Design and Synthesis of Some Novel Oxiconazole-Like Carboacyclic Nucleoside Analogues, as Potential Chemotherapeutic Agents

by **Mohammad Navid Soltani Rad***[a]), **Ali Khalafi-Nezhad***[b]), and **Somayeh Behrouz**[b])

[a]) Department of Chemistry, Faculty of Basic Sciences, Shiraz University of Technology, Shiraz 71555-313, Iran (phone: +98-711-7261392; fax: +98-711-7354523; e-mails: soltani@sutech.ac.ir; nsoltanirad@gmail.com)

[b]) Department of Chemistry, College of Sciences, Shiraz University, Shiraz 71454, Iran

The syntheses of some novel carboacyclic nucleosides, **17a**–**17o**, containing oxiconazole-like scaffolds, are described (*Schemes 1–3*). In this series of carboacyclic nucleosides, pyrimidine as well as purine and other imidazole derivatives were employed as an imidazole successor in oxiconazole. These compounds could be prepared in good yields by using two different strategies (*Schemes 1* and *2*). Due to *Scheme 1*, the *N*-coupling of nucleobases with 2-bromoacetophenones was attained for **18a**–**18e**, and their subsequent oximation affording **19a**–**19e** and finally *O*-alkylation with diverse alkylating sources resulted in the products **17a**–**17g**, **17n**, and **17o**. In *Scheme 2*, use of 2-bromoacetophenone oximes **20**, followed by *N*-coupling of nucleobases, provided **19f**–**19j** whose final *O*-alkylation produced **17h**–**17m** (*Scheme 2*). For the rational interpretation of the dominant formation of (*E*)-oxime ethers rather than (*Z*)-oxime isomers, PM3 semiempirical quantum-mechanic calculations were discussed and the calculations indicated a lower heat of formation for (*E*)-isomers.

Introduction. – The incidence of infections caused by pathogenic fungi has increased significantly over the years [1]. Nowadays, numerous antifungal drugs with various structures and scaffolds are known and available. However, their clinical uses have been limited by the emergence of drug resistance, high risk of toxicity, insufficiencies in their antifungal activity, and undesirable side effects. Hence, there is still a need to develop and extend the safe and efficient chemotherapeutic agents with a potent broad spectrum of antifungal activities.

Ergosterol is the major sterol of the fungal cell membrane. The azoles, which are a well-known class of antifungal agents, disrupt ergosterol biosynthesis through the inhibition of cytochrome P450-dependent 14α-lanosterol demethylase ($P\text{-}450_{14DM}$) [2][3]. The structures of several famous imidazole antifungal drugs **1**–**16** are shown in *Fig. 1*. One of the most established antifungal azole drugs having rational versatility in structures is the miconazole family **5**–**16** (*Fig. 1*). The principal structural outline to miconazole-analogue frameworks was attained by the structure–activity-relationship (SAR) studies of these antifungals. These studies reveal the presence of a pharmacophoric portion in all of these molecules, which is characterized by a phenyl ring linked by an ethane chain to an N-atom of an azole ring (*Fig. 2*) [4].

Oximes and oxime ether derivatives are a prominent structural motif found in numerous pharmaceutically active compounds. Many well-known drugs with various chemotherapeutic activities, such as antiviral (*e.g.*, enviroxime) [5] and anti-inflam-

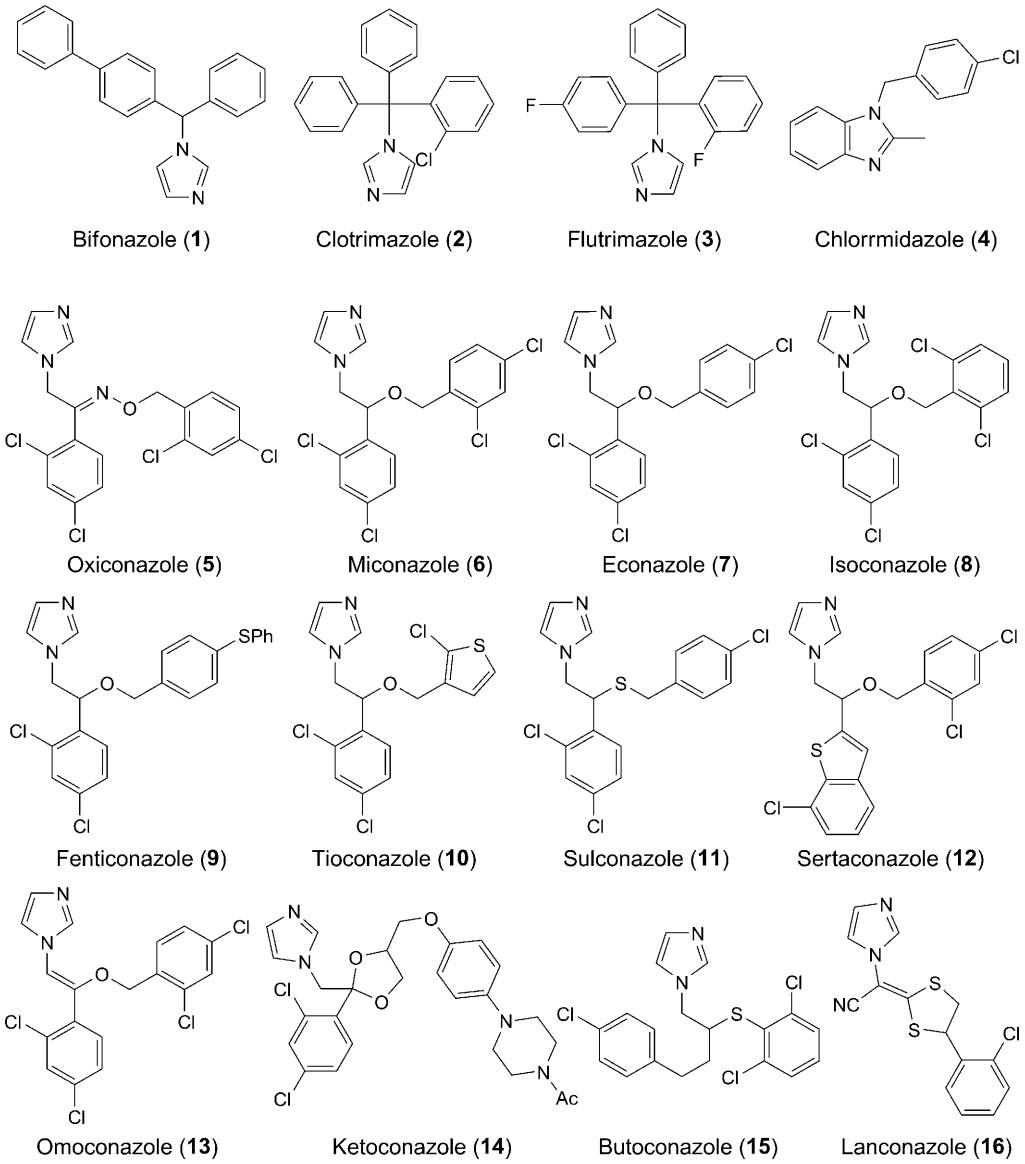


Fig. 1. *The structures of well-known imidazole antifungals*

matory agents (*e.g.*, pifoxime) [6], antidepressants (*e.g.*, fluvoxamine) [6], nerve agent antidotes (*e.g.*, pralidoxime) [6][7], cephalosporin antibiotics (*e.g.*, cefixime) [8], macrolide antibiotics (*e.g.*, roxithromycin) [9], and thromboxane synthase inhibitors (*e.g.*, ridogrel) [10], contain an oxime or oxime ether moiety in their structures. Furthermore, oxiconazole **5** [11] is a well-known established antifungal drug that also includes the oxime ether moiety. Recently, various structurally related oxiconazole

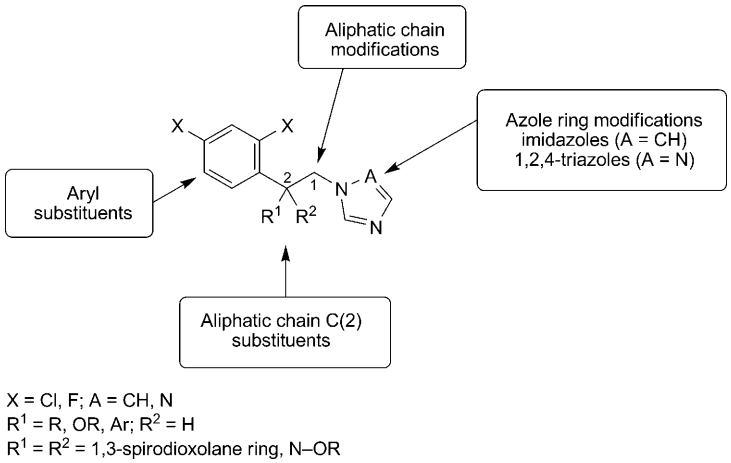
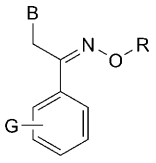


Fig. 2. *The SAR outline for azole antifungals analogue to miconazole* **5**–**16**

bioactive compounds including chromanone [12], nafimidone [13], and tetrahydronaphthyl [14] derivatives have been reported.

The significance of nucleoside chemistry in drug discovery is well demonstrated and fully established in medicinal chemistry [15]. Carboacyclic nucleosides are one of the most famous acyclic nucleoside subclasses which were proved to have remarkable chemotherapeutic activities against cancer and infections caused by viruses, microbes, and other pathogenic microorganisms.

Inspired by the oxiconazole scaffold and also in continuation of our interest in the design and synthesis of novel carboacyclic nucleosides [16], we report the synthesis of some novel carboacyclic nucleosides containing oxiconazole-like scaffolds. In these compounds the pyrimidine as well as purine and other imidazole derivatives were considered as imidazole moiety successors in oxiconazole. The general structure of the title compounds is shown in *Fig. 3*.



