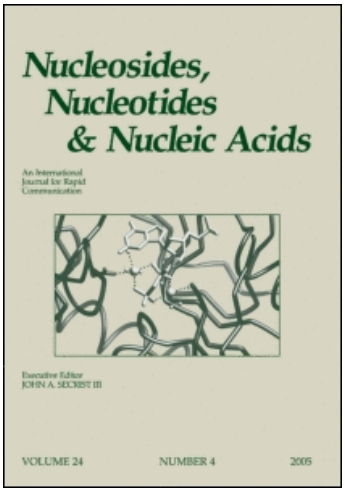


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

An Efficient Route to Novel 4,5-Di- and 2,4,5-Tri Substituted Imidazoles from Imidazo[1,5-*a*]-1,3,5-triazine (5,8-Diaza-7,9-dideazapurine) Derivatives

Bozenna Golankiewicz[a]; Piotr Januszczyk[a]; Joanna Zeidler[a]; Mariusz Popenda[a]
[a] Institute of Bioorganic Chemistry, Polish Academy of Sciences, Poznan, Poland

Online publication date: 02 October 2004

To cite this Article Golankiewicz, Bozenna , Januszczyk, Piotr , Zeidler, Joanna and Popenda, Mariusz(2004) 'An Efficient Route to Novel 4,5-Di- and 2,4,5-Tri Substituted Imidazoles from Imidazo[1,5-*a*]-1,3,5-triazine (5,8-Diaza-7,9-dideazapurine) Derivatives ', Nucleosides, Nucleotides and Nucleic Acids, 23: 1, 127 — 136
To link to this Article: DOI: 10.1081/NCN-120027822
URL: http://dx.doi.org/10.1081/NCN-120027822

NUCLEOSIDES, NUCLEOTIDES & NUCLEIC ACIDS
Vol. 23, Nos. 1 & 2, pp. 127–136, 2004

An Efficient Route to Novel 4,5-Di- and 2,4,5-Tri Substituted Imidazoles from Imidazo[1,5-*a*]-1,3,5-triazine (5,8-Diaza-7,9-dideazapurine) Derivatives[†]

Bozenna Golankiewicz,[*] Piotr Januszczyk, Joanna Zeidler, and Mariusz Popenda

Institute of Bioorganic Chemistry, Polish Academy of Sciences, Poznan, Poland

ABSTRACT

Two new types of imidazole derivatives: N-(2-R^1-5-R^2-1*H*-imidazol-4-yl) thioureas **7a–g** and N-(2-R^1-5-R^2-1*H*-imidazol-4-yl) formamides **8b,c,g** were obtained in high yields by the hydrolytic degradation of 6-R^1-8-R^2-2-thioxo-2,3-dihydroimidazo[1,5-*a*]-1,3,5-triazin-4(1*H*)-ones **5a–g** and 6-R^1-8-R^2-imidazo[1,5-*a*]-1,3,5-triazin-4(3*H*)-ones **6b,c,d**, respectively. The tautomeric preferences of the new imidazoles were determined.

Key Words: Hydrolytic degradation; Desulfurization; N-(1*H*-imidazol-4-yl) thiourea; N-(1*H*-imidazol-4-yl) formamide; Tautomeric preferences; NMR.

[†]In honor and celebration of the 70th birthday of Professor Leroy B. Townsend.

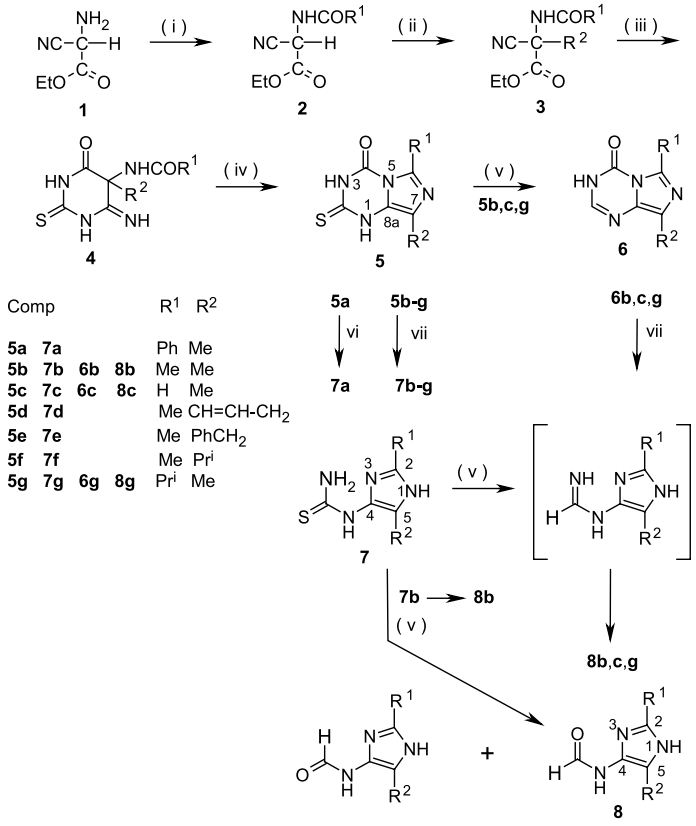
[*]Correspondence: Bozenna Golankiewicz, Institute of Bioorganic Chemistry, Polish Academy of Sciences, Noskowskiego 12/14, 61-704 Poznan, Poland; E-mail: bogolan@ibch.poznan.pl.

