N*-(5-Chloropyrazolo[1,5-*a*]pyrimidin-7-yl)-*N*-(2′-cyanobiphenyl-4-ylmethyl)carbamic Acid *tert*-Butyl Ester (17)** A mixture of **13** (1.8 g, 5 mmol), di-*tert*-butyldicarbonate ($(Boc)_2O$) (1.2 g, 5.5 mmol) and *N*,*N*-dimethylaminopyridine (DMAP) (733 mg, 6 mmol) in dioxane was stirred for 16 h at room temperature. The solvent was evaporated *in vacuo*, and the resulting mixture was poured into aqueous $NaHCO_3$ solution and extracted with three 30 ml portions of CH_2Cl_2. The combined extracts were washed with water (30 ml) and saturated brine and then dried ($MgSO_4$). The solvent was evaporated *in vacuo* and the residue was purified by flash chromatography (CH_2Cl_2 : CH_3CN=40 : 1) to give **17** as white prisms (93%). mp 162—163 °C. ^{1}H-NMR ($CDCl_3$) *δ*: 1.40 (9H, s), 5.12 (2H, s), 6.65 (1H, s), 6.68 (1H, d, *J*=2.2 Hz), 7.36—7.78 (8H, m), 8.17 (1H, d, *J*=2.2 Hz). IR (Nujol): 3158, 2219, 1718, 1616 cm^{-1}. *Anal.* Calcd for $C_{20}H_{15}N_5 \cdot 0.4H_2O$: C, 72.23; H, 4.79; N, 21.06. Found: C, 72.34; H, 4.76; N, 20.76.

4′-[(5-Methoxypyrazolo[1,5-*a*]pyrimidin-7-yl)aminomethyl]biphenyl-2-carbonitrile (18a) A solution of **17** (600 mg, 1.67 mmol) and 0.5 N NaOMe (4.68 ml, 2.34 mmol) in THF (4 ml) and MeOH (5 ml) was stirred for 1 h at 70 °C. The mixture was poured into CH_2Cl_2, washed with water and saturated brine, and then dried ($MgSO_4$). The solvent was evaporated *in vacuo* and the residue was recrystallized from acetone–*n*-hexane to give 514 mg of Boc intermediate as white prisms (87%). mp 164—165 °C. ^{1}H-NMR ($CDCl_3$) *δ*: 1.40 (9H, s), 3.97 (3H, s), 5.06 (2H, s), 6.13 (1H, s), 6.41 (1H, d, *J*=2.2 Hz), 7.37—7.78 (8H, m), 8.01 (1H, d, *J*=2.2 Hz). IR (Nujol): 2226, 1718, 1640, 1597 cm^{-1}. *Anal.* Calcd for $C_{26}H_{25}N_5O_3$: C, 68.56; H, 5.53; N, 15.37. Found: C, 68.71; H, 5.67; N, 15.35.

A solution of Boc intermediate (440 mg, 0.966 mmol) in trifluoroacetic acid (TFA) (2.5 ml) and CH_2Cl_2 (5 ml) was stirred for 30 min in an ice bath. The solvent was evaporated *in vacuo*, and the resultant mixture was poured into diluted $NaHCO_3$ solution and extracted with three 30 ml portions of CH_2Cl_2. The combined extracts were washed with water (30 ml) and saturated brine and then dried ($MgSO_4$). The solvent was evaporated *in vacuo* and the residue was recrystallized from CH_2Cl_2–EtOH to give 330 mg of **18a** as colorless needles (96%). mp 158—159 °C. ^{1}H-NMR ($CDCl_3$) *δ*: 3.95

Table 5. Physical Data for Pyrazolo[1,5-*a*]pyrimidines **11**, **15**, **16**, **19**, **22** and **25**

