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Design New Pyrano Quinoline Derivatives and Study of their Anti-Microbial Activity

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ABSTRACT

4,5,7-Trichloro-3-(2-chloroethyl)-2-methylbenzo[h][1,6]naphthyridine 1 was selectively converted to 5-iminoether 5 by the reaction with sodium alkoxy in corresponding alcohol and to 2-methylbenzo[h][1,6]naphthyridin-5(6H)-one 2 by acetic acid reflux. The reaction selectively occurs at C5-position of the benzo[h][1,6]naphthyridine. Further, 2-methylbenzo[h][1,6] naphthayridin-5(6H)-one 2 furnish O and N alkylation products 3 and 4 with bromoethylacetate respectively. The reaction of 2 with bromoacetamide yield O-acetanilide i.e. 2-(4-chloro-12-methyl-16,17-dihydro-15-thia-6,11-diaza-cyclopenta[a]phenanthren-7-ylsulfanyl)-N-phenyl acetamide 6 in major amount.

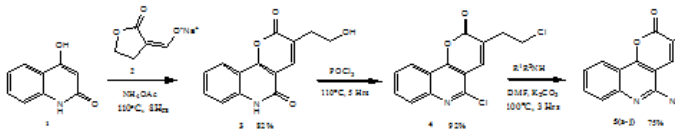
Keywords: Pyranoqunoline Reactions, benzo[h][1,6]Naphthyridines, Antimicrobial Activity

I. INTRODUCTION

Multifunctional benzo[*h*][1,6]naphthyridines showed broad spectrum of biological activities[1-3] including high affinity on 5-HT_4 receptors and high selectivity versus other receptors[4-7] and also promising antimalarial activity.[1] Here, we report the synthesis of benzo[*h*][1,6]naphthyridines derivatives linked with active C_5-iminoether and N_6- acetic acid ethyl ester. *sulfanyl)-N-(2,4-dichloro-phenyl)-acetamide* . iminotiaoether. at position of cyclopenta[*a*]phenanthren -7-ylsulfanyl)-*N*-phenyl acetamide. Further we report the novel synthesis of thiazolidinone derivatives on iminothioether linkers at C_7 position. 4-Thiazolidinone derivatives showed remarkable antimicrobial,[8-9] antibacterial,[10] antifungal,[11] anticonvulsant,[12] anticancer,[13] antituberculosis,[14] and anti-human immunodeficiency virus type 1 (HIV-1) activities.[15] We undertook the synthesis and investigated reactions of some new benzo[*h*][1,6]naphthyridine derivatives, which might good biological and medicinal applications.

In this paper, report the synthesis of derivatives having linkers of iminoether 2 position of benzo[*h*][1,6]naphthyridines In view of all these facts and as the continuation of our work on the synthesis of new heterocyclic derivatives by using α-acetyl γ-butyrolactone and heterocyclic amines.[16-18] We undertook the synthesis and investigated reactions of some new benzo[*h*][1,6]naphthyridine derivatives, which might have good biological and medicinal applications.

II. RESULTS AND DISCUSSION



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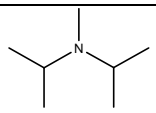
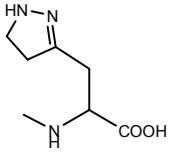
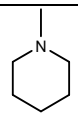
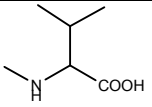
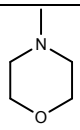
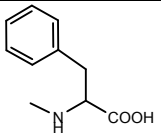
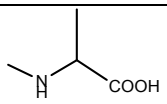
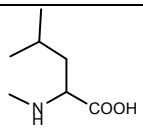
a		**e**	
b		**f**	
c		**g**	
d		**h**	

The starting compound 4,5,7-trichloro-3-(2-chloroethyl)-2-methylbenzo[*h*][1,6]naphthyridine **1** was synthesized according to our previous reported procedure. The substitution of Cl at C_5 in compound **1** with alkoxide in corresponding alcohol was done refluxing compound **1** in sodium methoxide in corresponding ethanol yield pyranoqunoline derivative **5** in good yield. The C_5 position is more electron diffident than C_6 due to neighboring sp^2 nitrogen and also inductive effect of C_7-Cl, hence attack of nucleophile is preferred at C5, was proved with the help of X-ray crystallography of Compound **2**.

