Synthesis of some novel hydrazono acyclic nucleoside analogues

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Abstract

The syntheses of novel hydrazono acyclic nucleosides similar to miconazole scaffolds are described. In this series of acyclic nucleosides, pyrimidine as well as purine and other azole derivatives replaced the imidazole function in miconazole and the ether group was replaced with a hydrazone moiety using phenylhydrazine. To interpret the dominant formation of (E)-hydrazone derivatives rather than (Z)-isomers, PM3 semiempirical quantum mechanic calculations were carried out which indicated that the (E)-isomers had the lower heats of formation.

Introduction

In recent years, fungal infections have become an important complication and a major cause of morbidity and mortality in immune-compromised individuals who suffer from tuberculosis, cancer or AIDS, and who undergo organ transplants [1,2]. Up to now, there has been an increase in the number of antifungal drugs available with various structures and scaffolds. However, their clinical value has been limited by the emergence of drug resistance, high risk of toxicity, insufficiencies in their antifungal activity as well as undesirable side effects. This situation has led to an ongoing search for safe and efficient chemotherapeutic agents with potent broad-spectrum antifungal activities.

Some of the best known antifungal azole drugs having rational versatility in structures are miconazole (A), oxiconazole (B) and related compounds, namely aryl azoles (Figure 1). Pharmacokinetic properties and cellular permeability of a drug can be modulated by derivatization to bio-reversible forms of the drug, namely hydrazones [3]. Hydrazone derivatives are prominent structural motifs in numerous pharmaceutically active compounds. Many well known drugs with various clinical activities, such as chemotherapeutic (e.g. nitrofurantoin [4,5]), antihypertensive (e.g. endralazine [4,6]), antibiotic (e.g. rifampicin [4]), tuberculostatic (e.g. glyconiazide [4,7,8]),...
The significance of nucleoside chemistry in drug discovery is well-known and fully established in medicinal chemistry [13-16]. Acyclic nucleosides constitute a special class of nucleoside analogues which have attracted great interest due to their broad-spectrum chemotherapeutic activities against cancer and infections caused by viruses, microbes and other pathogenic microorganisms. Moreover, antitumor and antiviral activities of various hydrazone derivatives of nucleosides have also been reported [16-18].

Inspired by the miconazole scaffold and also as an extension of our ongoing research in the design and synthesis of novel acyclic nucleosides [19-25], hereby, we wish to report the synthesis of some novel hydrazono acyclic nucleosides having similar scaffolds to the miconazole framework. In these compounds, the nucleobases including pyrimidines, purines and other azole derivatives were substituted as heterocyclic cores and the ether bond in miconazole (i.e. CHOCH₂) was replaced with hydrazono bond (i.e. C=NNH) in the newly synthesized compounds. Figure 1 shows the general structure of hydrazono acyclic nucleoside compound C.

Results and Discussion

The synthetic pathways for compounds 2a-2g and 2h-2o are outlined in Scheme 1 and Scheme 2. Two different strategies were considered for the synthesis of the title compounds taking into account the differences in chemical behavior of purine and pyrimidine nucleobases compared to azoles. Because of their better solubility, reactivity and ease of separation of products, the reactions of the azole derivatives were conducted according to Scheme 1.

As shown in Scheme 1, condensation of imidazole, 2-phenylimidazole, hydantoin, benzimidazole and benzotriazole with 2-bromoacetophenone and 4′-methoxy-2-bromoacetophenone gave the key intermediates, ketones 1a-1g. Based on our literature survey, we recognized that among published methods for N-alkylation of imidazole derivatives [26-34], the method developed by Liu et al. [35] was the most appropriate one for N-alkylation of azidazole derivatives [26-34], the method developed by Liu et al. [35] was the most appropriate one for N-alkylation of azoles and their derivatives, since in this method the formation of quaternary imidazolium salts is largely
prevented. However, from our experience, using triethylamine (TEA) as a homogeneous base instead of K$_2$CO$_3$ (which was previously employed by Liu et al.) produced more satisfactory results. Hence, the reaction of imidazole or benzimidazole derivatives with 2-bromoacetophenones and TEA in the presence of a catalytic amount of n-tetrabutylammonium bromide (TBAB) in refluxing anhydrous acetonitrile (MeCN) provided ketones 1a–1g in good yields (60–70%). Subsequently, the