DOI: 10.1081/NCN-120027822 1525-7770 (Print); 1532-2335 (Online)

INTRODUCTION

The imidazole family of compounds attracts significant attention as already used or very promising chemotherapeutic agents. Their numerous applications include, among others, treatment of fungal diseases[1] brain disorders[2] as well as antiinflammatory[3] and antitumor[4] therapy.

In this article we report a simple and convenient preparation of diversely substituted 4,5-di and 2,4,5-tri-substituted imidazoles by the hydrolytic degradation of imidazo[1,5-*a*]-1,3,5-triazine(5,8-diaza-7,9-dideaza purine) derivatives. In our previous work we developed the synthetic routes towards a number of such ring isomers of 9-substituted guanines, 2-thioxanthines and hypoxanthines.[5–8] The steps of the general synthetic route (compounds **1–4**) to 6-R^1-8-R^2-2-thioxo-2,3-dihydroimidazo[1,5-*a*]-1,3,5-triazine-4(1*H*)ones (**5**) employed inexpensive starting materials and reagents and made it possible to introduce a variety of substituents (Scheme 1).



Scheme 1.

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

2-Thioxo derivatives **5** could be subsequently transformed into hypoxanthine analogues **6**. In the course of preparation of the 8-methyl-6-phenyl derivative **5a** we found that it transformed spontaneously into a new compound, which was tentatively identified as N-[4(5)-methyl-2-phenyl-1*H*-imidazol-5(4)-yl] thiourea **7a**. Similarly, when desulfurization reaction **5b** to **6b** was performed too long, original product **5b** was cleaved to another new type of imidazolyl derivative: N-[2,4(5)-dimethyl-1*H*-imidazol-5(4)-yl] formamide, **8b**.

These two observations encouraged us to study in more detail whether imidazotriazinones of type **5** and **6** may be useful intermediates to supply new imidazole derivatives of potential biological value. Having in mind that in some cases the tautomeric form of imidazole is crucial for its biological activity[2] it was also of interest to establish the tautomeric preferences for both types of new derivatives.

RESULTS AND DISCUSSION

In contrast to 6-aryl-substituted 2-thioxo 2,3-dihydroimidazo[1,5-*a*]-1,3,5-triazine-4(1*H*)one **5a**, analogous 6-unsubstituted and 6-alkyl-derivatives **5b–g** turned out to be stable in water solution or water suspension for at least several days at room temperature. We found however that heating them in refluxing water for 3.5–14 hours afforded imidazolylthiourea derivatives **7b–g** in high yields (75–94%).

2-Thioxoimidazotriazinones **5b–f** used as substrates were described earlier.[5–7] Compound **5g** was presently added to the series to check whether a bulky isopropyl substituent would be tolerated by the cyclization–rearrangement reaction (**4** to **5**) and whether it would have an influence on the imidazotriazine system stability. The modification was shown not to change considerably either the routine course of the reaction or the stability of its product.

Very characteristic signals appeared for novel degradation products in the ^{1}H NMR spectra: for protons bound to N1H of imidazole (in the range δ_H 11.37–11.94, very broad) and for three protons of the thiourea portion (NH_2 9.23–9.58, broadened; 8.31–9.00, broad; NH 7.70–7.86, broad) as well as in the ^{13}C NMR for thiocarbonyl (δ_C 179.66–180.31).

8-Substituted imidazo[1,5-*a*]-1,3,5-triazine-4(1*H*)-one **6c** and its 6,8-disubstituted congeners **6b** and **6g** when heated in refluxing water (6–24 h) furnished imidazolylformamide derivatives **8b,c,g** also in high yields (80–85%). Imidazolylthiourea derivatives **7**, when subjected to a desulfurization medium of NH_3aq, and deactivated Raney Ni at 100°C, could also afford respective formamide derivatives as was exemplified by the transformation of **7b** into **8b**.

Figure 1. Partially double bond character of amidic bond in formamides **8 b**,**c**,**g**.

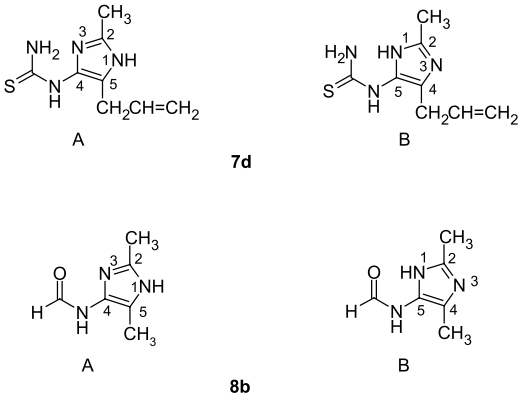


Figure 2. Possible tautomeric forms of imidazolyl portions of compounds **7d** and **8b**.