The synthetic strategy adopted to obtain the target compounds are depicted in Schemes 1-3. The iminechloride (-N=C-Cl) moiety in compound **1** was converted to lactum cabonyl[30] by refluxing in glacial acetic acid furnished 4,7-dichloro-3-(2chloroethyl)-2-methylbenzo[*h*][1,6] naphthyridin 5(*6H*)-one **2** in 93% yield. The structure of compound **2** was assigned by spectroscopic and analytical methods e.g. IR of compound **2** showed lactum carbonyl (C=O) stretching at 1676 cm^{-1} and NH at 3339 $cm.^{-1}$

Biological activity

The antimicrobial activities of all synthesized compounds were evaluated in vitro for three Gram-positive and Gram-negative organisms including Staphylococcus aureus, Bacillus subtilis, and Methicillin-resistant S. aureus and three Gram-negative organisms including Escherichia coli. The compounds 5a-h was tested against microorganism species at 1000 ppm concentration. The observed results of antibacterial screening reported in above table indicate that benzo[h][1,6]naphthyridine derivatives 5e, 5f and 5g are active against S. Aureus; compounds 5h and 5d are active against E. Coli; compound 5e active against P.Sedoaurious; compound 5e and 5f are active against streptococcus and compound 47d and 49a are active against B-megaterium. However, compounds 5b, 5c and 5i are less active against bacterial species while the other compounds showed mild activities against bacterial species.

Table 1. Antimicrobial screening of compounds 5a-t: Inhibition Zone in Diameter (mm) at 40 µg / mL

Compound No.	Conc. (µg/mL)	*E.coli*	*S.aureus*	*P.Sedoaurious*	*B. subtilis*
5a	40	15±0.8	16±0.9	18±1.1	17±0.9

5b	40	16±1.2	17±0.5	17±0.9	15±0.7
5c	40	18±0.8	18±0.6	17±0.6	18±0.6
5d	40	19±0.9	15±0.7	17±0.5	18±0.8
5e	40	19±1.3	18±0.8	**21±0.4**	**22±0.5**
5f	40	**20±0.3**	19±0.6	19±1.1	**20±0.8**
5g	40	18±0.6	18±0.7	17±0.7	**22±0.3**
5h	40	19±0.3	18±0.4	18±0.5	18±0.9
5i	40	15±0.8	14±1.3	16±1.1	18±0.9
Gentamycin	10	21±0.8	23±0.3	NT	NT
Flucouezole	20	NT	NT	24±0.2	22±0.5

III. EXPERIMENTAL

Common reagents grade chemicals are either commercially available and were used without further purification or prepared by standard literature procedures. The melting points were measured on Barnstead Electro Thermal melting point apparatus Mod. No. IA-9200 in open capillary tubes and were uncorrected. Elemental analyses were determined using Thermo Quest Model No. flash EA 1112-Elemental Analyzer. The IR spectra of compounds were recorded on Shimadzu IR-408, instrument in potassium bromide pellets. All mass spectra were recorded on Mat 112 Varian Mat Bremen mass spectrometer. Routine ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on VARIAN XL-300 instrument at 25 ^{o}C. The measurements were done using pronated solvents $CDCl_3$ and DMSO-d_6, with TMS as an internal reference standard. Coupling constants (*J*) are quoted to the nearest 0.1 Hz and chemical shift (δ-scale) are quoted in parts per million (ppm) using abbreviations s=singlet, d=doublet, t=triplet, q= quartet, m= multiplet, br =broad. Column chromatography was performed using silica gel with particle size (60-120 mesh, Merck). All reactions were monitored by TLC carried out 0.2 mm silica gel 60 F_{254} (Merck) plates using 254 and 366 nm UV light for detection.