Compd.	Yield (%)	mp (°C)	Formula	Analysis Calcd (Found)			IR (cm^{-1})
				C	H	N	
11a	19	243—245	$C_{21}H_{18}N_8 \cdot 1.3H_2O$	62.15 (62.38	5.12 5.08	27.61 27.34)	3525, 3100, 1620
11b	49	211—213	$C_{22}H_{20}N_8$	66.65 (66.52	5.08 5.21	28.26 28.01)	3282, 2408
11c	57	230—232	$C_{23}H_{22}N_8$	67.30 (67.25	5.40 5.54	27.30 27.09)	3282, 2408
11d	62	218—222	$C_{26}H_{20}N_8$	70.26 (70.00	4.54 4.54	25.21 25.21)	
11e	32	157—159	$C_{22}H_{20}N_8 \cdot 0.5H_2O$	65.17 (65.24	5.22 5.38	27.64 27.62)	3300, 1666
11f	48	168—170	$C_{23}H_{22}ClN_8 \cdot 0.25$ MeOH $\cdot 1.8 H_2O$	61.93 (62.30	5.95 5.54	24.85 24.39)	3478, 3396, 2666
11g	59	172—175	$C_{23}H_{22}N_8 \cdot 1.0$EtOH	65.77 (65.65	6.18 6.22	24.54 24.58)	3101, 1663, 1611
11h	77	143—145	$C_{24}H_{24}N_8 \cdot 0.5$EtOH $\cdot 0.5H_2O$	65.77 (65.92	6.18 6.28	24.54 24.16)	3334, 3202, 1619
11i	55	139—141	$C_{25}H_{26}N_8 \cdot 1.0$EtOH	66.92 (66.83	6.66 6.69	23.21 23.07)	3339, 3210, 1621
11j	64	Amorphous	$C_{28}H_{24}N_8 \cdot 0.6H_2O$	69.58 (69.41	5.26 5.38	23.18 23.27)	
11k	66	216—217	$C_{23}H_{22}N_8O \cdot 0.2$EtOH $\cdot 0.2H_2O$	63.98 (63.89	5.42 5.34	25.51 25.77)	
11l	63	227—229	$C_{22}H_{19}ClN_8 \cdot 0.6$MeOH $\cdot 0.9H_2O$	58.20 (58.39	5.01 4.67	24.02 23.89)	3248, 1622, 1586
11m	48	250—252	$C_{25}H_{24}N_8O_2$	64.09 (63.97	5.16 5.20	23.92 23.70)	3336, 1702
15	28	151—155	$C_{20}H_{16}N_8 \cdot 0.55$MeOH	63.94 (63.85	4.75 4.66	29.03 29.22)	3396, 1617, 1586
16	62	138—144	$C_{20}H_{15}ClN_8 \cdot 0.5$MeOH	58.78 (58.63	4.09 3.96	26.75 26.70)	2922, 2853, 1619, 1607, 1589
19a	63	250—252	$C_{21}H_{18}N_8O$	63.30 (63.34	4.55 4.69	28.12 27.91)	3401, 1634, 1582
19b	77	234—235	$C_{22}H_{20}N_8O$	64.07 (64.21	4.89 4.98	27.17 26.93)	3368, 1633, 1579
19c	76	209—210	$C_{21}H_{18}N_8S$	60.85 (60.89	4.38 4.54	27.63 27.99)	3400, 1617, 1580
19d	60	215—216	$C_{22}H_{21}N_9 \cdot 0.5$EtOH	63.58 (63.34	5.56 5.61	29.01 28.72)	3313, 1656, 1630, 1578
22a	22	Amorphous	$C_{22}H_{19}N_7 \cdot 0.35$ dioxane $\cdot 0.25H_2O$	67.44 (67.17	5.39 5.46	23.52 23.49)	3434, 1622
22b	34	Amorphous	$C_{23}H_{21}N_7 \cdot 0.5$ dioxane $\cdot 0.6H_2O$	66.68 (66.77	5.86 5.98	21.77 21.56)	3432, 1623, 1526
25a	84	114—117	$C_{21}H_{17}N_7O \cdot 1.1$MeOH	63.40 (63.13	5.15 5.24	23.42 23.45)	3411, 1638
25b	17	235—236	$C_{21}H_{17}N_7S \cdot 0.7H_2O$	61.21 (61.53	4.50 4.49	23.79 23.57)	3433, 1610
25c	54	136—140	$C_{22}H_{20}N_8 \cdot 0.8$ benzene	70.26 (69.97	5.46 5.55	24.28 24.21)	3430, 1634