Imidazolylformamides **8b,c,g** exist in two isomeric forms, *cis* (*Z*) and *trans* (*E*), due to restricted rotation around the amidic bond as depicted by Figure 1.

The observation of such isomerism by NMR is well documented in the literature.[9,10]

In ^{1}H NMR spectra of **8b,c,g** the signals of almost all protons are doubled, ^{13}C NMR spectra demonstrate different signals not only for amide carbonyl but also for all carbons of imidazole. An unusual feature of these formamides, which may deserve further attention, is *E*:*Z* proportions of 1:1.

It is somewhat surprising that imidazole derivatives discussed above, connecting two structural moieties, imidazole and thiourea, known as carriers of diverse biological and therapeutic activity have not been described in the literature so far.

The tautomeric preferences of novel imidazole derivatives to carry the group substituent either at 4 or 5 position (A or B, Figure 2) were ascribed on the basis of ^{1}H NMR NOE experiments performed on one representative of each series **7d** and **8b**.

For the NOE experiment with compound **7d** the $-CH_2-$ signal of the allyl group was chosen as the site of irradiation. The experiment was performed in pyridine d_5 because the $-CH_2-$ signal overlapped with the d_5 DMSO pattern. Irradiation resulted in 0.9% NOE enhancement on the signal of the heterocyclic N1H (possible only in tautomer A), 4.6% on 4-NH, 9% on $CH{=}CH_2$ and negative ($-$ 0.1%) effect on the 2-Me substituent.

In compound **8b** irradiation of heterocyclic NH showed 1.7% and 1.5% NOE enhancement on signals of 2- and 5- methyl groups respectively.

The distance between NH proton and averaged methyl protons positions calculated for this model compound is about 3.2 Å for both methyl groups. In form B the distance between 2-CH_3 and N1H is the same as in form A, but N1H–4-CH_3 distance is about 4.95 Å. In the latter case only one NOE enhancement would be observed.

These tautomeric preferences seem to be promising in view of the finding that 4–1*H* substituted imidazole unit is essential for the histamine H_3 receptor activity.[2]

CONCLUSION

There have been a few reports on formation of imidazoles from condensed heterocycles (e.g. Refs. [11,12]) not suitable, however, to elaborate on their basis a

Marcel Dekker, Inc.
270 Madison Avenue, New York, New York 10016

more general preparative approach. Degradative hydrolysis of condensed imidazotriazines presently described is to our knowledge the first attempt to reach this goal.

Because of the variety of substituents that can be introduced at the imidazole moiety and the ability to impose the defined tautomeric preferences by combination with a thiourea or formamide moiety, the method seems promising for further development of imidazole therapeutic agents.

EXPERIMENTAL SECTION

General: Melting points were determined on a MEL-TEMP II capillary melting point apparatus and are uncorrected. UV spectra were recorded on a Beckman DU-65 spectrophotometer in ethanol. Electron impact mass spectra were obtained at 70 eV on a JEOL JMS-D-100 spectrometer. Elemental analyses were performed by Microanalytical Laboratories of Institute of Organic Chemistry Polish Academy of Sciences in Warsaw. ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 on a Unity 300 Varian spectrometer operating at 299.95 MHz and 75.43 MHz respectively. For tautomers assignments 1D^{1}H differential NOE and 2D NOESY spectra were measured. Tetramethylsilane was used as the internal standard, and the chemical shifts are reported in ppm (δ scale). Analytical TLC and preparative layer chromatography (PLC) were conducted on Merck precoated silica gel F_{254} type 60 plates of layer thickness 0.25 and 2.0 mm, respectively. Short column chromatography was carried out on Merck silica gel 60H (5–40 μm or 40–63 μm). The compounds **5b**, **c**, **d**, **e**, **f** and **6b**, **c** were prepared as described previously.[6,7]

Ethyl 2-cyano-2-isobutyrylaminoacetate (2g). Ethyl isonitrosocyanoacetate (14.2 g, 100 mmol) was reduced to ethyl 2-amino-2-cyanoacetate **(1)** with sodium dithionite (52.3 g, 300 mmol) according to a literature method.[6] Amino-ester was acylated with isobutyric anhydride (15.83 g, 100 mmol). The precipitated product **2g** was filtered off and recrystallized from ethanol: 6.6 g (35%), Mp 134°C; ^{1}H NMR 9.09 (d, 1H, NH), 5.68 (d, 1H, *CH*CN), 4.18 (q, 2H, CH_3CH_2OCO), 2.46 (m, 1H, $(CH_3)_2CH$), 1.20 (t, 3H, CH_3CH_2OCO), 1.03 [d, 6H, $(CH_3)_2CH$].

