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1-Alkyl-3-amino-5-aryl-1*H*-[1,2,4]triazoles: Novel Synthesis Via Cyclization of *N*-Acyl-*S*-methylisothioureas with Alkylhydrazines and Their Potent Corticotropin-Releasing Factor-1 (CRF_1) Receptor Antagonist Activities

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Abstract—Cyclizations of alkylhydrazines with *N*-acyl-*S*-methylisothioureas, readily synthesized from acyl chlorides, sodium thioisocyanate, dialkylamines then methyl iodide in a one-pot reaction, gave 1-alkyl-3-dialkylamino-5-phenyltriazoles **7** as major products. The regioisomers were assigned through the use of NOE NMR experiments. While bearing a *N*-bis(cyclopropyl)methyl-*N*-propylamino group, this series of compounds shows very good binding affinity on the human CRF_1 receptor. Among them, 1-methyl-3-[*N*-bis(cyclopropyl)methyl-*N*-propylamino]-5-(2,4-dichlorophenyl)-1*H*-[1,2,4]triazole **7a** had the best binding affinity for the CRF_1 receptor ($K_i = 9$ nM).

Corticotrophin-releasing factor (CRF), a 41-amino acid peptide, is the key regulator of an organism's response to stress as it mediates the endocrine, autonomic, behavioral and immune effects to stressful stimuli. The activity of CRF in the pituitary is exerted through binding and activation to the CRF_1 receptor, a member of the seven-transmembrane G protein-coupled receptors, to release of ACTH and other proopiomelanocortin peptides.[1] Prolonged activation of brain CRF receptors is thought to be related to the psychological effects of stress leading to anxiety and depression. Therefore, blockage of CRF_1 receptor activation has been proposed as a novel approach for the treatment of these psychiatric disorders.[2]

Recent discovery of nonpeptide antagonists for CRF_1 receptor has demonstrated the success of this endeavor because several small molecules have been reported to have good CRF_1 receptor antagonistic activity.[3] For example, pyrrolo[2,3-*d*]pyrimidine (**1**, antalarmin)[4] and anilinopyrimidine (**2**, NBI 27914)[5] show good binding affinity as well as in vivo activity (Fig. 1). While all these compounds are comprised of a core heterocyclic ring incorporating amino, methyl and substituted aryl functionalities, the prototypical weak CRF_1 antagonist **3** has a relatively simple structure.[6] In an effort of searching for more novel structures based on this simple molecule we discovered the heterocyclic templates 1-alkyl-2-dialkylamino-5-phenyltriazoles (e.g., structure **4**), which have a topographical similarity to known CRF_1 receptor antagonists **3** (Fig. 1).[7] In this paper, we report the discovery of a novel cyclization for 1-alkyl-3-dialkylamino-5-aryltriazoles and the structure–activity relationship studies around this nucleus that led to a potent class of CRF_1 receptor antagonists.

For SAR purposes, we required a general synthetic method for 3-dialkylamino-5-aryltriazoles **7** that would be amenable to rapid preparation of a large number of analogues.[8] While the *N*-acyl-*N*′,*N*′-dialkylthioureas are well known and readily prepared from the corresponding acid chlorides, sodium or ammonium thioisocyanate and dialkylamines,[9] to our knowledge, neither their cyclization with alkylhydrazines,[10] nor conversion to the corresponding *S*-methylisothioureas is well documented (Table 1).[11] We found that treatment of *N*-acyl-*N*′,*N*′-dialkylthioureas **9** with methyl iodide and sodium carbonate in acetone gave the desired *N*-acyl-*N*′,*N*′-dialkyl-