(3H, s), 4.61 (2H, d, J=6.0 Hz), 5.44 (1H, s), 6.28 (1H, d, J=2.2 Hz), 6.67 (1H, t, J=6.2 Hz), 7.42—7.80 (8H, m), 7.89 (1H, d, J=2.0 Hz). IR (Nujol): 3300, 3120, 2226, 1636, 1591 cm^{-1}. *Anal.* Calcd for $C_{21}H_{17}N_5O$: C, 70.97; H, 4.82; N, 19.70. Found: C, 71.10; H, 5.02; N, 19.69.

4′-[(5-Ethoxypyrazolo[1,5-*a*]pyrimidin-7-yl)aminomethyl]biphenyl-2-carbonitrile (18b) A solution of **17** (600 mg, 1.67 mmol) and 0.66 N NaOEt (3.55 ml, 2.34 mmol) in THF (4 ml) and EtOH (6.5 ml) was stirred for 0.5 h at 70 °C. The mixture was poured into CH_2Cl_2, washed with water (30 ml) and saturated brine and then dried ($MgSO_4$). The solvent was evaporated *in vacuo* and the residue was recrystallized from acetone–*n*-hexane to give 571 mg of Boc intermediate as colorless prisms (93%). mp 152—153 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.40 (9H, s), 1.39 (3H, t, J=7.4 Hz), 4.40 (2H, q, J=7.4 Hz), 5.06 (2H, s), 6.14 (1H, s), 6.38 (1H, d, J=2.2 Hz), 7.38—7.78 (8H, m), 8.00 (1H, d, J=2.0 Hz). IR (Nujol): 2220, 1718, 1649 cm^{-1}. *Anal.* Calcd for $C_{27}H_{27}N_5O_3$: C, 68.93; H, 5.78; N, 14.89. Found: C, 68.75; H, 5.95; N, 14.84.

The title compound was prepared according to the procedure described for the preparation of **18a** (96%). mp 120—121 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.38 (3H, t, J=7.0 Hz), 4.39 (2H, q, J=7.0 Hz), 4.60 (2H, d, J=5.8 Hz), 5.44 (1H, s), 6.26 (1H, d, J=2.2 Hz), 6.64 (1H, t, J=5.4 Hz), 7.40—7.80 (8H, m), 7.88 (1H, d, J=2.0 Hz). IR (Nujol): 3294, 2221, 1634, 1591 cm^{-1}. *Anal.* Calcd for $C_{22}H_{19}N_5O$: C, 71.53; H, 5.18; N, 19.00. Found: C, 71.53; H, 5.32; N, 18.85.

4′-[(5-Methylthiopyrazolo[1,5-*a*]pyrimidin-7-yl)aminomethyl]-biphenyl-2-carbonitrile (18c) A solution of **17** (300 mg, 0.692 mmol) and sodium thiomethoxide (59 mg, 0.789 mmol) in THF (2 ml) and 2-propanol (7 ml) was stirred for 2 h at 55 °C. The mixture was poured into CH_2Cl_2, washed with water (30 ml) and saturated brine and then dried ($MgSO_4$). The solvent was evaporated *in vacuo* and the residue was recrystallized from ether–*n*-hexane to give 283 mg of Boc intermediate as colorless crystalline (92%). mp 140—141 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.39 (9H, s), 5.05 (2H, s), 6.43 (1H, s), 6.53 (1H, d, J=1.8 Hz), 7.39—7.80 (8H, m), 8.04 (1H, d,