Ethyl 2-cyano-2-isobutyrylaminopropionate (3g). To a solution of sodium ethoxide (0.46 g Na in 16 ml of absolute ethanol, 20 mmol) was added **2g** (3.96 g, 20 mmol) followed by iodomethane (3.28 g, 23 mmol). The reaction mixture was heated at reflux for 40 min, then cooled and evaporated under vacuum to give an oily residue.The latter was dissolved in water and extracted with dichloromethane (3 × 20 ml). The organic solution was dried over $MgSO_4$, filtered and concentrated under vacuum. A crude product was crystallized from benzene: 3.8 g of **3g** (90%) Mp 112°C: ^{1}H NMR 9.08 (s, 1H, NH), 4.16 (q, 2H, CH_3CH_2OCO), 2.47 [m, 1H, $(CH_3)_2CH$], 1.71(s, 3H, CH_3CN), 1.19 (t, 3H, CH_3CH_2OCO), 1.02 [d, 6H, $(CH_3)_2CH$].

6-Imino-5-isobutyrylamino-5-methyl-2-thioxo-1,2,5,6-tetrahydropyrimidin-4(3*H*)-one (4g). To a solution of sodium ethoxide (2.3 g Na in 150 ml of absolute ethanol, 100 mmol) were added **3g** (7.0 g, 33 mmol) and thiourea (3.8 g, 50 mmol). The solution was refluxed for 90 min then cooled to 5°C, and pH was adjusted to 5.5 with acetic acid. The precipitated yellow product was collected by filtration and washed with cold water. Finally, it was recrystallized from 50% aqueous ethanol: 4.4 g of **4g**

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

(55%), Mp 236°C dec.; Anal. Calcd for $C_9H_{14}N_4OS$: C 44.62, H 5.78, N 23.14, S 13.22; Found C 44.38, H 5.65, N 22.87, S 13.10. ^{1}H NMR 11.55 (br s, 1H, N-3H), 8.92 (br s, 1H, N-1H), 8.83 (s, 1H, C-5–NH), 8.40 (br s, 1H, C-6═NH), 2.46 [m, 1H, $(CH_3)_2CH$], 1.48 (s, 3H, C-5–CH_3), 0.98 [dd, 6H, $(CH_3)_2$CH]. ^{13}C NMR 187.12 (C-2), 176.37 (C-6), 172.02 (C-4), 168.47 [$(CH_3)_2$CHCO], 54.12 (C-5), 32.61 [$(CH_3)_2CH$], 24.05 (C-5–CH_3), 18.86 [$(CH_3)_2$CH].

6-Isopropyl-8-methyl-2-thioxo-2,3-dihydroimidazo[1,5-*a*]-1,3,5-triazin-4(3*H*)-one (5g). Chlorotrimethylsilane (4.40 g, 40 mmol) was added to a stirred solution of **4g** (4.84 g, 20 mmol) in anhydrous pyridine (80 ml). The stirring was continued for 30 min at 20°C then hexamethyldisilazane (17.78 g, 110 mmol) was added and the reaction mixture was gently heated at reflux under nitrogen for 20 h. The volatiles were removed under vacuum and a residue treated with absolute ethanol (25 ml).The solvent was evaporated and the solid mass dissolved in warm ethanol (10 ml). Crystalline **5g** was obtained in two crops: 1.6 g and 0.8 g (75%), Mp 196°C dec.; MS m/z 225 (M^+, 81), 210 (12), 209 (100), 166 (32), 150 (69), 141 (43). Anal. Calcd for $C_9H_{12}N_4OS$: C 48.21, H 5.36, N 25.00, S 14.29; Found C 48.10, H 5.38, N 24.95, S 14.28. ^{1}H NMR 12.99 (br s, 1H, N-3H); 12.14 (br s, 1H, N-1H), 3.61 [m, 1H, $(CH_3)_2CH$], 2.14 (s,3H, C-8–CH_3), 1.20 [d, 6H, $(CH_3)_2$CH], ^{13}C NMR 170.77 (C-2), 146.59 (C-6), 142.06 (C-4), 124.36 (C-8a), 113.97 (C-8), 27.41 [$(CH_3)_2CH$], 21.17 [$(CH_3)_2$CH], 11.12 (C-8–CH_3).