### Table 1: Synthesized hydrazono acyclic nucleoside analogues.

| Entry | Product (2) | mp (°C) | Yield$^a$ (%) |
|-------|-------------|---------|---------------|
| a     | ![Image](image1.png) | 169.2   | 87            |
| b     | ![Image](image2.png) | 171.3   | 84            |
| c     | ![Image](image3.png) | 174.5   | 82            |
| d     | ![Image](image4.png) | 200.1   | 89            |
| e     | ![Image](image5.png) | 165.9   | 75            |
| f     | ![Image](image6.png) | 148.4   | 81            |

\(^a\) Yield calculated based on the reaction mixture.
|   | Structure | Mass (g) | Activity (%) |
|---|-----------|----------|--------------|
| g | ![Structure](image-g) | 137.9    | 82           |
| h | ![Structure](image-h) | 300.1    | 78           |
| i | ![Structure](image-i) | 213.8    | 80           |
| j | ![Structure](image-j) | 205.1    | 75           |
| k | ![Structure](image-k) | 181.5    | 79           |
| l | ![Structure](image-l) | 173.9    | 74           |
ketones 1a–1g were converted to the pure hydrazone derivatives 2a–2g by treatment with phenylhydrazine in the presence of a catalytic amount of acetic acid in ethanol, followed by heating at reflux (Scheme 1).

For the synthesis of the purine and pyrimidine analogues of target compounds 2h–2o, we envisaged that there might be substantial problems in the synthesis of the desired ketones using similar method as outlined in Scheme 1. This proved to be the case, and the corresponding ketones 1h–1o could not be obtained satisfactorily by this method. The main limitation of using the aforementioned pathway for purines and pyrimidines is their low solubility in acetonitrile, which results in low yields of the corresponding ketones 1h–1o. Thus, we have modified Scheme 1 by using DMF as the solvent of choice for nucleobases (Scheme 2).

| m | n | o |
|---|---|---|
| ![Structure m](image) | ![Structure n](image) | ![Structure o](image) |
| 100.1 | 104.7 | 209.3 |

Table 1: Synthesized hydrazono acyclic nucleoside analogues. (continued)

\[ \text{Isolated yield.} \]
Thus, the condensation of purine and pyrimidine nucleobases as well as theophylline and theobromine with 2-bromoacetophenones using K₂CO₃ in anhydrous DMF under reflux conditions provides the N-alkylation adducts 1h–1o in moderate yields (Scheme 2). Subsequently, treatment of the obtained ketones 1h–1o with phenylhydrazine in refluxing ethanol in the presence of a catalytic amount of acetic acid afforded the desired compounds 2h–2o. The structures of synthesized compounds are shown in Table 1. As Table 1 indicates, the N-alkylation reactions of nucleobases were achieved regioselectively. In the case of pyrimidine nucleobases, N(1)-alkylated compounds 1h–1l were the major products (43%, 40%, 51%, 47% and 28%); however, N(1),N(3)-dialkylated adduct was also observed in trace amounts (<10%). Moreover, N-benzyl adenine derivative 1o was obtained as the N(9)-isomer in 76% yield, while theophylline was mostly alkylated at N(7) to afford 1m (69%).

All compounds were fully characterized and their structures confirmed by ¹H and ¹³C NMR, elemental analysis, mass and IR spectroscopy. Although compounds 2a–2o are expected to be produced as two geometrical isomers (E)- or (Z)-isomer, ¹H and ¹³C NMR analysis indicated that the (E)-isomer was obtained as major product; the minor (Z)-isomer was detected in trace amounts (<5%). To interpret the preference for the (E)-isomers, PM3 semiempirical quantum mechanical calculations were carried out using MOPAC in CS Chem 3D Ultra 8 (Cambridge Soft, 2004) or Hyperchem (Hypercube Inc., Version 7). The results are summarized in Table 2; ΔE refers to the energy difference between the (Z)- and (E)-isomer (ΔE = E_Z – E_E (kcal/mol)). As can be seen in Table 2, calculated ΔE values for all hydrazone derivatives 2a–2o are positive. There is accord between the experimental observations and calculated data (Table 2) which supports the greater stability of the (E)-isomers over the (Z)-isomers and hence predominant formation of the (E)-products.