Table 6. ^{1}H-NMR Spectral Data for Pyrazolo[1,5-*a*]pyrimidines **11**, **15**, **16**, **19**, **22** and **25**

Compd.	Solvent	Chemical shift (δ)
11a	DMSO-d_6	2.33 (3H, s), 4.59 (2H, m), 6.01 (1H, s), 6.28 (1H, d, J=2.4 Hz), 7.06 (2H, m), 7.33 (2H, m), 7.49—7.70 (4H, m), 8.03 (1H, d, J=2.4 Hz), 8.48(1H, m)
11b	DMSO-d_6	1.18 (3H, t, J=7.6 Hz), 2.60 (2H, q, J=7.6 Hz), 4.60 (2H, d, J=6.6 Hz), 6.02 (1H, s), 6.31 (1H, d, J=2.2 Hz), 7.06—7.35 (4H, m), 7.47—7.74 (4H, m), 8.04 (1H, d, J=2.2 Hz)
11c	DMSO-d_6	0.87 (3H, t, J=7.2 Hz), 1.64 (2H, m), 2.48—2.58 (2H, m), 4.60 (2H, m), 6.02 (1H, s), 6.30 (1H, d, J=2.4 Hz), 7.06 (2H, m), 7.34 (2H, m), 7.50—7.70(4H, m), 8.04 (1H, d, J=2.4 Hz)
11d	DMSO-d_6	4.76 (2H, d, J=6.4 Hz), 6.49 (1H, d, J=2.4 Hz), 6.67 (1H, s), 7.05—7.09 (2H, m), 7.38—7.66 (8H, m), 8.05—8.10 (3H, m), 8.13 (1H, d, J=2.4 Hz), 8.67 (1H, m)
11e	DMSO-d_6	2.17 (3H, s), 2.34 (3H, s), 4.58 (2H, d, J=6.2 Hz), 5.95 (1H, s), 7.05, 7.31 (each 2H, ABq, J=7.8 Hz), 7.46—7.74 (4H, m), 7.89 (1H, s), 8.37 (1H, t, J=6.2 Hz)
11f	DMSO-d_6	1.18 (3H, t, J=7.6 Hz), 2.19 (3H, s), 2.60 (2H, q, J=7.6 Hz), 4.58 (2H, d, J=6.4 Hz), 5.95 (1H, s), 7.05, 7.31 (each 2H, ABq, J=8.0 Hz), 7.43—7.69 (4H, m), 7.89 (1H, s), 8.32 (1H, t, J=6.4 Hz)
11g	DMSO-d_6	1.05 (3H, t, J=7.6 Hz), 2.33 (3H, s), 2.64 (2H, q, J=7.6 Hz), 4.57 (2H, d, J=6.6 Hz), 5.94 (1H, s), 7.05, 7.31 (each 2H, ABq, J=8.2 Hz), 7.51—7.71 (4H, m), 7.92 (1H, s), 8.37 (1H, t, J=6.6 Hz)
11h	$CDCl_3$+CD_3OD	1.29 (3H, t, J=7.6 Hz), 1.30 (3H, t, J=7.6 Hz), 2.73 (2H, q, J=7.6 Hz), 2.78 (2H, q, J=7.6 Hz), 4.57 (2, s), 5.84 (1H, s), 7.15, 7.31 (each 2H, ABq, J=8.4 Hz), 7.46—7.66 (3H, m), 7.77—7.81 (1H, m), 7.84 (1H, s)
11i	$CDCl_3$+CD_3OD	0.99 (3H, t, J=7.6 Hz), 1.21 (3H, t, J=7.0 Hz), 1.70 (2H, m), 2.71 (2H, t, J=7.4 Hz), 2.73 (2H, q, J=7.6 Hz), 4.58 (2H, s), 5.84 (1H, s), 7.16, 7.32 (each 2H, ABq, J=8.4 Hz), 7.43—7.66(3H, m), 7.75—7.79(1H, m), 7.83(1H, s)
11j	$CDCl_3$+CD_3OD	1.35 (3H, t, J=7.6 Hz), 2.80 (2H, q, J=7.6 Hz), 4.62 (2H, s), 5.94 (1H, s), 7.15—8.06 (13H, m), 8.28 (1H, s)
11k	$CDCl_3$+CD_3OD	1.28 (3H, t, J=7.4 Hz), 2.72 (2H, t, J=7.4 Hz), 3.97 (3H, s), 4.61 (2H, s), 5.83 (1H, s), 7.16, 7.32 (each 2H, ABq, J=8.4 Hz), 7.48—7.74 (4H, m), 7.81 (1H, s)
11l	$CDCl_3$+CD_3OD	1.31 (3H, t, J=7.6 Hz), 2.78 (2H, q, J=7.6 Hz), 4.61 (2H, s), 5.91 (1H, s), 7.15—7.79 (9H, m), 7.93 (1H, s)