6-Isopropyl-8-methylimidazo[1,5-*a*]-1,3,5-triazine-4(3*H*)-one (6g). A solution of **5g** (0.112 g, 0.5 mmol) in 2% aqueous ammonia (10 ml) was treated with moist Raney nickel catalyst (0.65 g) and refluxed for 5 min. The reaction mixture was cooled to 40°C and the catalyst was filtered off. The filtrate was concentrated under vacuum. The product **6g** was purified by PLC with chloroform/methanol 18:1 (v/v) as eluent. Upon crystallization from methanol 0.070 g (73%) of **6g** was obtained: Mp 205°C dec.; MS: m/z 192 (M^+, 47), 178 (10), 177 (100), 151 (6), 150 (60), 134 (35). Anal. Calcd for $C_9H_{12}N_4O$: C 56.25, H 6.25, N 29.16; Found C 56.24, H 6.22, N 28.92. ^{1}H NMR 11.72 (br s, 1H, N-3H), 7.49 (s, 1H, C-2–H), 3.79 [(m, 1H, $(CH_3)_2CH$)], 2.21 (C-8–CH_3), 1.25 [d, 6H, $(CH_3)_2$CH)], ^{13}C NMR 146.25 (C-6). 144.80 (C-4), 138.40 (C-2), 132.41 (C-8a), 125.14 (C-8), 27.71 [$(CH_3)_2CH$)], 21.59 [$(CH_3)_2$CH], 11.37 (C-8–CH_3).

5-Benzoylamino-6-imino-5-methyl-2-thioxo-1,2,5,6-tetrahydropyrimidin-4(3*H*)-one (4a) was prepared as described earlier,[13] and it was subjected to a cyclization-rearrangement reaction: 0.662 g of **4a** (2.4 mmol) in anhydrous pyridine (8 ml) was treated with chlorotrimethylsilane (0.52 g, 4.8 mmol) and the mixture was stirred at 20°C for 40 min. Hexamethyldisilazane (2.10 g, 13 mmol) was added and the reaction mixture was heated at reflux under argon for 8 h. The volatiles were removed under vacuum and the residue treated with absolute ethanol (6 ml). Unreacted starting material **4a** was recovered by filtration (0.096 g). The filtrate contained two main products: very unstable **8-methyl-6-phenyl-2-thioxo-2,3-dihydroimidazo[1,5-*a*]-1,3,5-triazine-4(3*H*)-one (5a)** and **N-(5-methyl-2-phenyl-1*H*-imidazol-4-yl)thiourea (7a)**. The filtrate was evaporated and the products separated on a silica gel column with chloroform/ethanol 96:4 (v/v) as eluent. Fractions containing imidazotriazinone derivative **5a** were collected and evaporated to an oily residue (0.017 g, 3%): MS m/z 258

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

(M^+, 24), 215 (100), 157 (4), 150 (15), 104 (37), 103 (15), 77 (21). ^{1}H NMR 12.45 (br s, N-1H, N-3H); 7.35–7.70 (m, C-6–Ph), 2.25 (s, C-8–CH_3). ^{13}C NMR 170.78 (C-2) 141.41 (C-4), 139.68 (C-6), 130.20, 129.65, 128.46, 127.46 (Ph), 125.16 (C-8a), 116.32 (C-8), 11.22 (C-8–CH_3).

The product **7a** recovered from the column was then crystallized from 50% aqueous ethanol. It afforded 0.230 g of white needles (43%); Mp 222°C; UV λ_{max} 237 nm (ε 13,000), 286 (ε 17,900); MS m/z 232 (M^+, 81), 215 (100), 214 (27), 104 (28). Anal. Calcd for $C_{11}H_{12}N_4S$: C 56.85, H 5.21, N 24.13 Found C 56.97, H 5.08, N 24.29; ^{1}H NMR 12.01 (s, 1H, N-1 H), 9.65, 8.27, 8.04 (3 × s, 3H, $NHCSNH_2$), 7.90–7.80 (m, 2H, Ph), 7.54–7.21 (m, 3H, Ph), 2.24 (s, 3H, CH_3); ^{13}C NMR 179.77 (CS). 140.15 (C-2), 135.02 (C-4), 129.87, 128.63, 127.76, 124.24 (Ph), 114.65 (C-5), 8.83 (CH_3).

General procedure for the synthesis of **N-(2-R^1-5-R^2-1*H*-imidazol-4-yl)thioureas (7b–7g)**. A 2-thioxodihydroimidazotriazinone (**5b–5g**, 1 mmol) was dissolved in water (10 ml) and heated at reflux for: cmpd **5b**—14 h, **5c**—3.5 h, **5d**—5 h, **5e**—8 h, **5f**—4 h and **5g**–12 h. According to TLC (chloroform/methanol 9:1) all starting material was transformed into a single more polar product. Products **7d** and **7f** could be obtained directly from the corresponding reaction mixture, if stored at room temperature for 24 h (yield ca 95%).The other products (**7b**, **7c**, **7e** and **7g**) had to be purified by PLC with the above–mentioned solvent system. Yields varied: 75–94%.