**Conclusion**

In summary, we have synthesized novel acyclic nucleosides 2a–2o containing a miconazole-like scaffold as well as hydrazine moieties. In this series of acyclic nucleosides, we employed various nucleobases and other imidazole derivatives in place of the imidazole in miconazole. To interpret the dominant formation of the (E)-hydrazone derivatives rather than the (Z)-isomers, PM3 semiempirical quantum mechanical calculations were carried out which showed that the heats of formation of the (E)-isomers were lower.

The biological studies of compounds 2a–2o are currently under investigation and will be reported in due course.

**Experimental**

**General**

All chemicals were purchased from Fluka or Merck. Solvents were purified and dried according to the reported methods [36] and stored over 0.3 nm molecular sieves. The progress of reaction was followed by TLC using silica gel SILG/UV 254 plates. Silica gel 60, 0.063–0.200 mm (70–230 mesh ASTM) was used for column chromatography. IR spectra were run on a Shimadzu FTIR-8300 spectrophotometer. The ¹H NMR (250 MHz) and ¹³C NMR (62.5 MHz) were run on a Bruker Avance DPX-250, FT-NMR spectrometer (δ in ppm, J in Hz). Mass spectra were recorded on a Shimadzu GC MS-QP 1000 EX apparatus. Microanalyses were performed on a Perkin-Elmer 240-B microanalyzer. Melting points (mp) were recorded on a Büchi 510 apparatus in open capillary tubes and are uncorrected.

**General procedure for the synthesis of ketones 1a–1g**

In a two-neck round-bottom flask (100 mL) equipped with a condenser, a mixture of the appropriate N-heterocycle (0.01 mol), the 2-bromoacetophenone (0.012 mol), anhydrous TEA (1.01 g, 0.01 mol) and a catalytic amount of TBAB (0.1 g) was dissolved in dry acetonitrile (40 mL). The mixture was then heated at reflux for 10 h (TLC control). The solvent was evaporated at reduced pressure, the residue dissolved in CHCl₃ (200 mL) and washed with H₂O (2 × 100 mL). The organic layer was dried (10 g of Na₂SO₄) and concentrated to afford the crude product, which was purified by column chromatography on silica gel eluting with an appropriate solvent.

### Table 2: Calculated heat of formation of synthesized hydrazones 2a–2o using PM3.

| Entry | Eₖa | Eₖb | ΔEc |
|-------|-----|-----|-----|
| 2a    | 123.87244 | 129.56016 | 5.68772 |
| 2b    | 85.14540 | 91.62108 | 6.47568 |
| 2c    | 148.47301 | 153.04860 | 4.57559 |
| 2d    | 14.42535 | 21.51980 | 7.09445 |
| 2e    | 142.60529 | 146.16960 | 3.56431 |
| 2f    | 103.74787 | 117.44982 | 13.70195 |
| 2g    | 183.51786 | 198.25266 | 14.68080 |
| 2h    | 26.07071 | 28.66346 | 2.59275 |
| 2i    | -13.34542 | -9.56043 | 3.78499 |
| 2j    | 21.58339 | 24.58239 | 2.99900 |
| 2k    | 17.75077 | 20.31085 | 2.56008 |
| 2l    | 52.80499 | 55.83149 | 3.02560 |
| 2m    | 21.96581 | 24.58239 | 2.66346 |
| 2n    | 52.57276 | 60.37796 | 7.80520 |
| 2o    | 176.15399 | 185.18056 | 9.02517 |