11m	DMSO-d_6	1.21 (3H, t, J=7.6 Hz), 1.29 (3H, t, J=7.0 Hz), 2.67 (2H, q, J=7.6 Hz), 4.24 (2H, q, J=7.0 Hz), 4.63 (2H, d, J=6.4 Hz), 6.30 (1H, s), 7.07, 7.35 (each 2H, ABq, J=8.2 Hz), 7.47—7.73 (4H, m), 8.45 (1H, s), 8.82 (1H, t, J=6.4 Hz)
15	$CDCl_3$+DMSO-d_6	4.61 (2H, d, J=6.0 Hz), 5.96 (1H, d, J=5.4 Hz), 6.47 (1H, d, J=2.2 Hz), 7.14, 7.29 (each 2H, ABq, J=8.2 Hz), 7.44—7.75 (4H, m), 8.00 (1H, d, J=2.2 Hz), 8.16 (1H, d, J=5.4 Hz)
16	DMSO-d_6	4.64 (2H, d, J=6.2 Hz), 6.22 (1H, s), 6.43 (1H, d, J=2.4 Hz), 7.07, 7.33 (each 2H, ABq, J=8.4 Hz), 7.53—7.70 (4H, m), 8.16 (1H, d, J=2.4 Hz), 9.02 (1H, t, J=6.2 Hz)
19a	DMSO-d_6	3.80 (3H, s), 4.55 (2H, d, J=6.4 Hz), 5.48 (1H, s), 6.21 (1H, d, J=2.2 Hz), 7.06, 7.32 (each 2H, ABq, J=8.0 Hz), 7.52—7.72 (4H, m), 7.97 (1H, d, J=2.4 Hz), 8.24 (1H, t, J=6.6 Hz)
19b	DMSO-d_6	1.27 (3H, t, J=7.0 Hz), 4.26 (2H, q, J=7.0 Hz), 4.64 (2H, d, J=6.6 Hz), 5.50 (1H, s), 6.18—6.20 (1H, m), 7.06, 7.32 (each 2H, ABq, J=7.8 Hz), 7.45—7.98 (4H, m), 8.50 (1H, t, J=6.8 Hz)
19c	DMSO-d_6	2.47 (3H, s), 4.59 (2H, d, J=6.4 Hz), 5.98 (1H, s), 6.31 (1H, d, J=2.0 Hz), 7.07, 7.33 (each 2H, ABq, J=8.2 Hz), 7.52—7.72 (4H, m), 8.02 (1H, d, J=1.8 Hz), 8.53 (1H, t, J=6.6 Hz)
19d	DMSO-d_6	2.97 (6H, s), 4.55 (2H, d, J=6.8 Hz), 5.33 (1H, s), 5.88 (1H, d, J=1.8 Hz), 7.06, 7.35 (each 2H, ABq, J=8.2 Hz), 7.52—7.71 (4H, m), 7.78 (1H, d, J=2.4 Hz), 8.00 (1H, t, J=6.6 Hz)
22a	$CDCl_3$	1.27 (3H, t, J=7.6 Hz), 2.75 (2H, q, J=7.6 Hz), 4.39 (2H, s), 6.37 (1H, s), 6.49 (1H, d, J=2.4 Hz), 7.06, 7.19 (each 2H, ABq, J=8.2 Hz), 7.40—7.67 (3H, m), 7.93 (1H, d, J=2.4 Hz), 8.00—8.05 (1H, m)
22b	$CDCl_3$	1.28 (3H, t, J=7.6 Hz), 2.19 (3H, s), 2.73 (2H, q, J=7.6 Hz), 4.32 (2H, s), 6.23 (1H, s), 6.99, 7.13 (each 2H, ABq, J=8.2 Hz), 7.41—7.67 (4H, m), 8.00—8.05 (1H, m)
25a	$CDCl_3$	3.97 (3H, s), 4.34 (2H, s), 6.06 (1H, s), 6.39 (1H, d, J=2.0 Hz), 7.14, 7.26 (each 2H, ABq, J=8.4 Hz), 7.42—7.66 (3H, m), 7.89 (1H, d, J=2.0 Hz), 8.06—8.10 (1H, m)
25b	DMSO-d_6	2.55 (3H, s), 4.41 (2H, s), 6.57 (1H, d, J=2.2 Hz), 6.71 (1H, s), 7.05, 7.34 (each 2H, ABq, J=8.0 Hz), 7.42—7.72 (4H, m), 8.13 (1H, d, J=2.2 Hz)
25c	DMSO-d_6	3.08 (6H, s), 4.33 (2H, s), 6.04 (1H, d, J=2.2 Hz), 6.43 (1H, s), 7.04, 7.35 (each 2H, ABq, J=8.2 Hz), 7.52—7.72 (4H, m), 7.84 (1H, d, J=2.2 Hz)