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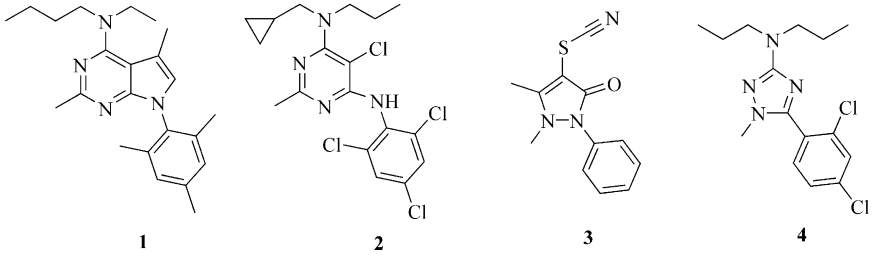
S-methylisothioureas **10** in quantitative yields. The isothioureas **10** were then subjected to a cyclization with hydrazine in refluxing dioxane to give the 3-dialkylamino-5-aryl-1*H*-[1,2,4]triazoles **11** in good yields.[12] When alkylhydrazines were used in the cyclization reactions, 1-alkyl-3-dialkylamino-5-aryl-1*H*-[1,2,4]triazoles **7** were obtained as the major products, although, in some cases, the isomeric 1-alkyl-3-aryl-5-dialkylamino-1*H*-[1,2,4]triazoles **12** and the corresponding desmethyl product **11** were also isolated as minor products. The mechanism for the formation of **11** from the alkylhydrazine is not clear, we speculated that the extra amount of alkylhydrazine in the reaction mixture attacks the alkyl group of the triazole **7** or **12** and dealkylated the product. This hypothesis, however, could not be confirmed since refluxing pure **7c** with methylhydrazine in dioxane did not give detectable amount of **11c** by mass spectrometry. The synthesis of the desired triazoles **7** is outlined in Scheme 1. Attempts to cyclize **10** with phenylhydrazine under similar conditions was not successful. Formation of **10** could also be accomplished from the relevant acid chloride and amine in a one-pot reaction. Thus, sequential treatment of a solution of sodium thiocyanate in acetone with an acid chloride, a secondary amine, then methyl iodide and sodium carbonate gave **10** in very good to excellent yields after a simple workup and purification.[13]

Alkylation of the 3-dialkylamino-5-aryl-1*H*-[1,2,4]triazoles **11** with alkyl halides in the presence of sodium hydride in dry THF afforded two regioisomers **7** and **12**, which were separated by chromatography on silica gel.[14] The regioisomer 1-alkyl-3-dialkylamino-5-aryl-1*H*-[1,2,4]triazole **7** was always the major product. The structures of these two regioisomers **7** and **12** were assigned based on NMR analysis and confirmed by NOE NMR experiments (Fig. 2).

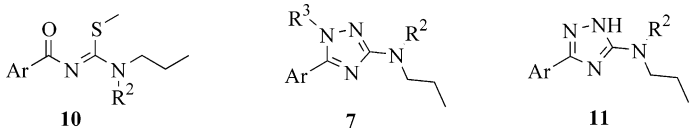
The CRF_1 receptor binding assay was performed with cloned human CRF_1 receptors expressed in CHO-cells using [^{125}I]o-CRF as the labeled ligand in a manner similar to the previously reported protocol[5] and the results are summarized in Table 2. The phenotypic compound in this series was the 1-methyl-3-{*N*-bis(cyclopropyl)methyl-*N*-propylamino}-5-(2,4-dichlorophenyl)-1*H*-[1,2,4]triazole **7a**, which was found to have good binding affinity for $hCRF_1$ receptor (K_i = 9 nM). Removal of the 1-methyl group resulted in almost 250-fold loss of activity (**11a**, 2.4 μM). Replacement of the 1-methyl with a larger group such as ethyl or allyl (**7b** and **7c**, K_i = 80 nM and inhibition = 77% at 10 μM, respectively) reduced the activity. Similar results were



1 **2** **3** **4**

Figure 1. Compounds **1** and **2** have been reported as potent CRF1 antagonists.

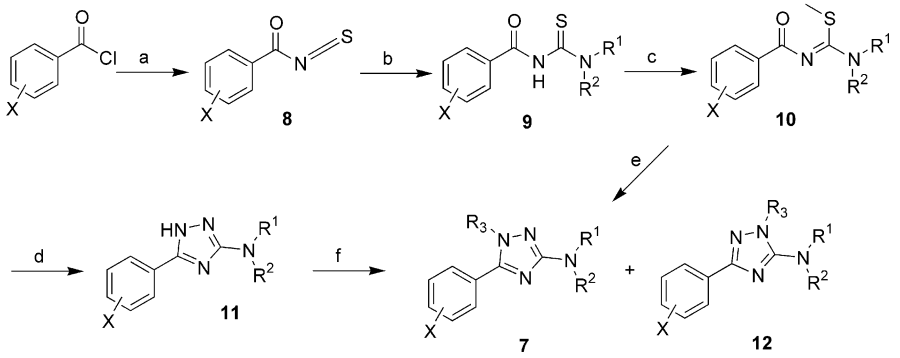
Table 1. Synthesis of *N*,*N*-dialkyl-*N*′-benzoyl-*S*-methylisothioureas **10** and their cyclizations with hydrazine and alkylhydrazines to triazoles **7** and **11**