aHeat of formation of (E)-isomer (kcal/mol).
bHeat of formation of (Z)-isomer (kcal/mol).
cΔE = E_Z – E_E (kcal/mol).
General procedure for the synthesis of ketones 1h–1o
In a two-neck round-bottom flask (100 mL) equipped with a condenser, a mixture of the appropriate nucleobase (0.01 mol), the 2-bromoacetophenone (0.012 mol), K$_2$CO$_3$ (1.38 g, 0.01 mol) and a catalytic amount of TBAB (0.1 g) was dissolved in dry DMF (30 mL). The mixture was then heated at reflux for 2–3 h (TLC control). The reaction mixture was then stored in a refrigerator overnight. It was filtered and concentrated under reduced pressure, the residue dissolved in CHCl$_3$ (200 mL) and washed with H$_2$O (2 × 100 mL). The organic layer was dried over anhydrous Na$_2$SO$_4$ and concentrated to a small volume. The residue was dissolved in cold ethanol (2 × 5 mL) and recrystallized from MeOH/H$_2$O (2 × 5 mL) and washed cold ethanol (2 × 5 mL) and recrystallized from MeOH/H$_2$O to afford the pure phenylhydrazone derivatives.

General procedure for the synthesis of hydrazono acyclic nucleoside analogues 2a–2o
In a two-neck round-bottom flask (100 mL) equipped with a condenser, a mixture of the appropriate ketone 1a–1o (0.01 mol), phenylhydrazine (1.62 g, 0.015 mol) and acetic acid (3 drops) was dissolved in ethanol (15 mL) and the mixture was heated at reflux for 15 h (TLC control). The reaction mixture was then stored in a refrigerator overnight. It was filtered and washed with cold ethanol (2 × 5 mL) and recrystallized from MeOH/H$_2$O to afford the pure phenylhydrazone derivatives.

Supporting Information
Supporting information features physical and spectroscopic data for all novel compounds 2a–2o.

Supporting Information File 1
Synthesis of some novel hydrazono acyclic nucleoside analogues
[http://www.beilstein-journals.org/bjoc/content/supporting/1860-5397-6-49-S1.pdf]