17

B = purine, pyrimidine, *N*-heterocycles
R = benzyl, allyl, alkyl
G = H, Ph

Fig. 3. *The general structure of oxiconazole-like carboacyclic nucleoside* **17**

Results and Discussion. – The synthetic pathways for compounds **17a**–**7g** and **17h**–**17m** are outlined in *Schemes 1* and *2*, respectively. Two different strategies were considered for the synthesis of the title compounds with regard to discrepancies in chemical behaviors of purine and pyrimidine nucleobases in comparison with the azole family. The azole derivatives were synthesized according to *Scheme 1* due to their

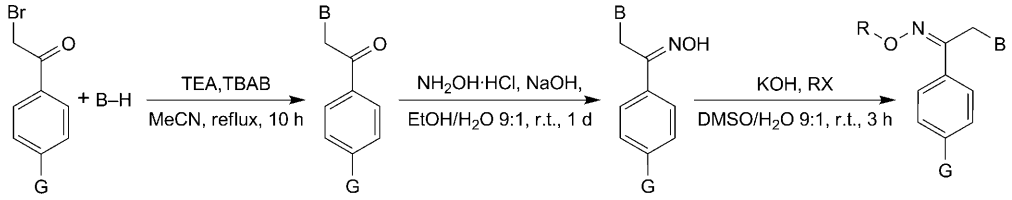
better solubility, reactivity, and ease of separating of reaction products. According to *Scheme 1*, the condensation of benzimidazole, benzotriazole, imidazole, and 2-phenylimidazole was initially achieved with 2-bromoacetophenone for the synthesis of ketones **18a**–**18e** as key intermediates. On the basis of a literature survey, we recognized that among published methods for *N*-alkylation of imidazole derivatives [17], a method established by *Liu et al.* [18] is the most appropriate one for *N*-alkylation of azoles and their derivatives, because in this method the formation of quaternary imidazolium salts is largely prevented. However, in our experience, using Et_3N (TEA) as a homogeneous base instead of K_2CO_3, which was previously employed by *Liu et al.*, afforded more satisfactory results. Hence, the reaction of imidazole or benzimidazole derivatives with 2-bromoacetophenones and TEA in the presence of a catalytic amount of Bu_4NBr (TBAB) in refluxing anhydrous acetonitrile (MeCN) provided the ketones **18a**–**18e** in good yields (61–71%). Subsequently, the ketones **18a**–**18e** were converted to the oxime derivatives **19a**–**19e** by stirring with hydroxylamine hydrochloride in the presence of aqueous NaOH in EtOH at room temperature for one day (*Scheme 1*).

Oximes **19a**–**19e** are significant and attractive precursors for the synthesis of the title compounds. They can react with diverse alkyl halides or other sources of carbon electrophiles. For example, the reaction of oximes **19a**, **19c**, and **19e** with benzyl bromide in a solution of KOH in H_2O/DMSO (1:9) by stirring at room temperature afforded the products **17a**, **17c**, and **17f** in good yields, respectively (88, 87, and 87%). Furthermore, other alkyl halides such as (2-chloroethoxy)benzene and allyl bromide were condensed with oximes **19a** and **19b**, and 1-chloro-4-(3-chloropropoxy)benzene with oxime **19d** gave the corresponding products **17b**, **17d**, and **17e** in good to reasonable yields, accordingly. We have recently published the aqueous-mediated ring opening of epoxides with oximes for obtaining β-hydroxy oxime *O*-ethers as potential β-adrenergic blocking agents [19]. In that context, we synthesized compound **17g** from the regioselective ring opening of 2-(phenoxymethyl)oxirane by oxime **19a** in 78% yield.

For the synthesis of the nucleoside analogs of the target compounds **17h**–**17m**, we envisaged a substantial problem for processing the synthesis using a similar pathway as shown in *Scheme 1*. Unfortunately, the corresponding oximes **19f**–**19j** were not obtained by the method described for the synthesis of compounds **19a**–**19e** in *Scheme 1*. There are two main factors that limited the usage of the aforementioned pathway described in *Scheme 1* for nucleobases: *i*) the low yield of the synthesis of corresponding oximes **19** from ketones **18** (20–30%), *ii*) cumbersome purification processes and failure of separation using conventional column chromatography for the ketones **18**. Thus, we have modified the procedure of *Scheme 1* by first performing an oximation of 2-bromoacetophenone [20], and subsequently coupling the attained oxime **20** with the desired nucleobases (*Scheme 2*).

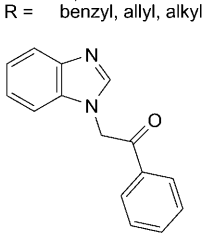
As shown in *Scheme 2*, the oximation of 2-bromoacetophenone provided an considerable amount of 2-bromo-1-phenylethanone oxime **20** for the next reaction step. The coupling of base-activated purine and pyrimidine nucleobases as well as theophylline and 2-methyl-4(5)-nitro-1*H*-imidazole by K_2CO_3 in anhydrous DMF under reflux provided the *N*-alkylation adducts **19f**–**19j** in moderate yields (31, 40, 45, 54, and 61%, resp.). In these syntheses, the *N*-alkylation reactions of nucleobases were achieved regioselectively. In the case of uracil, the *N*(1)-alkylated compound **19f** was

Scheme 1

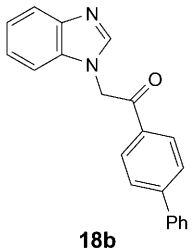


18a – 18e **19a – 19e** **17a – 17g**

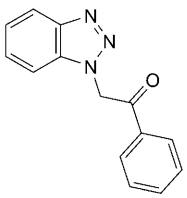
B–H = benzimidazole, benzotriazole, imidazole, 2-phenylimidazole
G = H, Ph
R = benzyl, allyl, alkyl



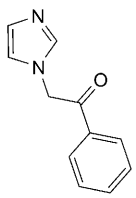
18a



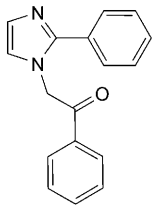
18b



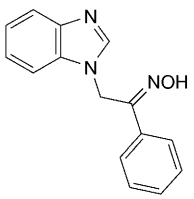
18c



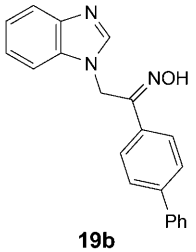
18d



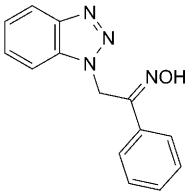
18e



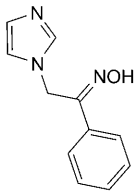
19a



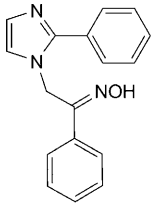
19b



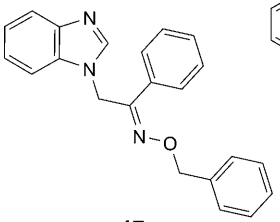
19c



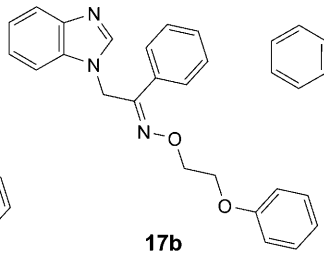
19d



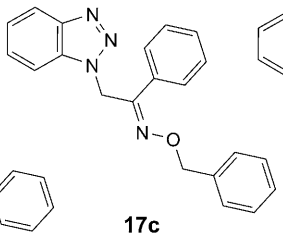
19e



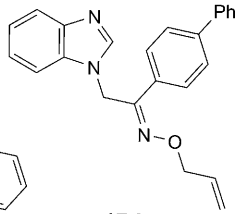
17a



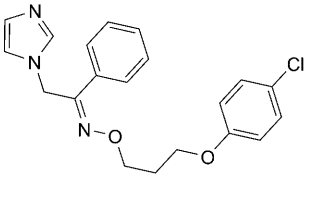
17b



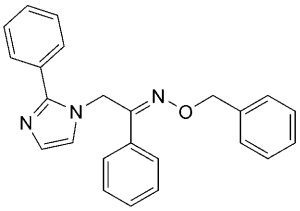
17c



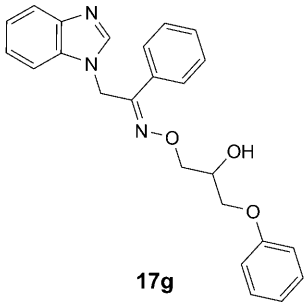
17d



17e

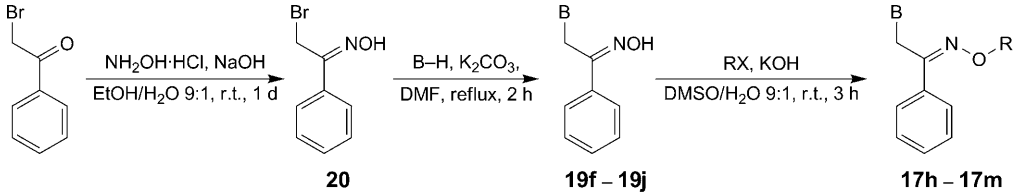


17f



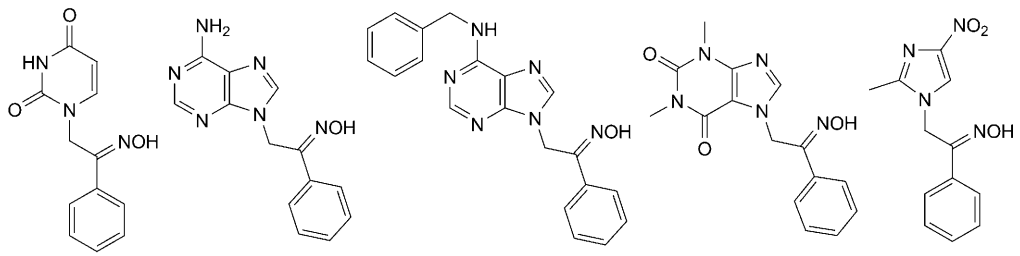
17g

Scheme 2

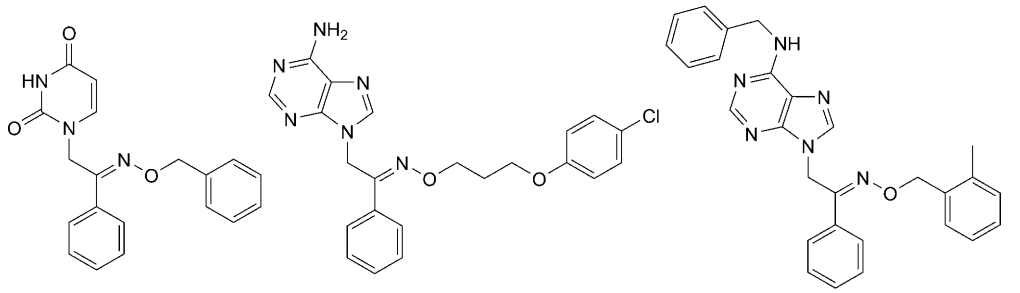


20 **19f – 19j** **17h – 17m**

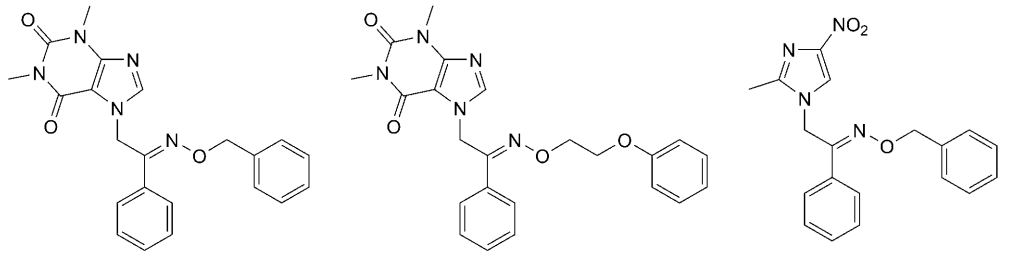
B–H = uracil, adenine, *N*-benzyladenine, theophylline, 2-methyl-4(5)-nitro-1*H*-imidazole
R = benzyl, alkyl