10 **7** **11**

Entry	Ar	R^2	Yield[a]		R^3	Yield[b]	
			10	(%)		**7** or **11**	(%)
1	2,4-Dichlorophenyl	Bis(cyclopropane)methyl	**10a**	87	H	**11a**	90
2					Me	**7a**	65
3	2,4-Dichlorophenyl	Propyl	**10b**	92	H	**11c**	43[c]
4					Me	**7e**	35[d]
5					$HOCH_2CH_2$	**7q**	44
6	2,4,6-Trimethylphenyl	Bis(cyclopropane)methyl	**10c**	91	H	**11b**	78
7					Me	**7g**	52
8					CF_3CH_2	**7i**	56
9	2-Methoxy-4-chlorophenyl	Bis(cyclopropane)methyl	**10d**	85	Me	**7n**	50
10	6-Methoxynaphthyl	Cyclopropanemethyl	**10e**	99	H	**11d**	72
11					Me	**7r**	46[e]

[a]See a typical procedure in ref 12.
[b]See a typical procedure in ref 13.
[c]3-Methylthio-5-(2,4-dichlorophenyl)-1*H*-[1,2,4]triazole (48%) was also isolated.
[d]1-Methyl-3-methylthio-5-(2,4-dichlorophenyl)-1*H*-[1,2,4]triazole (42%) was also isolated.
[e]Isomeric 1-methyl-3-(6-methoxynaphthyl)-5-(*N*-cyclopropylmethyl-*N*-propylamino)-1*H*-[1,2,4]triazole **12b** isolated in 28% yield.



Scheme 1. Reagents and conditions: (a) $NaSCN/Me_2CO$; (b) R^1R^2NH/THF; (c) $MeI/Na_2CO_3/THF$; (d) $NH_2NH_2/EtOH$, reflux; (e) $R^3NHNH_2/EtOH$, reflux; (f) $R^3X/NaH/THF$.

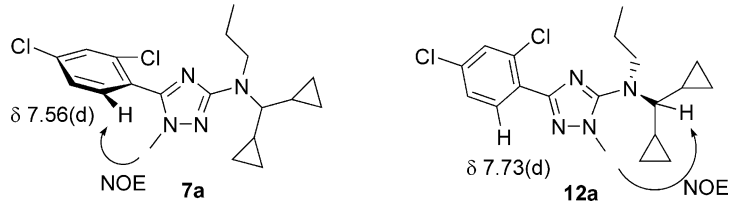
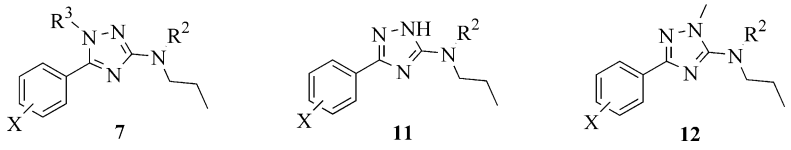


Figure 2. NOE was observed between 1-methyl and *ortho*-proton of phenyl group for **7a**, and between 1-methyl and *N*-methine group for **12a**. Chemical shift of *ortho*-proton of **12a** phenyl was more downfield due to extra deshielding effect from the triazole ring.