J=1.8 Hz). IR (Nujol): 2221, 1728, 1626, 1594 cm^{-1}. *Anal.* Calcd for $C_{26}H_{25}N_5O_2S$: C, 66.22; H, 5.34; N, 14.85; S, 6.80. Found: C, 66.25; H, 5.43; N, 14.74; S, 6.71.

The title compound was prepared according to the procedure described for the preparation of **18a** (quant.). mp 158—160 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.58 (3H, s), 5.86 (1H, s), 6.38 (1H, d, J=2.2 Hz), 6.66 (1H, t, J=6.2 Hz), 7.42—7.80 (8H, m), 7.92 (1H, d, J=2.2 Hz). IR (Nujol): 3267, 2225, 1619, 1586 cm^{-1}. *Anal.* Calcd for $C_{21}H_{17}N_5S$: C, 67.90; H, 4.61; N, 18.85; S, 8.43. Found: C, 68.13; H, 4.61; N, 18.85; S, 8.43.

4′-[(5-Dimethylaminopyrazolo[1,5-*a*]pyrimidin-7-yl)aminomethyl]-biphenyl-2-carbonitrile (18d) A solution of **17** (500 mg, 1.1 mmol) and 50% dimethylamine in H_2O solution (1.5 ml) in THF (2 ml) and MeOH (2.5 ml) was stirred for 3 h at 80 °C. The mixture was poured into CH_2Cl_2, washed with water (30 ml) and saturated brine and then dried ($MgSO_4$). The solvent was evaporated *in vacuo* and the residue was purified by flash chromatography (CH_2Cl_2 as an eluent) to give 469 mg of Boc intermediate as an amorphous (91%). ^{1}H-NMR ($CDCl_3$) δ: 1.41 (9H, s), 3.05 (6H, s), 5.01 (2H, s), 5.89 (1H, s), 6.16 (1H, d, J=1.8 Hz), 7.40—7.82 (8H, m), 7.90 (1H, d, J=1.8 Hz).