19f **19g** **19h** **19i** **19j**



17h **17i** **17j**



17k **17l** **17m**

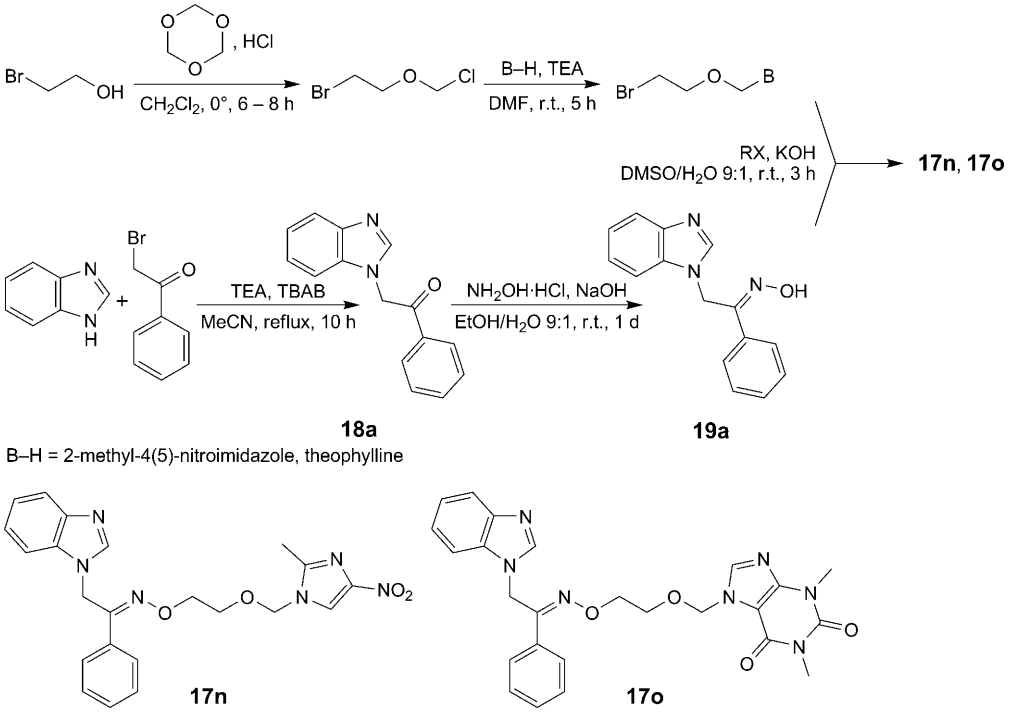
obtained dominantly (31%); however, the *N*(1),*N*(3)-dialkylated adduct was also observed in trace amounts (<10%). Moreover, adenine and *N*-benzyl adenine derivatives **19g** and **19h** were obtained as the N(9)-isomer in yields of 40 and 45%; while theophylline was mostly alkylated to yield the N(7)-isomer **19i** (54%).

From 2-methyl-4(5)-nitro-1*H*-imidazole which possesses considerable medical applications as a chemotherapeutic agent and is of potential agricultural interest

[21], the oxime **19j** was synthesized. In agreement with [18][22], the *N*-alkylation of 2-methyl-4(5)-nitro-1*H*-imidazole with **20** afforded mainly the respective 4-NO_2-isomer **19j** rather than the 5-NO_2-isomer. The oxiconazole nucleoside analogs **17a**–**17m** were prepared by treatment of oximes **19a**–**19j** with various alkyl halides in the presence of aqueous KOH in DMSO at room temperature (*Schemes 1* and *2*).

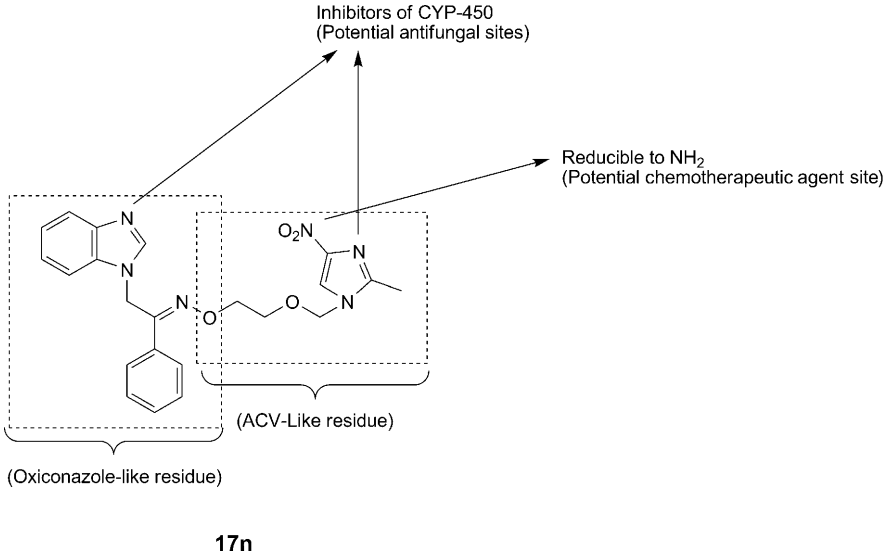
Inspired by the acyclovir (ACV, *Zovirax*) framework as potent antiviral agent against herpes simplex virus 1&2 (HSV-1, 2), we designed and synthesized the novel oxiconazole-like compounds **17n** and **17o** consisting of two ACV- and oxiconazole-like substructures. The synthetic route for compounds **17n** and **17o** is summarized in *Scheme 3.* As shown in *Scheme 3*, for the synthesis the ACV-like part of compounds **17n** and **17o**, we first prepared the prerequisite α-chloro ether (1-bromo-2-(chloromethoxy)ethane) using 2-bromoethanol and 1,3,5-trioxane solutions in anhydrous CH_2Cl_2, which was exposed to continuous dry HCl gas stream line at 0° for 6–8 h [16a][23]. 1-Bromo-2-(chloromethoxy)ethane was then coupled with 2-methyl-4(5)-nitro-1*H*-imidazole (for the preparation of compound **17n**) or theophylline (for the preparation of compound **17o**) using an equimolar solution of TEA in anhydrous DMF at room temperature for 5 h. The obtained ACV-like part molecule was then coupled with the oxime **19a**, the synthesis of which was described above in *Scheme 1.*

Scheme 3



Our approach to the synthesis of compounds **17n** and **17o** was to design a novel therapeutic agent based on the remarkable biological activity of 2-methyl-4(5)-nitro-

1*H*-imidazole as a potent chemotherapeutic agent as well as theophylline as an attractive agent with coronary vasodilation, cardiotonic, bronchodilatoion, antihistaminic, and antiasthmatic properties [6]. For instance, we think that compound **17n** (*Fig. 4*) can have more than a single biological activity, as it is known in the case of oxiconazole to be only an antifungal agent. We assume that the 2-methyl-4(5)-nitro-1*H*-imidazole part can be a useful residue in potential biological activities upon enzymatic reduction of the 4-NO_2 group into a free amine [21a]. Furthermore, the benzimidazole residue in the oxiconazole-like as well as in the imidazole core in ACV-like residues potentially can inhibit CYP-450 to prevent membrane cell construction in fungi [2][3].



17n

Fig. 4. *The structural designing view of compound* **17n**

All compounds were fully characterized, and their structures were confirmed by ^{1}H- and ^{13}C-NMR, elemental analysis, mass and IR spectroscopy. Compounds **17a**–**17o** were expected to be produced as two geometrical isomers ((*E*)- or (*Z*)-isomer); however, (*E*)-isomers were obtained dominantly as its structure was identified by ^{1}H- and ^{13}C-NMR analysis; the minor (*Z*)-isomer was also detected in trace amounts (< 7%). For a rational interpretation of the excessive formation of (*E*)-isomers rather than (*Z*)-isomers, a PM3 semiempirical quantum mechanic calculation was applied using MOPAC in CS Chem 3D Ultra 8 (*Cambridge Soft*, 2004) or Hyperchem (*Hypercube Inc.*, Version 7). The results are summarized in the *Table*, in which ΔE refers to the discrepancy of energy between the (*Z*)- and (*E*)-isomer ($\Delta E = E_Z - E_E$ (kcal/mol)). As can be seen (*Table*), calculated ΔE for all oxime ethers **17a**–**17o** have a positive value. There is conformity to the experimental observations and calculated data (*Table*) which endorses the higher stability of (*E*)-isomers in comparison with (*Z*)-isomers, and hence predominant formation of (*E*)-products.

Table. *Calculated Heat of Formation of Synthesized Oxime Ethers* **17a**–**17o** *Using PM3*

	E_E[a])	E_Z[b])	ΔE[c])
17a	118.28791	118.78426	0.49635
17b	89.16137	93.41994	4.25857
17c	41.98483	48.64398	6.65915
17d	138.67261	144.26355	5.59094
17e	155.37681	161.41013	6.03332
17f	57.15787	59.56520	2.40733
17g	124.89792	134.90852	10.01060
17h	1.20885	11.06290	9.85405
17i	80.60935	85.65297	5.04362
17j	142.43687	147.01618	4.57931
17k	23.16306	25.06594	1.90288
17l	– 13.67089	– 12.78417	0.88672
17m	251.47961	351.12156	99.64195
17n	228.66448	249.38301	20.71853
17o	18.53776	20.02120	1.48344

[a]) Heat of formation of the (*E*)-isomer (kcal/mol). [b]) Heat of formation of the (*Z*)-isomer (kcal/mol). [c]) $\Delta E = E_Z - E_E$ (kcal/mol).

The biological studies of **17a**–**17o** are currently under investigation and will be reported in due course.