Table 2. Triazoles **7** and **11** and their $hCRF_1$ receptor binding data



Compd	X	R^2	R^3	K_i (nM)
7a	2,4-Cl	Bis(cyclopropane)methyl	Me	9.0 (±2.0)
7b	2,4-Cl	Bis(cyclopropane)methyl	Et	80 (±14)
7c	2,4-Cl	Bis(cyclopropane)methyl	Allyl	77%[a]
7d	2,4-Cl	Cyclopropanemethyl	Me	>10,000
7e	2,4-Cl	Propyl	Me	2600
7f	2,4-Cl	2-MeOPh	Me	3400
7g	2,4,6-Me	Bis(cyclopropane)methyl	Me	120 (±76)
7h	2,4,6-Me	Bis(cyclopropane)methyl	Et	310
7i	2,4,6-Me	Bis(cyclopropane)methyl	CF_3CH_2	1500
7j	2,4,6-Me	Bis(cyclopropane)methyl	Allyl	2200
7k	2,4-Me	Bis(cyclopropane)methyl	Me	72
7l	2-Me-4-Br	Bis(cyclopropane)methyl	Me	10 (±8)
7m	2-Me-4-Cl	Bis(cyclopropane)methyl	Me	22 (±4)
7n	2-MeO-4-Cl	Bis(cyclopropane)methyl	Me	26 (±15)
7o	4-Cl	Bis(cyclopropane)methyl	Me	33 (±5)
7p	2,4-Cl-5-F	Bis(cyclopropane)methyl	Me	15 (±13)
11a	2,4-Cl	Bis(cyclopropane)methyl	H	2400
11b	2,4,6-Me	Bis(cyclopropane)methyl	H	3200
12a	2,4-Cl	Bis(cyclopropane)methyl	Me	>10,000

[a]Percentage of inhibition at 10 μM.

obtained from the 2,4,6-trimethylphenyl analogues (**7g**–**7j** and **11b**). Replacement of the important bis(cyclopropyl)methyl group with either cyclopropylmethyl, propyl or 2-methoxyphenyl group[15] greatly decreased activity to micromolar range (**7d, 7e** and **7f**, $K_i \geq 10$ μM, 2.6 and 3.4 μM, respectively).

Next, the effect of the substitution on the phenyl ring was examined. The 2,4,6-trimethylanalogue **7g** was found to have a K_i of 120 nM affinity for the CRF_1 receptor, much less active than **7a**. Removal of 6-methyl from 2,4,6-trimethylphenyl of **7g** actually led to almost 2-fold increase in binding affinity (**7k**, $K_i = 72$ nM). Replacement of the 4-methyl with a bromine or chlorine atom of the 2,4,6-trimethylphenyl triazole **7g** resulted in over 7- or 3-fold increase in binding activity (**7l** and **7m**, $K_i = 10$ and 22 nM, respectively). Removal or replacement of the 2-chlorine of compound **7a** with a methoxy group afforded compounds **7o** or **7n**, which was about 3-fold less active. Finally, introducing a fluorine atom at

5-position of 2,4-dichlorophenyl group of **7a** had little effect on binding activity (**7q**, $K_i = 14$ nM). While **7a** showed very good binding affinity, its regioisomer **12a** had no activity at all. Compounds **7q**, **7r**, **11c**, **11d**, and **12b** (Table 1) were also inactive at 10 μM concentration. From these SAR data we conclude that the bis(cyclopropyl)methyl group on the 3-aminotriazole is required for high CRF_1 activity, and the small methyl group at 1-position of the triazole core is also very important.

In summary, a series of 1-methyl-3-[*N*-bis(cyclopropyl)methyl-*N*-propylamino]-5-aryl-1*H*-[1,2,4]triazoles exemplified by **7a**, **7l**, and **7p** were synthesized through a novel cyclization of *N*,*N*-dialkyl-*N*′-benzoyl-*S*-methylisothioureas with methylhydrazine. Moreover, compounds from this series were found to have good binding affinity for the CRF_1 receptor. The results of the SAR study suggest that the bis(cyclopropyl)methyl group on the 3-amino functionality of the triazole core structure is important for high CRF_1 receptor binding affinity. From these studies a number of 3-dialkylamino-5-aryltriazoles having high binding affinity for the CRF_1 receptor were characterized. Further studies detailing the SAR and the consequences of their antagonist effects towards the CRF_1 receptor in vitro and in vivo will be reported elsewhere.