The title compound was prepared according to the procedure described for the preparation of **18a** (74%). mp 90—92 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.27 6H, s), 4.71 (2H, d, J=6.0 Hz), 5.06 (1H, s), 6.48 (1H, d, J=2.0 Hz), 7.44—7.80 (8H, m), 7.82 (1H, d, J=2.2 Hz). IR (Nujol): 3341, 2231, 1701, 1667, 1611 cm^{-1}. *Anal.* Calcd for $C_{22}H_{20}N_6 \cdot 2H_2CO_3$: C, 58.44; H, 4.76; N, 17.12. Found: C, 58.53; H, 4.91; N, 17.06.

4′-[(5-Ethylpyrazolo[1,5-*a*]pyrimidin-7-yl)methyl]biphenyl-2-carbonitrile (21a) To a suspension of zinc dust (activated with 1,2-dibromoethane and chlorotrimethylsilane; 1.63 g, 25 mmol) in THF (1.5 ml) at 0 °C was added dropwise a solution of 4-bromomethyl-2′-cyanobiphenyl (545 mg, 2 mmol) in THF (4 ml) over a period of 30 min. The resulting mixture was stirred for 1 h at 0 °C, then left standing for 1 h at 0 °C. The supernatant was transferred to a solution of **9b** (290 mg, 1.5 mmol) and tetrakis(triphenylphosphin)palladium(0) (55 mg, 0.05 mmol) in THF (2 ml), and heated under reflux for 1 h. The mixture was poured into saturated ammonium chloride solution and ice, and extracted with three 30 ml portions of EtOAc, then combined extracts were washed with water (20 ml) and saturated brine (20 ml) and then dried ($MgSO_4$). The solvent was evaporated *in vacuo* and the residue was purified by flash chromatography (toluene : EtOAc=20 : 1 as an eluent) to give **21a** (360 mg, 53%) as colorless prisms. mp 124—126 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.31 (3H, t, J=7.4 Hz), 2.81 (2H, q, J=7.4 Hz), 4.55 (2H, s), 6.38 (1H, s), 6.64 (1H, d, J=2.4 Hz), 7.41—7.81 (8H, m), 8.13 (1H, d, J=2.4 Hz). *Anal.* Calcd for $C_{22}H_{18}N_4$: C, 78.08; H, 5.36; N, 16.56. Found:

C, 78.05; H, 5.54; N, 16.21.

4′-[(5-Ethyl-3-methylpyrazolo[1,5-*a*]pyrimidin-7-yl)methyl]biphenyl-2-carbonitrile (**21b**): The title compound was prepared from **9f** according to the procedure described for the preparation of **21a** as a pale yellow amorphous powder (79%). ^{1}H-NMR ($CDCl_3$): 1.30 (3H, t, J=7.8 Hz), 2.39 (3H, s), 2.81 (2H, q, J=7.8 Hz), 4.51 (2H, s), 6.33 (1H, s), 7.41—7.80 (8H, m), 7.96 (1H, s). IR (Nujol): 2925, 2854, 2221, 1624, 1541 cm^{-1}. *Anal.* Calcd for $C_{23}H_{20}N_4$: C, 78.38; H, 5.72; N, 15.90. Found: C, 78.57; H, 5.94; N, 16.81.