We appreciate *Shiraz University of Technology* and *Shiraz University Research Councils* for partial support of this work. We are also grateful to Mr. *H. Sajedian Fard* for recording NMR spectra.

Experimental Part

1. *General*. All chemicals were obtained from *Fluka* or *Merck*. Solvents were purified and dried by standard procedures, and stored over 3-Å molecular sieves. Reactions were followed by TLC using *SILG/UV 254* silica-gel plates. Column chromatography (CC): silica gel *60* (SiO_2; 0.063–0.200 mm, 70–230 mesh; *ASTM*). Melting points (M.p.): *Büchi 510* apparatus; in open capillaries (uncorrected). IR Spectra: *Shimadzu FT-IR-8300* spectrophotometer; in cm^{-1}. ^1H- and ^{13}C-NMR Spectra: *Bruker Avance-DPX-250* spectrometer; at 250/62.5 MHz, resp., δ in ppm, *J* in Hz. GC/MS: *Shimadzu GC/MS-QP 1000-EX* apparatus; in *m/z* (rel. %). Elemental analyses (CHNS) were performed on a *Perkin-Elmer 240-B* micro-analyzer.

2. *General Procedure for the Synthesis of Ketones* **18a**–**18e**. In a double-necked round bottomed flask (100 ml) equiped with a condenser, a mixture of the appropriate *N*-heterocyle (0.01 mol), 2-bromoacetophenone (2.38 g, 0.012 mol), anh. TEA (1.01 g, 0.01 mol), and cat. amounts of TBAB (0.1 g) were dissolved in dry MeCN (40 ml). Then, the mixture was heated to reflux for 10 h (TLC control). The solvent was evaporated at reduced pressure, the residue was dissolved in $CHCl_3$ (200 ml), and washed with H_2O (2 × 100 ml). The org. layer was dried (10 g of Na_2SO_4) and concentrated to afford the crude product, which was purified by CC on SiO_2 eluting with appropriate solvents.

3. *General Procedure for the Synthesis of Oximes* **19a**–**19e**. In a round bottomed flask (100 ml) a mixture of the appropriate ketone **18a**–**18e** (0.01 mol), hydroxylamine hydrochloride (1.03 g, 0.015 mol), NaOH (0.6 g, 0.015 mol), and H_2O (minimum amount for solvation of hydroxylamine hydrochloride and NaOH) was dissolved in EtOH (20 ml), and then the soln. was stirred for 24 h at r.t. Afterwards, the mixture was poured into 20 g ice/10 g H_2O. Oxime precipitate immediately formed which was filtered and washed with cold H_2O and dried. Recrystallization from hot MeOH/H_2O afforded pure oximes **19a**–**19e** which were used for the next step.

4. *General Procedure for the Synthesis of Compounds* **19f**–**19j**. In a double-necked round bottomed flask (100 ml) equiped with a condenser, a mixture of the appropriate nucleobase (0.01 mol) and K_2CO_3 (1.38 g, 0.01 mol) was dissolved in DMF (30 ml) and stirred for 20 min under reflux. Subsequently, oxime **20** (2.20 g, 0.013 mol) was added to the mixture and heated under reflux for 1.5 h (TLC control). The solvent was evaporated at reduced pressure, the residue was dissolved in AcOEt (200 ml), and washed with H_2O (2×100 ml). The org. layer was dried (10 g of Na_2SO_4) and concentrated to afford the crude product, which was purified by CC on SiO_2 eluting with appropriate solvents.

5. *General Procedure for the Synthesis of Compounds* **17a**–**17o**. In a double-necked round bottomed flask (100 ml) equipped with a condenser, an appropriate alkyl halide (0.013 mol) was added portionwise to a soln. of the appropriate oxime (0.01 mol), KOH (0.56 g, 0.01 mol), and 2 ml of H_2O in DMSO (20 ml). The mixture was stirred for 2–4 h at r.t. (TLC control). Then, the crude product was dissolved in $CHCl_3$ (150 ml) and washed with H_2O (3×200 ml). The org. layer was dried (10 g of Na_2SO_4) and concentrated to afford the crude product, which was purified by CC on SiO_2 eluting with proper solvents.

6. *Synthesis of 1-Bromo-2-(chloromethoxy)ethane.* In a three-necked bottom flask (250 ml), a soln. of 2-bromoethanol (12.4 g, 0.1 mol) and 1,3,5-trioxane (3.5 g, 0.04 mol) in anh. CH_2Cl_2 (150 ml) was stirred for moments to provide a homogeneous mixture. Then, the flask was immersed in an ice bath, and dry HCl gas was bubbled through the mixture for 8 h. Afterwards, the mixture was diluted with 100 ml of dry CH_2Cl_2 and transferred into a canonical flask (150 ml) equipped with moisture absorbent tube, containing 20 g anh. $CaCl_2$. The mixture was shaken vigorously for 15 min. The mixture was then flash-filtered, and the solvent was evaporated in a rotavapor. The remaining liquid was corked and stored in refrigerator.

*2-(1*H*-Benzimidazol-1-yl)-1-phenylethanone* (**18a**). Purified by CC (SiO_2; AcOEt/hexane 8:2). Yield: 1.49 g (63%). Pale-yellow crystals. R_f (AcOEt) 0.39. M.p. 150–152°. IR (KBr): 3047.3*m*, 2939.3*m*, 1710.8*s*, 1596.9*m*, 1581.5*m*, 1373.2*m*. ^{1}H-NMR ($CDCl_3$): 8.01–7.16 (*m*, 9 arom. H, H–C(2) of benzimidazole); 5.43 (*s*, NCH_2). ^{13}C-NMR ($CDCl_3$): 50.31; 109.40; 120.37; 122.30; 123.23; 128.02; 129.12; 134.10; 134.23; 134.44; 143.46; 143.87; 191.43. MS: 236.09 (30.8, M^+). Anal. calc. for $C_{15}H_{12}N_2O$ (236.27): C 76.25, H 5.12, N 11.86; found: C 76.17, H 5.07, N 11.94.

*2-(1*H*-Benzimidazol-1-yl)-1-(1,1′-biphenyl-4-yl)ethanone* (**18b**). Purified by CC (SiO_2; AcOEt/hexane 8:2). Yield: 1.90 g (61%). Yellow crystals. R_f (AcOEt) 0.36. M.p. 222–224°. IR (KBr): 3078.2*m*, 2823.6*m*, 1715.8*s*, 1596.9*s*, 1488.9*m*. ^{1}H-NMR ((D_6)DMSO): 8.22–7.20 (*m*, 13 arom. H, H–C(2) of benzimidazole); 6.07 (*s*, NCH_2). ^{13}C-NMR ((D_6)DMSO): 50.72; 110.54; 119.29; 121.42; 122.29; 127.02; 128.55; 128.89; 129.11; 133.22; 134.67; 138.66; 143.12; 144.95; 145.26; 145.31; 192.93. MS: 312.12 (24.1, M^+). Anal. calc. for $C_{21}H_{16}N_2O$ (312.36): C 80.75, H 5.16, N 8.97; found: C 80.67, H 5.24, N 8.91.

*2-(1*H*-Benzotriazol-1-yl)-1-phenylethanone* (**18c**). Purified by CC (SiO_2; AcOEt/hexane 2:8). Yield: 1.54 g (65%). Pale-yellow crystals. R_f (AcOEt) 0.75. M.p. 112–114°. IR (KBr): 3024.2*m*, 2908.4*m*, 1951.8*m*, 1710.5*s*, 1604.7*s*, 1488.9*m*. ^{1}H-NMR ($CDCl_3$): 8.04–7.27 (*m*, 9 arom. H); 6.06 (*s*, NCH_2). ^{13}C-NMR ($CDCl_3$): 53.82; 109.61; 119.97; 123.99; 127.77; 128.23; 128.47; 129.10; 133.94; 134.51; 146.00; 190.52. MS: 237.09 (19.6, M^+). Anal. calc. for $C_{14}H_{11}N_3O$ (237.26): C 70.87, H 4.67, N 17.71; found: C 70.96, H 4.75, N 17.63.

*2-(1*H*-Imidazol-1-yl)-1-phenylethanone* (**18d**). Purified by CC (SiO_2; AcOEt). Yield: 1.13 g (61%). Yellow-orange crystals. R_f (AcOEt) 0.27. M.p. 116–118°. IR (KBr): 3047.3*m*, 2954.7*m*, 2908.4*m*, 1714.5*s*, 1589.2*s*, 1434.9*s*. ^{1}H-NMR ((D_6)DMSO): 8.03–8.00 (*m*, 2 arom. H); 7.55–7.50 (*m*, 3 arom. H, H–C(2) of imidazole); 7.14 (*s*, H–C(4) of imidazole); 6.96 (*s*, H–C(5) of imidazole); 5.76 (*s*, NCH_2). ^{13}C-NMR ((D_6)DMSO): 52.57; 120.90; 127.42; 127.93; 128.57; 133.88; 134.42; 138.33; 193.56. MS: 186.07 (33.2, M^+). Anal. calc. for $C_{11}H_{10}N_2O$ (186.21): C 70.95, H 5.41, N 15.04; found: C 70.86, H 5.35, N 15.11.

*1-Phenyl-2-(2-phenyl-1*H*-imidazol-1-yl)ethanone* (**18e**). Purified by CC (SiO_2; AcOEt/hexane 8:2). Yield: 1.86 g (71%). Bright brown oil. R_f (AcOEt) 0.49. IR (film): 3053.1*m*, 2954.7*m*, 2829.4*m*, 1715.7*s*, 1606.6*s*, 1506.3*s*, 1172.6*s*. ^{1}H-NMR ($CDCl_3$): 8.00–7.95 (*m*, 2 arom. H); 7.71–7.68 (*m*, 3 arom. H); 7.58–7.51 (*m*, 5 arom. H); 7.03 (*s*, H–C(4) of imidazole); 6.82 (*s*, H–C(5) of imidazole); 5.28 (*s*, NCH_2). ^{13}C-NMR ($CDCl_3$): 44.75; 119.11; 119.81; 127.41; 124.74; 132.01; 133.48; 134.52; 134.85; 142.16; 142.72; 150.35; 193.04. MS: 262.11 (29.9, M^+). Anal. calc. for $C_{17}H_{14}N_2O$ (262.31): C 77.84, H 5.38, N 10.68; found: C 77.79, H 5.42, N 10.71.