N-(2,5-dimethyl-1*H*-imidazol-4-yl)thiourea (7b): (82%); Mp. 195°C; UV λ_{max} 228 nm (ε 8,000), 251 (ε 9,350)I; MS m/z 170 (M^+, 30), 153 (85), 152 (18), 111 (21), 110 (21); Anal. Cacld for $C_6H_{10}N_4S$: C 42.35, H 5.88, N 32.94, S 18.82, Found C 42.40, H 5.75, N 31.96, S 18.52. ^{1}H NMR 11.52 (s, 1H, N-1–H), 9.33, 8.47, 7.77 (3 × s, 3H, $NHCSNH_2$), 2.12 (s, 3H, 2-CH_3), 2.00 (s, 3H, 5-CH_3); ^{13}C NMR 179.66 (CS), 139.08 (C-2), 133.45 (C-4), 111.61 (C-5), 13.92 (2-CH_3), 8.72 (5-CH_3).

N-(5-methyl-1*H*-imidazol-4-yl)thiourea (7c): (80%); Mp 205°C; UV λ_{max} 228 nm (ε 7,350), 253 (ε 10,600); MS m/z 156 (M^+, 85),139 (56), 97 (61), 96 (62). Anal. Calcd for $C_5H_8N_4S$: C 38.46, H 5.13, N 35.89, S 20.51 Found C 38.36, H 4.92, N 35.13, S 20.90. ^{1}H NMR 11.94 (s, 1H, N-1–H), 9.40, 8.56, 7.82 (3 × s, 3H, $NHCSNH_2$), 7.40 (s, 1H, 2-H), 2.05 (s, 3H, CH_3); ^{13}C NMR 179.98 (CS), 134.15 (C-4), 130.68 (C-2), 111.68 (C-5), 8.77 (CH_3).

N-(5-allyl-2-methyl-*1H*-imidazol-4-yl)thiourea (7d): (94%)′ Mp 204°C, UV λ_{max} 231 nm (ε 10,000)I, 252 (ε 12,000); MS m/z 196 (M^+, 212), 179 (100), 178 (150, 137 (31), 136 (16); Anal. Calcd for $C_8H_{12}N_4S$: C 48.97, H 6.12, N 28.57, S 16.32, Found C 48.80, H 6.18, N 28.67, S 16.31. ^{1}H NMR 11.79 (s, 1H, N-1-H), 9.31, 8.77, 7.78 (3 × s, 3H, $NHCSNH_2$), 5.63 (m, 1H, ═CH), 4.86 (m, 2H, ═CH_2), 3.22 (d,2H, CH_2), 2.13 (s, 3H, CH_3); ^{13}C NMR 179.76 (CS), 139.89 (C-2), 135.66 (═CH), 133.39 (C-4), 115.94 (═ CH_2), 113.76 (C-5), 27.24 (CH_2), 13.87 (CH_3).

N-(5-benzyl-2-methyl-1*H*-imidazol-4-yl)thiourea (7e): (75%); Mp 204°C; UV λ_{max} 231 nm (ε 11,450)I, 251 (ε 12,700); MS m/z 246 (M^+, 32), 229 (100), 228 (19), 187 (18), 186 (22); Anal. Calcd for $C_{12}H_{14}N_4S$: C 56.54, H 5.69, N 22.76, S 13.01, Found C 58.58, H 5.83, N 22.62, S 12.97. ^{1}H NMR 11.62 (s,1H, N-1–H), 9.58. 9.00, 7.86 (3 × s, 3H, $NHCSNH_2$), 7.16 (s, 5H, Ph), 3.95 (s,2H, CH_2), 2.15 (s,3H, CH_3); ^{13}C

NMR 179.83 (CS), 139.89 (C-2), 134.36 (C-4), 128.41 and 128.38 (Ph), 113.94 (C-5), 28.72 (CH_2), 13.87 (CH_3).

N-(5-isopropyl-2-methyl-1*H*-imidazol-4-yl)thiourea (7f): (94%); Mp 210°C; UV λ_{max} 249 nm (ε 12,300); MS m/z 198 (M^+, 88), 181 (53), 180 (7), 139 (9), 138 (22), 124 (100); Anal. Calcd for $C_8H_{14}N_4S \times H_2O$: C 44.44, H 7.40, N 25.96, S 14.82, Found C 44.47, H 7.65, N 26.30, S 15.01. ^{1}H NMR 11.37 (s, 1H, N-1–H), 9.23,8.31, 7.75 (3 × s, 3H, $NHCSNH_2$), 2.99 (m, 1H, CH), 2.13 (s, 3H, CH_3), 1.05 (d, 6H, 2 × CH_3); ^{13}C NMR 180.31 (CS), 139.68 (C-2), 130.79 (C-4), 123.48 (C-5), 23.19 (CH), 22.38 (2 × CH_3), 13.92 (CH_3).