References and Notes

1. Dieterich, K. D.; Lehnert, H.; De Souza, E. B. *Endocrinol. Diabetes* **1998**, *105*, 65.
2. Heit, S. O.; Michael, J.; Plotsky, P.; Nemeroff, C. B. *Neuroscientist* **1997**, *3*, 186.
3. For a recent review, see: Grigoriadis, D. E.; Haddach, M.; Ling, N.; Saunders, J. *Curr. Med. Chem.* **2001**, *1*, 63.
4. Chen, Y. L.; Mansbach, R. S.; Winter, S. M.; Brooks, E.; Collins, J.; Corman, M. L.; Dunaiskis, A. R.; Faraci, W. S.; Gallaschun, R. J.; Schmidt, A.; Schulz, D. W. *J. Med. Chem.* **1997**, *40*, 1749.
5. Chen, C.; Dagnino, R., Jr.; De Souza, E. B.; Grigoriadis, D. E.; Huang, C. Q.; Kim, K. I.; Liu, Z.; Moran, T.; Webb, T. R.; Whitten, J. P.; Xie, Y. F.; McCarthy, J. R. *J. Med. Chem.* **1996**, *39*, 4358.
6. Abreu, M. E.; Rzwszotarski, W.; Kyle, D. J.; Hiner, R. L. U.S. Patent 5,063,245, 1991.
7. Part of this work was reported: Chen, C.; Dagnino, R., Jr.; Huang, C.; Wilcoxen, K.; Xie, M.; Grigoriadis, D. E.; DeSouza, E. B.; McCarthy, J. R. *Abstracts of Papers, Part 2*, 218th American Chemical Society National Meeting, New Orlean, LA, August 22–26, 1999; American Chemical Society: Washington, DC, 1999; MEDI 113.
8. Cyclization of *N*-(morpholino-thiocarbonyl)benzimidechloride with methylhydrazine in refluxing methanol gave 1-methyl-3-morpholino-5-phenyl-1,2,4-triazole in 36% yield. Weber, G.; Hartung, J.; Beyer, L. Z. *Chem.* **1986**, *26*, 70.
9. (a) Scozzafava, A.; Supuran, C. T. *J. Med. Chem.* **2000**, *43*, 1858. (b) Rolfs, A.; Liebscher, J. *J. Org. Chem.* **1997**, *62*, 3480.
10. Cyclization of *N*,*N*-diethyl-*N*′-benzoylthiourea with hydrazine gave diethyl-(5-phenyl-1*H*-[1,2,4]triazol-3-yl)-amine in low yield, Whitefield, L. L.; Papadopoulos, P. *J. Heterocycl. Chem.* **1981**, *18*, 1197.
11. Fazylov, S. D.; Gazaliev, A. M.; Zhivotova, T. S.; Zhurinov, M. Z. *Russ. J. Gen. Chem.* **1999**, *65*, 841.
12. Typical procedure: A mixture of *N*-bis(cyclopropyl)methyl-*N*-propyl-*N*′-2,4,6-trimethylbenzoyl-*S*-methylisothiourea (**10c**, 124 mg, 0.33 mmol) and hydrazine (8 drops, excess) in dioxane (10 mL) was heated at reflux for 16 h. The mixture was concentrated in vacuo and the product was purified by chromatography on silica gel with 1:5 ethyl acetate/hexanes to give 3-[*N*-bis(cyclopropyl)methyl-*N*-propylamino]-5-(2,4,6-trimethylphenyl-1*H*-[1,2,4]triazole (**11b**, 88 mg, 78% yield) as a colorless solid. ^{1}H NMR (TMS/$CDCl_3$) δ 0.35 (m, 6H), 0.58 (m, 2H), 0.89 (t, $J = 7.6$ Hz, 3H), 1.08 (m, 2H), 1.75 (m, 2H), 2.10 (s, 6H), 2.26 (s, 3H), 3.06 (t, $J = 7.2$ Hz, 1H), 3.30 (t, $J = 6.8$ Hz, 2H), 6.82 (s, 2H). MS (EI) *m*/*e* 339 (M + H). Anal. for $C_{21}H_{30}N_4$ (338.49): calcd C%, 74.51; H%, 8.93; N%, 16.55. Found C%, 74.89; H%, 9.12; N%, 16.25.
13. Typical procedure: A solution of sodium isothiocyanate (480 mg, 6 mmol) in acetone (20 mL) was added dropwise into a solution of 2,4,6-trimethylbenzoyl chloride (910 mg, 5 mmol), which was made fresh from the corresponding acid and oxallyl chloride in THF. A white suspension formed immediately. This mixture was heated to reflux for 10 min and *N*-bis(cyclopropyl)methyl-*N*-propylamine (765 mg, 5 mmol) was added. The mixture was refluxed for 1 h before MeI (1.7 g, 12 mmol) and sodium carbonate (640 mg, 6 mmol) were introduced. The yellowish suspension was refluxed for another 3 h, cooled to room temperature, and filtered through a silica gel pad with ethyl acetate (~100 mL). The filter was concentrated in vacuo to give *N*-bis(cyclopropyl)methyl-*N*-propyl-*N*′-2,4,6-trimethylbenzoyl-*S*-methylisothiourea **10c** as a yellowish oil (1.86 g, quantitative), which was crystallized from ether–hexanes to give a white solid. ^{1}H NMR (TMS/$CDCl_3$) δ 0.45 (m, 5H), 0.68 (m, 2H), 0.96 (m, 4H), 1.95 (m, 2H), 2.26 (s, 3H), 2.41 (s, 6H), 2.59 (s, 3H), 3.61 (t, $J = 7.4$ Hz, 2H), 6.82 (s, 2H). MS (EI) *m*/*e* 373 (M + H). Anal. for $C_{22}H_{32}N_2OS$ (372.57): calcd C, 70.92; H, 8.66; N, 7.52. Found C, 71.21; H, 8.73; N, 7.36.
14. Typical procedure of alkylation: A solution of 3-(2-dichlorophenyl)-5-(*N*-propyl-*N*-bis(cyclopropyl)methylamino)-1*H*-[1,2,4]triazole (81 mg, 0.22 mmol) in dry THF was treated with NaH (44 mg) at room temperature for 20 min, followed by MeI (140 mg). The mixture was stirred for 2 h and TLC indicated two products (1:4, EtOAc/hexanes), which was separated by chromatography on silica gel.