*2-(1*H*-Benzimidazol-1-yl)*-N-*hydroxy-1-phenylethanimine* (**19a**). Recrystallized from MeOH/H_2O. Yield: 2.38 g (95%). Pale-yellow crystals. R_f (AcOEt) 0.53. M.p. 205–207°. IR (KBr): 3264.1 (br.), 3039.6*m*, 2864.1*m*, 1690.4*s*, 1593.1*m*, 1456.2*s*. ^{1}H-NMR ((D$_6$)DMSO): 12.27 (*s*, OH, exchangeable with D_2O); 8.31 (*s*, H–C(2) of benzimidazole); 7.63–7.48 (*m*, 4 arom. H); 7.21–7.11 (*m*, 5 arom. H); 5.66 (*s*, NCH_2). ^{13}C-NMR ((D$_6$)DMSO): 37.67; 110.14; 119.20; 121.80; 122.62; 126.24; 128.00; 128.38; 129.08; 133.76; 142.52; 144.34; 151.64. MS: 251.10 (17.5, M^+). Anal. calc. for $C_{15}H_{13}N_3O$ (251.28): C 71.70, H 5.21, N 16.72; found: C 71.65, H 5.22, N 16.68.

*2-(1*H*-Benzimidazol-1-yl)-1-(biphenyl-4-yl)*-N-*hydroxyethanimine* (**19b**). Recrystallized from MeOH/H_2O. Yield: 2.88 g (88%). White crystals. R_f (AcOEt) 0.50. M.p. 213–215°. IR (KBr): 3525.6 (br.), 3035.2*s*, 2839.0*s*, 1680.4*m*, 1488.9*s*. ^{1}H-NMR ((D$_6$)DMSO): 11.95 (*s*, OH, exchangeable with D_2O); 8.35 (*s*, H–C(2) of benzimidazole); 7.79–7.18 (*m*, 13 arom. H); 5.67 (*s*, NCH_2). ^{13}C-NMR ((D$_6$)DMSO): 36.71; 110.92; 119.13; 121.40; 122.23; 125.24; 126.31; 126.56; 127.25; 128.83; 133.74; 135.59; 138.57; 139.59; 143.06; 144.47; 147.35. MS: 327.13 (23.6, M^+). Anal. calc. for $C_{21}H_{17}N_3O$ (327.38): C 77.04, H 5.23, N 12.84; found: C 77.12, H 5.29, N 12.89.

*2-(1*H*-Benzotriazol-1-yl)*-N-*hydroxy-1-phenylethanimine* (**19c**). Recrystallized from MeOH/H_2O. Yield: 2.37 g (94%). White crystals. R_f (AcOEt) 0.76. M.p. 186–188°. IR (KBr): 3364.1 (br.), 3039.6*m*, 2864.1*m*, 1687.4*s*, 1593.1*m*, 1456.2*s*. ^{1}H-NMR ((D$_6$)DMSO): 12.22 (*s*, OH, exchangeable with D_2O); 8.15–7.28 (*m*, 9 arom. H); 6.07 (*s*, NCH_2). ^{13}C-NMR ((D$_6$)DMSO): 54.08; 119.04; 126.22; 127.30; 128.20; 128.32; 128.90; 129.10; 133.97; 134.22; 145.10; 150.65. MS: 252.10 (23.6, M^+). Anal. calc. for $C_{14}H_{12}N_4O$ (252.27): C 66.65, H 4.79, N 22.21; found: C 66.67, H 4.82, N 22.24.

N-*Hydroxy-2-(1*H*-imidazol-1-yl)-1-phenylethanimine* (**19d**). Recrystallized from MeOH/H_2O. Yield: 1.91 g (95%). White crystals. R_f (AcOEt): 0.24. M.p. 163–165°. IR (KBr): 3234.1 (br.), 3118.7*s*, 2988.2*m*, 1684.2*m*, 1575.7*m*, 14407*s*. ^{1}H-NMR ((D$_6$)DMSO): 12.29 (*s*, OH, exchangeable with D_2O); 7.68–7.34 (*m*, 5 arom. H, H–C(2) of imidazole); 7.05 (*s*, H–C(4) of imidazole); 6.84 (*s*, H–C(5) of imidazole); 5.33 (*s*, NCH_2). ^{13}C-NMR ((D$_6$)DMSO): 39.04; 119.53; 125.96; 128.30; 128.48; 129.10; 133.96; 137.59; 151.81. MS: 201.09 (35.7, M^+). Anal. calc. for $C_{11}H_{11}N_3O$ (201.22): C 65.66, H 5.51, N 20.88; found: C 65.69, H 5.53, N 20.87.

N-*Hydroxy-1-phenyl-2-(2-phenyl-1*H*-imidazol-1-yl)ethanimine* (**19e**). Recrystallized from MeOH/H_2O. Yield: 2.58 g (93%). Pale-yellow crystals. R_f (AcOEt) 0.51. M.p. 167–169°. IR (KBr): 3139.9 (br.), 3070.5*m*, 2977.9*m*, 1690.2*s*, 1527.5*s*, 1404.1*m*. ^{1}H-NMR ((D$_6$)DMSO): 12.03 (*s*, OH, exchangeable with D_2O); 7.55–7.21 (*m*, 10 arom. H); 7.09 (*d*, J = 1.0, H–C(4) of imidazole); 6.91 (*d*, J = 1.0, H–C(5) of imidazole); 5.42 (*s*, NCH_2). ^{13}C-NMR ((D$_6$)DMSO): 40.87; 121.57; 126.04; 127.70; 127.90; 127.98; 128.15; 128.32; 128.85; 130.52; 133.98; 146.84; 152.24. MS: 277.12 (56.8, M^+). Anal. calc. for $C_{17}H_{15}N_3O$ (277.32): C 73.63, H 5.45, N 15.15; found: C 73.69, H 5.48, N 15.12.

*1-[2-(Hydroxyimino)-2-phenylethyl]pyrimidine-2,4(1*H*,3*H*)-dione* (**19f**). Purified by CC (SiO_2; AcOEt/hexane 6:4). Yield: 0.76 g (31%). Pale-yellow crystals. R_f (AcOEt) 0.51. M.p. 164–166°. IR (KBr): 3321.2 (br.), 3254.9*s*, 3108.5*m*, 3047.3*m*, 2839.1*m*, 1690.8*m*, 1662*s*, 1659.2*s*, 1450.4*m*. ^{1}H-NMR ((D$_6$)DMSO): 12.01 (*s*, OH, exchangeable with D_2O); 10.75 (*s*, NH, exchangeable with D_2O); 7.65 (*d*, J = 7.2, H–C(6) of uracil); 7.85–7.19 (*m*, 5 arom. H); 5.24 (*d*, J = 7.2, H–C(5) of uracil); 5.01 (*s*, NCH_2). ^{13}C-NMR ((D$_6$)DMSO): 51.25; 100.64; 127.83; 128.57; 128.89; 134.15; 146.12; 151.02; 155.15; 163.80. MS: 245.08 (11.6, M^+). Anal. calc. for $C_{12}H_{11}N_3O_3$ (245.23): C 58.77, H 4.52, N 17.13; found: C 58.69, H 4.61, N 17.05.

*9-[2-(Hydroxyimino)-2-phenylethyl]-9*H*-purin-6-amine* (**19g**). Purified by CC (SiO_2; AcOEt/MeOH 10:1). Yield: 1.07 g (40%). White crystals. TLC (AcOEt/MeOH 10:1): R_f 0.45. M.p. 233–235°. IR (KBr): 3374.2 (br.), 3300–3100*s*, 3042.5*m*, 3019.2*m*, 2898.6*m*, 2338.1*m*, 1685.5*s*, 1579.7*m*, 1459.1*m*. ^{1}H-NMR ((D$_6$)DMSO): 12.00 (*s*, OH, exchangeable with D_2O); 8.13 (*s*, H–C(8) of adenine); 7.99 (*s*, H–C(2) of adenine); 7.63 (*s*, NH_2, exchangeable with D_2O), 7.28–7.18 (*m*, 5 arom. H); 5.42 (*s*, NCH_2). ^{13}C-NMR ((D$_6$)DMSO): 36.88; 118.01; 126.26; 128.26; 128.96; 133.99; 140.74; 149.38; 152.11; 152.51; 155.81. MS: 258.10 (15.1, M^+). Anal. calc. for $C_{13}H_{12}N_6O$ (268.27): C 58.20, H 4.51, N 31.33; found: C 58.25, H 4.49, N 31.37.

N-*Benzyl-9-[2-(hydroxyimino)-2-phenylethyl]-9*H*-purin-6-amine* (**19h**). Purified by CC (SiO_2; AcOEt/hexane 8:2). Yield: 1.61 g (45%). Pale-yellow crystals. R_f (AcOEt) 0.66. M.p. 176–178°. IR (KBr): 3342.5 (br.), 3276.8*s*, 3051.2*m*, 3024.2*m*, 2854.4*m*, 1690.2*s*, 1581.5*m*, 1456.2*m*. ^{1}H-NMR

((D$_6$)DMSO): 11.84 (*s*, OH, exchangeable with D$_2$O); 8.06–7.80 (*m*, H–C(2) and H–C(8) of *N*-benzyl adenine and NH); 7.44–7.42 (*m*, 2 arom. H); 7.03–6.99 (*m*, 8 arom. H); 5.21(*s*, NCH$_2$); 4.44 (*s*, PhC*H*$_2$N). ^{13}C-NMR ((D$_6$)DMSO): 36.89; 42.83; 118.36; 126.25; 126.51; 127.06; 128.10; 128.29; 128.99; 134.02; 136.25; 140.01; 140.76; 152.02; 152.50; 154.29. MS: 358.15 (15.8, M^+). Anal. calc. for $C_{20}H_{18}N_6O$ (358.39): C 67.02, H 5.06, N 23.45; found: C 67.09, H 5.14, N 23.41.

*7-[2-(Hydroxyimino)-2-phenylethyl]-1,3-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione* (**19i**). Purified by CC (SiO$_2$; AcOEt/hexane 8:2). Yield: 1.69 g (54%). Pale-yellow crystals. R_f (AcOEt) 0.58. M.p. 234–236°. IR (KBr): 3309.6 (br.), 3085.9*m*, 2939.3*m*, 2877.6*m*, 1889.5*s*, 1704.9*s*, 1680*s*, 1643.2*s*, 1434.9*s*. ^{1}H-NMR ((D$_6$)DMSO): 12.03 (*s*, OH, exchangeable with D$_2$O); 7.84 (*s*, H–C(8) of theophylline); 7.48–7.22 (*m*, 5 arom. H); 5.58 (*s*, NCH$_2$); 3.26 (*s*, Me–N(3)); 3.13 (*s*, Me–N(1)). ^{13}C-NMR ((D$_6$)DMSO): 27.38; 29.17; 40.10; 106.07; 126.18; 128.21; 128.89; 133.61; 142.22; 147.63; 150.66; 151.66; 154.32. MS: 313.11 (46.2, M^+). Anal. calc. for $C_{15}H_{15}N_5O_3$ (313.31): C 57.50, H 4.83, N 22.35; found: C 57.53, H 4.85, N 22.37.