N-(2-isopropyl-5-methyl-1*H*-imidazol-4-yl)thiourea (7g): (75%); Mp 150°C; UV λ_{max} 233 nm (ε 8,500), 252 (ε 9,850); MS m/z 198 (M^+, 88), 181 (100), 180 (7), 139 (26), 138 (15), 124 (87); Anal. Calcd for $C_8H_{14}N_4S \times H_2O$: C 44.44, H 7.40, N 25.96, S 14.82, Found C 44.32, H 7.45, N 26.25, S 14.93. ^{1}H NMR 11.48 (s,1H, N-1–H), 9.31, 8.73, 7.70 (3 × s, 3H, $NHCSNH_2$), 2.78 (m, 1H, CH), 2.03 (s,3H, CH_3), 1.12 (d, 6H, 2 × CH_3); ^{13}C NMR 179.72 (CS), 148.02 (C-2), 133.17 (C-4), 111.56 (C-5), 27.63 (CH), 21.47 (2 × CH_3), 8.67 (CH_3).

General procedure for the synthesis of **N-(2-R^1-5-R^2-1*H*-imidazol-4-yl)-formamides (8b**, **8c**, **8g)**. Imidazotriazinone (**6b**, **6c**, **6g,** 1 mmol) was dissolved in water (10 ml) and heated at reflux for 24 h (**6b**, **6c**) and 6 h (**6g**). According to TLC (chloroform/methanol 9:1) all starting material was transformed into a single more polar product. Solvent was removed under vacuum and the residue was purified by PLC with the above-mentioned solvent system. Corresponding products **8b** and **8c** were isolated as solids, while **8g** was an oil. The yield ranged: 80–85%.

N-(2,5-dimethyl-1*H*-imidazol-4-yl)formamide (8b): (85%); Mp 228°C dec.; MS m/z 139 (M^+, 22), 111 (35), 110 (21), 70 (10), 69 (11). Anal. Calcd for $C_6H_9N_3O$: C 51.79, H 6.47, N 30.22, Found C 51.56, H 6.46, N 30.36.^{1}H NMR 11.43 (br s, 1H, N-1–H), 9.46 and 9.40 (br d, d, 1H, 4-NH), 8.30 and 8.02 (d,J = 10.9 Hz, 0.5H, d, J = 1.7 Hz, 0.5H, CHO), 2.15 (s, 3H, 2-CH_3), 2.03 and 1.99 (2 × s, 2 × 1.5H, 5-CH_3). ^{13}C NMR 163.3 and 158.9 (CO), 139.6 and 139.2 (C-2), 131.1 and 128.7 (C-4), 116.5 and 113.1 (C-5), 13.6 (2-CH_3), 9.7 and 8.3 (5-CH_3).

N-(5-methyl-1*H*-imidazol-4-yl)formamide (8c): (80%); Mp 176°C dec.; MS m/z 125 (M^+, 26), 97 (65), 96 (36), 70 (7), 69 (21). Anal. Calcd for $C_5H_7N_3O$: C 48.00, H 5.60, N 33.60, Found C 47.82, H 5.55, N 33.60. ^{1}H NMR 11.88 (br s , 1H, N-1–H), 9.60 and 9.54 (br d, d, 1H, 4-NH), 8.34 and 8.06 (d, J = 11.1 Hz, 0.5H, d, J = 1.2 Hz, 0.5 H, CHO), 7.34 (s, 1H, 2-H), 2.09 and 2.04 (2 × s, 2 × 1.5 H, CH_3); ^{13}C NMR 163.5 and 150.2 (CO), 132.0 and 129.8 (C-4), 131.3 and 131.0 (C-2), 117.4 and 114.0 (C-5), 9.6 and 8.3 (CH_3).

N-(2-isopropyl-5-methyl-1*H*-imidazol-4-yl)formamide (8g): (83%); oil; MS m/z 167 (M^+, 47), 152 (33), 139 (53), 138 (18), 124 (100), 77 (67), 70 (35), 69 (24). Anal. Calcd for $C_8H_{13}N_3O \times 2H_2O$: C 47.29, H 8.37, N 20.68, Found C 47.80, H 8.04, N 20.89. ^{1}H NMR 11.37 (br s, 1H, N-1–H), 9.52 (br s, 1H, 4-NH), 8.42 and 8.03 (2 × br s, 2 × 0.5H, CHO), 3.61 (q, 1H, CH), 2.05 and 1.89 (2 × s, 2 × 1.5H, CH_3), 1.18 (d,

Marcel Dekker, Inc.
270 Madison Avenue, New York, New York 10016

6H, 2 × CH_3). ^{13}C NMR 163.5 and 158.9 (CO), 148.7 and 148.3 (C-2), 130.7 and 128.7 (C-4), 116.4 and 113.6 (C-5), 27.6 (CH), 21.5 (2 × CH_3), 9.9 and 8.4 (CH_3).

Desulfurization of **N-(2,5-dimethyl-1*H*-imidazol-4-yl)thiourea (7b)** to **N-(2,5-dimethyl-1*H*-imidazol-4-yl)formamide (8b)**. To a solution of **7b** (0.160 g, 1 mmol) in 2% aqueous ammonia (10 ml) moist Raney nickel catalyst (0.65 g) was added. The mixture was refluxed for 10 min. It was then cooled to room temperature and the catalyst was filtered off. The filtrate was concentrated under vacuum. The crude product **8b** was purified by PLC with chloroform/methanol 4:1 (v/v). It afforded 0.130 g (94%) of **8b** as a white powder.