4′-[(5-Chloropyrazolo[1,5-*a*]pyrimidin-7-yl)methyl]biphenyl-2-carbonitrile (23) To a suspension of zinc dust (activated with 1,2-dibromoethane and chlorotrimethylsilane; 330 mg, 5 mmol) in DMF (1.0 ml) at 0 °C was added dropwise a solution of 4′-bromomethyl-1,1′-biphenyl-2-carbonitrile (1.02 g, 3.75 mmol) in DMF (5 ml) over a period of 30 min. The resulting mixture was stirred for 1 h at 0 °C, then left standing for 1 h at 0 °C. The supernatant was transferred to a solution of **12** (376 mg, 2.0 mmol) and LiCl (206 mg, 41.39 mmol) in DMF (2 ml), and stirred for 1 h at room temperature. The mixture was poured into saturated ammonium chloride aqueous solution and ice, extracted with three 30 ml portions of EtOAc, and combined extracts were washed with water (20 ml) and saturated brine (20 ml) and then dried ($MgSO_4$). The solvent was evaporated *in vacuo* and the residue was purified by flash chromatography (toluene : EtOAc=20 : 1 as an eluent) to give 360 mg (52%) of **23** as colorless prisms: mp 154—155 °C; ^{1}H-NMR ($CDCl_3$) δ: 4.56 (2H, s), 6.49 (1H, s), 6.68 (1H, d, J=2.4 Hz), 7.42—7.82 (8H, m), 8.18 (1H, d, J=2.4 Hz); IR (Nujol): 2924, 2855, 2226, 1606, 1540 cm^{-1}. *Anal.* Calcd for $C_{20}H_{13}ClN_4$: C, 69.67; H, 3.80; Cl, 10.28; N, 16.25. Found: C, 69.68; H, 3.94; Cl, 10.14; N, 16.31.

4′-[(5-Methoxypyrazolo[1,5-*a*]pyrimidin-7-yl)methyl]biphenyl-2-carbonitrile (24a) A mixture of **23** (250 mg, 0.73 mmol) and 1 N NaOMe methanol solution (1 ml, 1 mmol) in methanol (15 ml) was heated under reflux for 5 h and the solvent was evaporated *in vacuo*. The resulting residue was poured into ice water (10 ml) then extracted with three 30 ml portions of EtOAc. The combined extracts were washed with water (20 ml) and saturated brine (20 ml) and then dried ($MgSO_4$). The solvent was evaporated *in vacuo* and the residue was recrystallized from methanol to give **24a** (219 mg, 88%) as colorless prisms. mp 132—133 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.97 (3H, s), 4.48 (2H, s), 5.99 (1H, s), 6.42 (1H, d, J=2.4 Hz), 7.41—7.81 (8H, m), 8.02 (1H, d, J=2.4 Hz). IR (Nujol): 3433, 2223, 1643 cm^{-1}. *Anal.* Calcd for $C_{21}H_{16}N_4O$: C, 74.10; H, 4.74; N, 16.46. Found: C, 73.83; H, 4.86; N, 16.38.

4′-[(5-Methylthiopyrazolo[1,5-*a*]pyrimidin-7-yl)methyl]biphenyl-2-carbonitrile (**24b**): The title compound was prepared from **23** and sodium thiomethoxide according to the procedure described for the preparation of **18c** as pale pink amorphous (72%). ^{1}H-NMR ($CDCl_3$) δ: 2.59 (3H, s), 4.49 (2H, s), 6.30 (1H, s), 6.54 (1H, d, J=1.4 Hz), 7.43—7.80 (8H, m), 8.05 (1H, d, J=1.4 Hz).

4′-[(5-Dimethylaminopyrazolo[1,5-*a*]pyrimidin-7-yl)methyl]biphenyl-2-carbonitrile (**24c**): The title compound was prepared from **23** and dimethylamine (50% in water) according to the procedure described for the preparation of **18d** as colorless prisms (86%). mp 141—142 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.09 (6H, s), 4.46 (2H, s), 5.90 (1H, s), 6.18 (1H, d, J=2.4 Hz), 7.41—7.80 (8H, m), 7.91 (1H, d, J=2.4 Hz). IR (Nujol): 3435, 2221, 1634 cm^{-1}. *Anal.* Calcd for $C_{22}H_{19}N_5$: C, 74.77; H, 5.42; N, 19.82. Found: C, 74.67; H, 5.51; N, 19.67.

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