N-*Hydroxy-2-(2-methyl-4-nitro-1*H*-imidazol-1-yl)-1-phenylethanimine* (**19j**). Purified by CC (SiO$_2$; AcOEt/hexane 8:2). Yield: 1.59 g (61%). White crystals. R_f (AcOEt) 0.63. M.p. 195–197°. IR (KBr): 3312.5 (br.), 3032.5*m*, 2962.3*m*, 2854.5*m*, 1685*s*, 1542.9*m*, 1535.2*s*, 1496.7*m*, 1388.7*s*. ^{1}H-NMR ((D$_6$)DMSO): 11.94 (*s*, OH, exchangeable with D$_2$O); 7.91 (*s*, H–C(5) of imidazole); 7.34–7.30 (*m*, 2 arom. H); 7.10–7.08 (*m*, 3 arom. H); 5.17 (*s*, NCH$_2$); 2.00 (*s*, Me). ^{13}C-NMR ((D$_6$)DMSO): 12.52; 40.73; 122.47; 126.49; 128.54; 129.30; 133.36; 144.99; 145.18; 151.04. MS: 260.09 (10.3, M^+). Anal. calc. for $C_{12}H_{12}N_4O_3$ (260.25): C 55.38, H 4.65, N 21.53; found: C 55.32, H 4.60, N 21.49.

*(1*E*)-2-(1*H*-Benzimidazol-1-yl)*-N-*(benzyloxy)-1-phenylethanimine* (**17a**). Purified by CC (SiO$_2$; AcOEt/hexane 5:5). Yield: 3.00 g (88%). White crystals. R_f (AcOEt) 0.57. M.p. 121–123°. IR (KBr): 3033.8*s*, 2922.0*s*, 2852.5*m*, 1764.7*m*, 1699.2*m*, 1666.4*m*, 1492.8*s*, 1020.8*s*. ^{1}H-NMR ((D$_6$)DMSO): 8.26 (*s*, H–C(2) of benzimidazole); 7.65–7.10 (*m*, 14 arom. H); 5.69 (*s*, NCH$_2$); 5.38 (*s*, NOCH$_2$). ^{13}C-NMR ((D$_6$)DMSO): 38.52; 76.36; 109.98; 119.47; 121.66; 122.50; 126.62; 128.11; 128.42; 128.60; 129.63; 132.80; 133.47; 135.27; 137.23; 143.09; 144.37; 153.29. MS: 341.15 (26.3, M^+). Anal. calc. for $C_{22}H_{19}N_3O$ (341.41): C 77.40, H 5.61, N 12.31; found: C 77.48, H 5.66, N 12.28.

*(1*E*)-2-(1*H*-Benzimidazol-1-yl)*-N-*(2-phenoxyethoxy)-1-phenylethanimine* (**17b**). Purified by CC (SiO$_2$; AcOEt/hexane 4:6). Yield: 3.04 g (82%). Pale-yellow crystals. R_f (AcOEt) 0.50. M.p. 108–110°. IR (KBr): 3033.8*m*, 2974.0*m*, 2864.1*m*, 1758.9*m*, 1658.7*m*, 1598.9*s*, 1444.6*m*, 1245.9*s*, 1080.1*s*. ^{1}H-NMR ((D$_6$)DMSO): 8.31 (*s*, H–C(2) of benzimidazole); 7.66–6.95 (*m*, 14 arom. H); 5.69 (*s*, NCH$_2$); 4.66 (*t*, J = 5.3, PhOC*H*$_2$); 4.37 (*t*, J = 5.3, NOCH$_2$). ^{13}C-NMR ((D$_6$)DMSO): 38.30; 65.86; 73.00; 109.97; 114.48; 119.44; 120.77; 121.66; 122.57; 126.70; 128.41; 129.55; 129.66; 132.69; 133.47; 143.06; 144.45; 153.43; 158.39. MS: 371.16 (43.1, M^+). Anal. calc. for $C_{23}H_{21}N_3O_2$ (371.43): C 74.37, H 5.70, N 11.31; found: C 74.31, H 5.77, N 11.35.

*(1*E*)-2-(1*H*-Benzotriazol-1-yl)*-N-*(benzyloxy)-1-phenylethanimine* (**17c**). Purified by CC (SiO$_2$; AcOEt/hexane 2:8). Yield: 2.97 g (87%). Pale-yellow crystals. R_f (AcOEt) 0.83. M.p. 75–77°. IR (KBr): 3055.0*m*, 2916.2*m*, 2898.5*m*, 1691.2*m*, 1612.4*m*, 1589.2*m*, 1450.4*s*, 1018.3*s*. ^{1}H-NMR ((D$_6$)DMSO): 7.74–7.28 (*m*, 14 arom. H); 6.09 (*s*, NCH$_2$); 5.33 (*s*, NOCH$_2$). ^{13}C-NMR ((D$_6$)DMSO): 62.99; 76.32; 119.10; 123.90; 127.32; 127.67; 127.97; 127.99; 128.38; 128.72; 128.78; 129.68; 132.94; 137.07; 142.50; 144.83; 152.12. MS: 342.14 (19.8, M^+). Anal. calc. for $C_{21}H_{18}N_4O$ (342.39): C 73.67, H 5.30, N 16.36; found: C 73.72, H 5.33, N 16.32.

*(1*E*)-2-(1*H*-Benzimidazol-1-yl)-1-(biphenyl-4-yl)*-N-*(prop-2-en-1-yloxy)ethanimine* (**17d**). Purified by CC (SiO$_2$; AcOEt/hexane 8:2). Yield: 3.20 g (87%). White crystals. R_f (AcOEt) 0.26. M.p. 175–177°. IR (KBr): 3027.2*s*, 2917.1*s*, 2884.3*m*, 1759.6*m*, 1685.7*m*, 1664.1*m*, 1487.1*s*, 1019.1*s*. ^{1}H-NMR (CDCl$_3$): 8.02 (*s*, H–C(2) of benzimidazole); 7.60–7.24 (*m*, 13 arom. H); 6.16–5.94 (*m*, =CH), 5.43 (*s*, NCH$_2$); 5.35 (*d*, J = 5.3, NOCH$_2$); 4.84 (*dd*, J = 1.2, 4.7, =CH$_2$). ^{13}C-NMR (CDCl$_3$): 39.15; 49.05; 109.68; 110.39; 117.94; 118.82; 120.39; 122.30; 123.16; 126.74; 127.10; 127.18; 127.48; 127.79; 128.21; 128.85; 132.26; 133.41; 143.26; 151.68. MS: 367.16 (24.9, M^+). Anal. calc. for $C_{24}H_{21}N_3O$ (367.44): C 78.45, H 5.76, N 11.44; found: C 78.51, H 5.74, N 11. 50.

*(1*E*)*-N-*[3-(4-Chlorophenoxy)propoxy]-2-(1*H*-imidazol-1-yl)-1-phenylethanimine* (**17e**). Purified by CC (SiO$_2$; AcOEt). Yield: 3.14 g (85%). Bright-brown oil. R_f (AcOEt) 0.22. IR (film): 3031.8*m*, 2948.1*m*, 2839.4*m*, 1636.1*m*, 1612.3*m*, 1467.2*m*, 1024.6*s*. ^{1}H-NMR (CDCl$_3$): 7.45 (*s*, H–C(2) of imidazole);

7.43–7.41 (*m*, 2 arom. H); 7.25–7.22 (*m*, 3 arom. H); 7.12–7.09 (*m*, 2 arom. H); 6.85 (*s*, H–C(4) of imidazole); 6.76 (*s*, H–C(5) of imidazole); 6.72–6.68 (*m*, 2 arom. H); 5.03 (*s*, NCH_2); 4.37 (*t*, *J* = 6.2, $ArOCH_2$); 3.89 (*t*, *J* = 6.2, $NOCH_2$); 2.14–1.98 (*m*, $NOCH_2CH_2OAr$). ^{13}C-NMR ($CDCl_3$): 29.07; 40.72; 64.68; 71.57; 115.78; 119.29; 126.15; 127.67; 128.46; 128.82; 129.30; 129.94; 133.44; 137.36; 151.91; 157.43. MS: 369.12 (48.5, M^+). Anal. calc. for $C_{20}H_{20}ClN_3O_2$ (369.84): C 64.95, H 5.45, Cl 9.59, N 11.36; found: C 64.90, H 5.47, Cl 9.52, N 11.39.

*(1*E*)*-N-*(Benzyloxy)-1-phenyl-2-(2-phenyl-1*H*-imidazol-1-yl)ethanimine* (**17f**). Purified by CC (SiO_2; AcOEt/hexane 4:6). Yield: 3.19 g (87%). Pale-yellow crystals. R_f (AcOEt) 0.59. M.p. 91–93°. IR (KBr): 3024.2*m*, 2921.9*m*, 2848.7*m*, 1629.7*m*, 1604.7*m*, 1471.6*m*, 1018.3*s*. ^{1}H-NMR ((D_6)DMSO): 7.50–7.21 (*m*, 15 arom. H); 7.09 (*d*, *J* = 1.0, H–C(4) of imidazole); 6.92 (*d*, *J* = 1.0, H–C(5) of imidazole); 5.46 (*s*, NCH_2); 5.16 (*s*, $NOCH_2$). ^{13}C-NMR ((D_6)DMSO): 41.70; 75.93; 121.66; 126.56; 127.64; 127.85; 127.98; 128.01; 128.18; 128.25; 128.32; 128.44; 129.41; 130.48; 132.90; 142.50; 146.95; 153.88. MS: 367.16 (48.5, M^+). Anal. calc. for $C_{24}H_{21}N_3O$ (367.44): C 78.45, H 5.76, N 11.44; found: C 78.49, H 5.81, N 11.48.