REFERENCES

1. Tafi, A.; Costi, R.; Botta, M.; Di Santo, R.; Corelli, F.; Massa, S.; Ciacci, A.; Manetti, F.; Artico, M. Antifungal agents. 10. New derivatives of 1-[(aryl)[4-aryl-1*H*-pyrrol-3-yl]methyl]-1*H*-imidazole, synthesis, anti-Candida activity, and quantitative structure–analysis relationship studies. J. Med. Chem. **2002**, *45*, 2720–2732.
2. De Esch, I.J.P.; Gaffar, A.; Menge, W.M.P.B.; Timmerman, H. Synthesis and histamine H_3 receptor activity of 4-(n-alkyl)-1*H*-imidazoles and 4-(ω-phenylalkyl)-1*H*-imidazoles. Bioorg. Med. Chem. **1999**, *7*, 3003–3009.
3. Slee, D.H.; Romano, S.J.; Yu, J.; Nguyen, T.N.; John, J.K.; Raheja, N.K.; Axe, F.U.; Jones, T.K.; Ripka, W.C. Development of potent non-carbohydrate imidazole-based small molecule selection inhibitors with anti-inflammatory activity. J. Med. Chem. **2001**, *44*, 2094–2107.
4. Bell, I.M.; Gallicchio, S.N.; Abrams, M.; Beshore, D.C.; Buser, C.A.; Culberson, J.C.; Davide, J.; Ellis-Hutchings, M.; Fernandes, C.; Gibbs, J.B.; Graham, S.L.; Hartman, G.D.; Heimbrook, D.C.; Homnick, C.F.; Huff, J.R.; Kassahun, K.; Koblan, K.S.; Kohl, N.E.; Lobell, R.B.; Lynch, J.J., Jr.; Miller, P.A.; Omer, C.A.; Rodrigues, A.D.; Walsh, E.S.; Williams, T.M. Design and biological activity of (*S*)-4-(5-{[1-(3-chlorobenzyl)-2-oxopyrrolidin-3-ylamino]methyl}imidazol-1-ylmethyl)benzonitrile, a 3-aminopyrrolidinone farnesyltransferase inhibitor with excellent cell potency. J. Med. Chem. **2001**, *44*, 2933–2949.
5. Golankiewicz, B.; Holtwick, J.B.; Holmes, B.N.; Duesler, E.N.; Leonard, N.J. Synthesis of imidazo[1,5-*a*]-1,3,5-triazinones by cyclization-rearrangement. J. Org. Chem. **1979**, *44*, 1740–1742.
6. Holtwick, J.B.; Golankiewicz, B.; Holmes, B.N.; Leonard, N.J. Guanine, hypoxanthine and xanthine analogues. Synthesis of imidazo[1,5-*a*]-1,3,5-triazinones via rearrangement. J. Org. Chem. **1979**, *44*, 3835–3839.
7. Golankiewicz, B.; Zeidler, J.; De Clercq, E. Synthesis and biological activity of C-acyclic nucleosides of imidazo[1,5-*a*]-1,3,5-triazines. Nucleosides Nucleotides **1987**, *6*, 663–678.
8. Golankiewicz, B.; Januszczyk, P.; Ikeda, S.; Balzarini, J.; De Clercq, E. Synthesis and antiviral activity of benzyl-substituted imidazo[1,5-*a*]-1,3,5-triazine (5,8-diaza-7,9-dideazapurine) derivatives. J. Med. Chem. **1995**, *38*, 3558–3565.
9. Bourn, A.J.R.; Gillies, D.G.; Randall, E.W. *Cis-trans* isomerism in formanilide. Tetrahedron **1964**, *20*, 1811–1818 and references therein.

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

10. Barbarella, G.; Tugnoli, V.; Zambianchi, M. Imidazole ring opening of 7-methylguanosine at physiological pH. Nucleosides Nucleotides **1991**, *10*, 1759–1769 and references therein.
11. Fujii, T.; Sato, T.; Itaya, T.; Purines, V. The Dimroth rearrangement of 1-alkoxyadenines: The synthesis of N-alkoxyadenines. Chem. Pharm. Bull. **1971**, *19*, 1731–1734.
12. Fujii, T.; Saito, T.; Kawanishi, M. A general synthetic route to 3,9-dialkyladenines and their ring opening. Tetrahedron Lett. **1978**, *50*, 5007–5010.
13. Golankiewicz, B.; Zeidler, J.; Popenda, M. Determination of the tautomerism of 5,5-disubstituted analogues of 6-amino-2-thiouracil by ^{1}H and ^{13}C nuclear magnetic resonance spectroscopy. J. Chem. Soc., Perkin Trans. 2 **1990**, 1001–1004.

Received August 8, 2003
Accepted October 6, 2003

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

Request Permission or Order Reprints Instantly!