1-Methyl-3-(*N*-propyl-*N*-bis(cyclopropyl)methylamino)-5-(2,4-dichlorophenyl)-1*H*-[1,2,4]triazole (**7a**). Major product as a colorless solid. ^{1}H NMR (TMS/$CDCl_3$) δ 0.40 (m, 6H), 0.60 (m, 2H), 0.99 (t, $J = 7.2$ Hz, 3H), 1.15 (m, 2H), 1.82 (m, 2H), 3.06 (t, 1H), 3.40 (m, 2H), 3.60 (s, 3H), 7.35 (d, $J = 7.5$ Hz, 1H), 7.40 (d, $J = 7.5$ Hz, 1H), 7.56 (s, 1H); MS (IS) *m*/*z* 379 (M + H). Anal. for $C_{19}H_{24}Cl_2N_4$ (379.33): calcd C%, 60.16; H%, 6.38; N%, 14.77. Found C%, 60.23; H%, 6.59; N%, 14.54. 1-Methyl-3-(2,4-dichlorophenyl)-5-(*N*-propyl-*N*-bis(cyclopropyl)methylamino)-1*H*-[1,2,4]triazole (**12a**). Minor product as a colorless solid. ^{1}H NMR(TMS/$CDCl_3$) δ 0.17 (m, 2H), 0.26 (m, 2H), 0.46 (m, 2H), 0.55 (m, 2H), 0.91 (t, $J = 7.2$ Hz, 3H), 1.06 (m, 2H), 1.46 (tq, $J = 7.2$, 7.2 Hz, 2H), 1.93 (t, $J = 8.6$ Hz, 1H), 3.35 (t, $J = 7.2$ Hz, 2H), 3.76 (s, 3H), 7.28 (dd, $J = 1.9$, 8.2 Hz, 1H), 7.47 (d, $J = 1.9$ Hz, 1H), 7.73 (d, $J = 8.2$ Hz, 1H); MS (IS) *m*/*z* 380 (M + H). Anal. for $C_{19}H_{24}Cl_2N_4$ (379.33): calcd C, 60.16; H, 6.38; N, 14.77. Found C, 60.45; H, 6.57; N, 14.39.
15. A close analogue, 2-(*N*-quinolin-5-yl-*N*-propyl)-4-(2,4-dichlorophenyl)-5-methylthiazole (SR95577) was reported to have a IC_{50} of 80 nM, species not reported). Wermuth, C. G. *J. Heterocycl. Chem.* **1998**, *35*, 1091.