*1-({[(1*E*)-2-(1*H*-Benzimidazol-1-yl)-1-phenylethylidene]amino}oxy)-3-phenoxypropan-2-ol* (**17g**). Purified by CC (SiO_2; AcOEt/hexane 4:6). Yield: 3.13 g (78%). Pale-yellow oil. R_f (AcOEt) 0.61. IR (film): 3417.3 (br.), 2979.8*m*, 2921.9*m*, 2844.8*m*, 1662.5*m*, 1633.6*m*, 1600.8*m*, 1456.2*m*, 1234.3*s*. ^{1}H-NMR ($CDCl_3$): 8.00 (*s*, H–C(2) of benzimidazole); 7.39–6.85 (*m*, 14 arom. H); 5.15–5.11 (*m*, C*H*OH); 4.45 (*s*, OH, exchangeable with D_2O); 4.02–3.78 (*m*, NCH_2, $NOCH_2$, $PhOCH_2$). ^{13}C-NMR ($CDCl_3$): 54.77; 67.58; 69.52; 77.78; 114.44; 119.59; 120.45; 121.82; 122.72; 126.64; 128.10; 129.47; 129.71; 130.39; 132.84; 133.58; 143.10; 144.37; 153.25; 158.72. MS: 401.17 (48.5, M^+). Anal. calc. for $C_{24}H_{23}N_3O_3$ (401.46): C 71.80, H 5.77, N 10.47; found: C 71.89, H 5.78, N 10.52.

*1-{(2*E*)-2-[(Benzyloxy)imino]-2-phenylethyl}pyrimidine-2,4(1*H*,3*H*)-dione* (**17h**). Purified by CC (SiO_2; AcOEt/hexane 4:6). Yield: 1.88 g (56%). White crystals. R_f (AcOEt) 0.76. M.p. 162–164°. IR (KBr): 3242.1*s*, 3082.0*m*, 2956.7*m*, 1731.9*m*, 1697.2*m*, 1652.9*m*, 1558.4*s*, 1456.2*m*, 1234.3*s*. ^{1}H-NMR ((D_6)DMSO): 11.21 (*s*, NH, exchangeable with D_2O); 7.68 (*d*, *J* = 7.5, H–C(6) of uracil); 7.48–7.19 (*m*, 10 arom. H); 5.72 (*d*, *J* = 7.5, H–C(5) of uracil); 4.95 (*s*, NCH_2); 4.82 (*s*, $NOCH_2$). ^{13}C-NMR ((D_6)DMSO): 43.30; 50.81; 100.04; 127.06; 127.40; 127.96; 128.09; 128.26; 128.98; 131.51; 136.95; 144.83; 150.03; 150.99; 162.33. MS: 335.12 (14.8, M^+). Anal. calc. for $C_{19}H_{17}N_3O_3$ (335.36): C 68.05, H 5.11, N 12.53; found: C 68.11, H 5.14, N 12.60.

*9-[(2*E*)-2-{[3-(4-Chlorophenoxy)propoxy]imino}-2-phenylethyl]-9*H*-purin-6-amine* (**17i**). Purified by CC (SiO_2; AcOEt/MeOH 10:1). Yield: 2.71 g (62%). White crystals. R_f (AcOEt/MeOH 10:1) 0.33. M.p. 148–150°. IR (KBr): 3300–3100*s*, 3057.1*m*, 3024.9*m*, 2956.7*m*, 2831.4*m*, 1634.8*s*, 1569.1*m*, 1471.3*m*. ^{1}H-NMR ((D_6)DMSO): 8.09 (*s*, H–C(8) of adenine); 8.03 (*s*, H–C(2) of adenine); 7.61 (*s*, NH_2, exchangeable with D_2O); 7.30–7.23 (*m*, 7 arom. H); 6.92 (*d*, *J* = 8.8, 2 arom. H); 5.44 (*s*, NCH_2); 4.31 (*t*, *J* = 6.0, $PhOCH_2$); 3.98 (*t*, *J* = 6.0, $NOCH_2$); 2.11–2.06 (*m*, $NOCH_2CH_2OAr$). ^{13}C-NMR ((D_6)DMSO): 28.50; 38.00; 64.54; 70.91; 116.06; 118.03; 124.10; 126.69; 128.26; 129.14; 129.42; 133.18; 140.87; 149.41; 152.53; 153.26; 155.80; 157.28. MS: 436.14 (10.3, M^+). Anal. calc. for $C_{22}H_{21}ClN_6O_2$ (436.89): C 60.48, H 4.84, Cl 8.11, N 19.24; found: C 60.45, H 4.90, Cl 8.16, N 19.28.

N-*Benzyl-9-[(2*E*)-2-{[(2-methylbenzyl)oxy]imino}-2-phenylethyl]-9*H*-purin-6-amine* (**17j**). Purified by CC (SiO_2; AcOEt/hexane 6:4). Yield: 3.10 g (67%). White crystals. R_f (AcOEt) 0.43. M.p. 119–121°. IR (KBr): 3285.4*s*, 3057.1*m*, 2997.4*m*, 1745.9*m*, 1685.6*m*, 1651.9*m*, 1554.9*s*, 1451.6*m*, 1262.4*s*. ^{1}H-NMR ((D_6)DMSO): 8.17 (*s*, H–C(8) of *N*-benzyl adenine); 7.93 (*s*, H–C(2) of *N*-benzyl adenine); 7.64–7.62 (*m*, 2 arom. H); 7.30–7.13 (*m*, 12 arom. H); 5.46 (*s*, NCH_2); 5.28 (*s*, $NOCH_2$); 4.65 (*s*, NH, exchangeable with D_2O); 3.35 (*s*, $PhCH_2NH$); 2.29 (*s*, Me). ^{13}C-NMR ((D_6)DMSO): 18.50; 37.88; 42.82; 74.53; 125.66; 126.51; 126.67; 127.07; 128.09; 128.26; 128.31; 129.05; 129.49; 129.84; 129.97; 133.09; 135.10; 136.18; 136.56; 140.01; 140.59; 152.47; 153.32; 154.22. MS: 462.21 (12.5, M^+). Anal. calc. for $C_{28}H_{26}N_6O$ (462.55): C 72.71, H 5.67, N 18.17; found: C 72.68, H 5.69, N 18.14.

*7-{(2*E*)-2-[(Benzyloxy)imino]-2-phenylethyl}-1,3-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione* (**17k**). Purified by CC (SiO_2; AcOEt/hexane 4:6). Yield: 3.59 g (89%). White crystals. R_f (AcOEt) 0.74. M.p. 108–110°. IR (KBr): 3028.0*m*, 2931.6*m*, 2892.3*m*, 1701.1*s*, 1691.4*s*, 1654.8*s*, 1604.7*s*, 1446.5*m*, 1232.4*s*. ^{1}H-NMR ((D_6)DMSO): 7.88 (*s*, H–C(8) of theophylline); 7.60–7.28 (*m*, 10 arom. H); 5.61 (*s*, NCH_2); 5.21 (*s*, $NOCH_2$); 3.27 (*s*, Me–N(3)); 3.11 (*s*, Me–N(1)). ^{13}C-NMR ((D_6)DMSO): 27.36; 29.20; 41.62;

76.10; 106.18; 126.73; 127.64; 127.78; 128.01; 128.15; 129.68; 132.72; 137.05; 142.45; 147.59; 150.65; 153.41; 154.20. MS: 403.16 (34.6, M^+). Anal. calc. for $C_{22}H_{21}N_5O_3$ (403.43): C 65.50, H 5.25, N 17.36; found: C 65.43, H 5.20, N 17.31.

*1,3-Dimethyl-7-{(2*E*)-2-[(2-phenoxyethoxy)imino]-2-phenylethyl}-3,7-dihydro-1*H*-purine-2,6-dione* (**17l**). Purified by CC (SiO_2; AcOEt/hexane 4:6). Yield: 3.42 g (79%). White crystals. R_f (AcOEt) 0.70. M.p. 96–98°. IR (KBr): 3048.7*m*, 2945.1*m*, 2843.4*m*, 1699.2*s*, 1658.7*s*, 1600.8*s*, 1582.3*m*, 1442.7*m*, 1244.0*s*. ^{1}H-NMR ($CDCl_3$): 7.34–6.95 (*m*, 10 arom. H, H–C(8) of theophylline); 5.68 (*s*, NCH_2); 4.65 (*t*, $J = 5.1$, $PhOCH_2$); 4.30 (*t*, $J = 5.1$, $NOCH_2$); 3.51 (*s*, Me–N(3)); 3.38 (*s*, Me–N(1)). ^{13}C-NMR ($CDCl_3$): 27.95; 29.70; 39.45; 65.90; 73.34; 106.72; 114.55; 121.14; 126.40; 128.79; 129.53; 130.16; 132.51; 141.80; 148.30; 151.51; 152.69; 155.42; 158.43. MS: 433.17 (38.1, M^+). Anal. calc. for $C_{23}H_{23}N_5O_4$ (433.46): C 63.73, H 5.35, N 16.16; found: C 63.78, H 5.30, N 16.23.

*(1*E*)-*N*-(Benzyloxy)-2-(2-methyl-4-nitro-1*H*-imidazol-1-yl)-1-phenylethanimine* (**17m**). Purified by CC (SiO_2; AcOEt/hexane 5:5). Yield: 3.08 g (88%). Pale-yellow foam. R_f (AcOEt) 0.77. IR (KBr): 3021.5*m*, 2908.4*m*, 2848.7*m*, 2858.8*s*, 1533.2*m*, 1494.7*m*, 1334.6*s*, 1292.2*s*. ^{1}H-NMR ((D_6)DMSO): 8.17 (*s*, H–C(5) of imidazole); 7.66–7.30 (*m*, 10 arom. H); 5.46 (*s*, NCH_2); 5.31 (*s*, $NOCH_2$); 2.20 (*s*, Me). ^{13}C-NMR ((D_6)DMSO): 12.66; 41.52; 76.50; 126.77; 127.96; 128.15; 128.20; 128.30; 128.33; 128.61; 129.86; 132.48; 136.93; 145.17; 152.37. MS: 350.13 (22.2, M^+). Anal. calc. for $C_{19}H_{18}N_4O_3$ (350.37): C 65.13, H 5.18, N 15.99; found: C 65.19, H 5.24, N 16.06.