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References
1. Georgopapadakou, N. H.; Walsh, T. J. Antimicrob. Agents Chemother. 1996, 40, 279–291.
2. Fisher-Hoch, S. P.; Hultwagner, L. Clin. Infect. Dis. 1995, 21, 897–904.
3. Maccari, R.; Ottàna, R.; Monforte, F.; Vigorita, M. G. Antimicrob. Agents Chemother. 2002, 46, 294–299. doi:10.1128/AAC.46.2.294-299.2002
4. Kleeman, A.; Engel, J.; Kutscher, B.; Reichert, D. Pharmaceutical Substances, 3rd ed.; Thieme: Stuttgart, 1999.
5. Szarvasi, E.; Fontaine, L.; Belbeder-Matbet, A. J. Med. Chem. 1973, 16, 281–287. doi:10.1021/jm00261a027
6. Schenker, E.; Salzmann, R. Arzneim. Forsch. 1979, 29, 1835–1843.
7. Pennington, F. C.; Guevric, P. A.; Solomons, I. A. J. Am. Chem. Soc. 1953, 75, 2261. doi:10.1021/ja01105a514
8. Sah, P. P. T. J. Am. Chem. Soc. 1953, 75, 2512–2513. doi:10.1021/ja01106a516
9. Snyder, H. R., Jr.; Davis, C. S.; Bickerton, R. K.; Halliday, R. P. J. Med. Chem. 1967, 10, 807–810. doi:10.1021/jm00317a011
10. Murdock, K. C.; Child, R. G.; Lin, Y. I.; Warren, J. D.; Fabio, P. F.; Lee, V. J.; Izzo, P. T.; Lang, S. A., Jr.; Angier, R. B.; Citalere, R. V.; Wallace, R. E.; Durr, F. E. J. Med. Chem. 1982, 25, 505–518. doi:10.1021/jm00347a006
11. Mamolo, M. G.; Zampieri, D.; Falagiani, V.; Vio, L.; Ferraglia, M.; Ferrone, M.; Priti, S.; Barfi, E.; Scialinoc, G. ARKIVOC 2004, v, 231–250.
12. Dyer, R. L.; Eilam, G. J.; Hamill, B. J.; Manley, P. W.; Pope, A. M. S. J. Med. Chem. 1983, 26, 442–445. doi:10.1021/jm00357a003
13. De Clercq, E. In Advances in Antiviral Drug Design; Johnson, N. G., Ed.; JAI Press: Greenwich, 1993; Vol. 1, p 88.
14. Pathak, T. Chem. Rev. 2002, 102, 1623–1668. doi:10.1021/cr0104532
15. Agroflogeo, L. A.; Gialione, I.; Saito, Y. Chem. Rev. 2003, 103, 1875–1916. doi:10.1021/cr010374q
16. Huryn, D. M.; Okabe, M. Chem. Rev. 1992, 92, 1745–1768. doi:10.1021/cr00016a004
17. De Clercq, E. Nucleosides Nucleotides 1994, 13, 1271–1295. doi:10.1080/1525779408012151
18. Magdalena, J.; Fernández, S.; Ferrero, M.; Gotor, V. J. Org. Chem. 1998, 63, 8873–8879. doi:10.1021/jo981062z
19. Soltani Rad, M. N.; Khalafi-Nezhad, A.; Behrouz, S.; Asarzi, Z.; Behrouz, M.; Amini, Z. Synthesis 2009, 3067–3076. doi:10.1055/s-0029-1216887
20. Soltani Rad, M. N.; Khalafi-Nezhad, A.; Behrouz, S.; Faghihi, M. A.; Zare, A.; Parhami, A. Tetrahedron 2008, 64, 1778–1785. doi:10.1016/j.tet.2007.11.101
21. Khalafi-Nezhad, A.; Soltani Rad, M. N.; Moosavi-Movahedi, A. A.; Kosari, M. Helv. Chim. Acta 2007, 90, 730–737. doi:10.1002/hlca.200790073
22. Khalafi-Nezhad, A.; Soltani Rad, M. N.; Khoshnood, A. Synthesis 2004, 583–589. doi:10.1055/s-2004-815968
23. Khalafi-Nezhad, A.; Zarea, A.; Soltani Rad, M. N.; Mokhtari, B.; Parhami, A. Synthesis 2005, 419–424. doi:10.1055/s-2004-834950
24. Khalafi-Nezhad, A.; Soltani Rad, M. N.; Hakimelahi, G. H.; Mokhtari, B. Tetrahedron 2002, 58, 10341–10344. doi:10.1016/j.tet.2002090420(02)01414-1
25. Khalafi-Nezhad, A.; Zare, A.; Parhami, A.; Soltani Rad, M. N. ARKIVOC 2006, xii, 161–172.
26. Nardi, D.; Tajiana, A.; Leonardi, A.; Pennini, R.; Portioli, F.; Magistretti, M.; Subissi, A. J. Med. Chem. 1981, 24, 727–731. doi:10.1021/ja01138a017
27. Hofmann, K. The Chemistry of Heterocyclic Compounds: Imidazole and Its Derivatives; Interscience: London, 1953; Part 1.
28. Grimmett, M. R. In Comprehensive Heterocyclic Chemistry II; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996; Vol. 3, p 77.
29. Grimmett, M. R. Adv. Heterocycl. Chem. 1970, 12, 103–183. doi:10.1002/0470572725.0860973-3
30. Hodges, R.; Grimmett, M. R. Aust. J. Chem. 1966, 21, 1085–1087.
31. Häring, M. Helv. Chim. Acta 1959, 42, 1845–1846. doi:10.1002/hlca.19590420612
32. Mathias, L. J.; Burket, D. Tetrahedron Lett. 1979, 20, 4709–4712. doi:10.1016/S0040-4039(01)86690-9
33. Kikugawa, Y. Synthesis **1981**, 124–125.
34. de Savignac, A.; Roques, C.; Hinedi, M.; Michel, G.; Lattes, A. *Eur. J. Med. Chem.* **1990**, *25*, 449–454. doi:10.1016/0223-5234(90)90009-R
35. Liu, Z.-Z.; Chen, H.-C.; Cao, S.-L.; Li, R.-T. *Synth. Commun.* **1993**, *23*, 2611–2615. doi:10.1080/00397919308012596
36. Vogel, A. I. *Practical Organic Chemistry*; Longmans, Green and Co.: London, England, 1954; Chapter 2, pp 161–176.

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