*(1*E*)-2-(1*H*-Benzimidazol-1-yl)-*N*-{2-[(2-methyl-4-nitro-1*H*-imidazol-1-yl)methoxy]ethoxy}-1-phenylethanimine* (**17n**). Purified by CC (SiO_2; AcOEt/hexane 8:2). Yield: 3.60 g (83%). Pale-yellow oil. R_f (AcOEt) 0.20. IR (film): 3055.0*m*, 2925.8*m*, 2879.5*m*, 1612.4*m*, 1541.0*s*, 1494.7*s*, 1338.5*s*. ^{1}H-NMR ($CDCl_3$): 7.94–7.18 (*m*, 9 arom. H, H–C(2) of benzimidazole, H–C(5) of imidazole); 5.36 (*s*, OCH_2N); 5.16 (*s*, NCH_2); 4.35 (*t*, $J = 4.2$, $NOCH_2$); 3.71 (*t*, $J = 4.2$, CH_2O); 2.19 (*s*, Me). ^{13}C-NMR ($CDCl_3$): 12.81; 39.09; 67.33; 73.22; 77.11; 109.75; 119.85; 120.44; 122.10; 123.00; 126.24; 128.64; 129.91; 132.95; 133.57; 143.14; 143.46; 145.39; 146.05; 152.80. MS: 434.17 (18.9, M^+). Anal. calc. for $C_{22}H_{22}N_6O_4$ (434.45): C 60.82, H 5.10, N 19.34; found: C 60.89, H 5.16, N 19.29.

*7-{[2-({[(1*E*)-2-(1*H*-Benzimidazol-1-yl)-1-phenylethylidene]amino}oxy)ethoxy]methyl}-1,3-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione* (**17o**). Purified by CC (SiO_2; AcOEt/hexane 4:6). Yield: 4.13 g (85%). Pale-yellow crystals. R_f (AcOEt) 0.11. M.p. 93–95°. IR (KBr): 3037.3*m*, 2952.8*m*, 2877.6*m*, 1697.2*s*, 1647.1*s*, 1604.2*s*, 1446.5*m*, 1045.3*s*. ^{1}H-NMR ((D_6)DMSO): 8.30 (*s*, H–C(8) of theophylline); 8.19 (*s*, H–C(2) of benzimidazole); 7.59–7.10 (*m*, 9 arom. H); 5.73 (*s*, OCH_2N); 5.56 (*s*, NCH_2); 4.37 (*t*, $J = 4.6$, $NOCH_2$); 3.92 (*t*, $J = 4.6$, CH_2O); 3.30 (*s*, Me–N(3)); 3.12 (*s*, Me–N(1)). ^{13}C-NMR ((D_6)DMSO): 27.48; 29.42; 40.36; 66.84; 73.10; 74.88; 105.72; 109.82; 119.34; 121.54; 122.43; 126.50; 127.99; 128.35; 129.61; 132.63; 133.35; 143.23; 144.24; 148.37; 150.69; 153.06; 154.18. MS: 487.19 (31.7, M^+). Anal. calc. for $C_{25}H_{25}N_7O_4$ (487.51): C 61.59, H 5.17, N 20.11; found: C 61.50, H 5.09, N 20.05.

REFERENCES

[1] S. Shadomy, H. J. Shadomy, G. E. Wagner, in 'Antifungal Compounds', Eds. M. R. Siegel, H. D. Sisler, Marcel Dekker, New York 1977, Vol. 1, Chapter 1; J. E. Bennett, G. L. Mandell, R. G. Douglas, 'Principles & Practice of Infections Diseases', 3rd edn., Churchill Livingston, New York, 1990, Vol. 1.

[2] W. W. Turner, M. J. Rodriguez, *Curr. Pharm. Des.* **1996**, *2*, 209.

[3] G. P. Bodey, *Clin. Infect. Dis.* **1992**, *14*, S161.

[4] A. Rossello, S. Bertini, A. Lapucci, M. Macchia, A. Martinelli, S. Rapposelli, E. Herreros, B. Macchia, *J. Med. Chem.* **2002**, *45*, 4903.

[5] R. J. Phillpotts, D. C. Delong, J. Wallace, R. W. Jones, S. E. Reed, D. A. J. Tyrrell, *Lancet* **1981**, *317*, 1342; F. G. Hayden, J. M. Gawaltney Jr., *Antimicrob. Agents Chemother.* **1982**, *21*, 892; F. D. Miller, A. S. Monto, D. C. DeLong, A. Exelby, E. R. Bryan, S. Srivastava, *Antimicrob. Agents Chemother.* **1985**, *27*, 102.

[6] A. Kleeman, J. Engel, B. Kutscher, D. Reichert, 'Pharmaceutical Substances', 3rd edn., Thieme, Stuttgart, 1999.

[7] J. Kassa, *Clin. Toxicol.* **2002**, *40*, 803.
[8] K. Sakene, K. Kawabata, Y. Inamoto, H. Yamanaka, T. Takaya, *Yakugaku Zasshi* **1993**, *113*, 605.
[9] M. N. Mordi, M. D. Petta, V. Boote, G. A. Morris, J. Barber, *J. Med. Chem.* **2000**, *43*, 467; J. Gharbi-Benarous, M. Delaforge, C. K. Jankowski, J. P. Girault, *J. Med. Chem.* **1991**, *34*, 1117.
[10] F. De Clerck, J. Beetens, A. Van de Water, E. Vercammen, P. A. J. Janssen, *Thromb. Haemostasis* **1989**, *61*, 43; H. Vanden Bossche, G. Willemsens, D. Bellens, P. A. J. Janssen, *Biochem. Pharmacol.* **1992**, *43*, 739.
[11] G. Mixich, K. Thiele, *Arzneim. Forsch.* **1979**, *29*, 1510; M. Artico, R. Rango, G. C. Porretta, S. Massa, C. Musin, M. G. Spiga, S. Carrias, P. La Colla, *Med. Chem. Res.* **1996**, 137; Y. Wahbi, R. Caujolle, C. Tournaire, M. Payard, M. D. Linas, J. P. Seguela, *Eur. J. Med. Chem.* **1995**, *30*, 955.
[12] S. Emami, M. Falahati, A. Banifatemi, K. Moshiri, A. Shafiee, *Arch. Pharm.* **2002**, *335*, 318; S. Emami, M. Falahati, A. Banifatemi, M. Amanlou, A. Shafiee, *Bioorg. Med. Chem.* **2004**, *12*, 3971; S. Emami, M. Falahati, A. Banifatemi, A. Shafiee, *Bioorg. Med. Chem.* **2004**, *12*, 5881.
[13] A. Karakurt, S. Dalkara, M. Özlap, S. Özbey, E. Kendi, J. P. Stables, *Eur. J. Med. Chem.* **2001**, *36*, 421.
[14] K. Bhandari, N. Srinivas, G. B. S. Keshava, P. K. Shukla, *Eur. J. Med. Chem.* **2009**, *44*, 437.
[15] E. De Clercq, in 'Advances in Antiviral Drug Design', Ed. N. G. Johnsson, JAI Press, Greenwich, 1993, Vol. 1, p. 88; L. A. Agrofoglio, S. R. Challand, 'Acyclic, Carbocyclic and L-Nucleosides', Kluwer, Dordrecht, 1998; T. Pathak, *Chem. Rev.* **2002**, *102*, 1623; L. A. Agrofoglio, I. Gillaizeau, Y. Saito, *Chem. Rev.* **2003**, *103*, 1875; D. M. Huryn, M. Okabe, *Chem. Rev.* **1992**, *92*, 1745.
[16] a) A. Khalafi-Nezhad, M. N. Soltani Rad, A. A. Moosavi-Movahedi, M. Kosari, *Helv. Chim. Acta* **2007**, *90*, 730; b) A. Khalafi-Nezhad, M. N. Soltani Rad, A. Khoshnood, *Synthesis* **2004**, 583; c) A. Khalafi-Nezhad, A. Zarea, M. N. Soltani Rad, B. Mokhtari, A. Parhami, *Synthesis* **2005**, 419; d) M. N. Soltani Rad, A. Khalafi-Nezhad, S. Behrouz, M. A. Faghihi, A. Zare, A. Parhami, *Tetrahedron* **2008**, *64*, 1778; e) A. Khalafi-Nezhad, M. N. Soltani Rad, G. H. Hakimelahi, B. Mokhtari, *Tetrahedron* **2002**, *58*, 10341; f) A. Khalafi-Nezhad, A. Zare, A. Parhami, M. N. Soltani Rad, *ARKIVOC* **2006**, *xii*, 161.
[17] D. Nardi, A. Tajana, A. Leonardi, R. Pennini, F. Portioli, M. J. Magistretti, A. Subissi, *J. Med. Chem.* **1981**, *24*, 727; K. Hofmann, 'The Chemistry of Heterocyclic Compounds: Imidazole and its Derivatives', Part 1, Interescience, London, 1953; M. R. Grimmett, in 'Comprehensive Heterocyclic Chemistry II', Eds. A. R. Katritzky, C. W. Rees, E. F. V. Scriven, 1996, Vol. 3 (I. Shinkai), p. 77; M. R. Grimmett, *Adv. Heterocycl. Chem.* **1970**, *12*, 163; R. Hodges, M. R. Grimmett, *Aust. J. Chem.* **1968**, *21*, 1085; M. Häring, *Helv. Chim. Acta* **1959**, *42*, 1845; L. J. Mathias, D. Burkett, *Tetrahedron Lett.* **1979**, *20*, 4709; Y. Kikugawa, *Synthesis* **1981**, 124; A. Savignac, C. Roques, M. Hinedi, G. Michel, A. Lattes, *Eur. J. Med. Chem.* **1990**, *25*, 449.
[18] Z.-Z. Liu, H.-C. Chen, S.-L. Cao, R.-T. Li, *Synth. Commun.* **1993**, *23*, 2611.
[19] M. N. Soltani Rad, S. Behrouz, M. Dianat, *Synthesis* **2008**, 2055.
[20] J. Hartung, M. Schwarz, *Org. Synth.* **2002**, *79*, 228; J. Hartung, M. Schwarz, *Org. Synth., Coll. Vol.* **2004**, *10*, 437; J. S. Buck, W. S. Ide, *Org. Synth.* **1935**, *15*, 85; J. S. Buck, W. S. Ide, *Org. Synth., Coll. Vol.* **1943**, *2*, 622.
[21] a) R. F. Deorge, 'Wilson and Grisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry', 8th edn., J. B. Lippincott Company, 1982; b) G. Thomas, 'Medicinal Chemistry', 1st edn., John Wiley & Sons Ltd., 2000.
[22] A. Khalafi-Nezhad, M. N. Soltani Rad, H. Mohabatkar, Z. Asrari, B. Hemmateenejad, *Bioorg. Med. Chem.* **2005**, *13*, 1931; K. Butler, H. L. Howes, J. E. Lynch, D. K. Pirie, *J. Med. Chem.* **1967**, *10*, 891.
[23] C. K. Chu, S. J. Cutler, *J. Heterocycl. Chem.* **1986**, *23*, 289; H. J. Schaeffer, S. Gurwara, R. Vince, S. Bittner, *J. Med. Chem.* **1971**, *14*, 367.

Received February 17, 2009