3.1 4,7-Dichloro-3-(2-chloroethyl)-2-methylbenzo[h][1,6]naphthyridin-5(6H)-one **5a**. A mixture of 4,5,7-trichloro-3-(2-chloroethyl)-2-methylbenzo[h][1,6]naphthyridine **1** (3.60 g, 0.01 mol) in glacial acetic acid (25 mL) was refluxed for 15 min. After cooling down to room temperature, methanol (50 mL) was added, the crude product obtained was collected by suction filtration, dried and recrystallized from ethanol/DMF (9:1) to yield title compound **2** (3.17 g, 93%) as pink colored prisms; Rf (toluene/ethyl acetate 9:1) 0.51, mp 254 ^{o}C; IR (KBr): ν 3339 (NH), 3186, 3143, 1676 ($C=O_{lactum}$), 1249, 734 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.91 (s, 3H, CH_3), 3.57 (t, J = 7.1 Hz, 2H, CH_2), 3.83 (t, J = 7.1 Hz, 2H, CH_2Cl), 7.59 (t, J = 7.5 Hz, 1H, C_9H), 7.77 (d, J = 7.5 Hz, 1H, C_8H), 8.1 (s, 1H, NH, D_2O exchangeable), 8.97 (d, J = 7.5 Hz, 1H, $C_{10}H$); ^{13}C NMR ($CDCl_3$): δ 23.26, 30.95, 42.65, 119.40, 121.72, 122.14, 126.75, 128.00, 128.20, 128.63, 128.74, 136.66, 142.23, 161.54, 170.61; MS: m/z (%): 347 (M+6, 10), 345 (M+4, 30), 343 (M+2, 50), 341 (M, 100), 274 (20), 198 (20), 99 (10); Anal. Calcd for $C_{15}H_{11}Cl_3N_2O$ (341.62): C, 52.74; H, 3.25; N, 8.20. Found: C, 52.47; H, 3.31; N, 8.29.

3.2 [4,7-Dichloro-3-(2-chloroethyl)-2-methyl-benzo[h][1,6]naphthyridin-5-yloxy]-acetic acid ethyl ester **5b**. Anhydrous potassium carbonate (0.136 g, 0.01 mmol) was added to the stirred solution of 4,7-dichloro-3-(2-chloroethyl)-2-methylbenzo[h][1,6] naphthyridine-5-(6H)-one **2** (0.341 g, 0.01 mmol) and 2-bromo-N-phenyl-acetamide (0.012 mmol) in DMF at 25^{o}C. The resulting reaction mixture was kept stirring for 2 h. The

progress of the reaction was monitored by TLC (toluene/ethyl acetate 8:2). After completion of reaction, the mixture was stirred in cold water (100 mL). The obtained solid was filtered washed with water, dried and purified by column chromatography eluting with gave title compound 6 was purified on silica column eluting with toluene. Yellow prisms; yield (0.328 g, 77%); Rf (toluene/ethyl acetate, 8:2) 0.53, mp 211 ^{o}C; IR (KBr): ν 2977, 2898, 1749 (C=O), 1589, 1562, 1375, 1213, 1060, 748 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.31 (t, J = 7.2 Hz, 3H, OCH_2CH_3), 2.92 (s, 3H, CH_3), 3.53 (t, J = 7.5 Hz, 2H, CH_2), 3.81 (t, J = 7.5 Hz, 2H, CH_2Cl), 4.28 (q, J = 7.2 Hz, 2H, OCH_2), 5.20 (s, 2H, CH_2), 7.44 (t, J = 7.8 Hz, 1H, C_9H), 7.76 (d, J = 7.8 Hz, 1H, C_8H), 8.88 (d, J = 7.8 Hz, 1H, $C_{10}H$); MS: m/z (%): 432 (M+6, 10), 430 (M+4, 15), 428 (M+2, 30), 426 (M+, 40) , 391 (30), 381 (50), 341 (60), 91 (40), 85 (100), 77 (30). Anal. Calcd for $C_{19}H_{17}Cl_3N_2O_3$ (427.72): C, 53.36; H, 4.01; N, 6.55. Found: C, 53.39; H, 4.07; N, 6.51.

3.3 [4,7-Dichloro-3-(2-chloro-ethyl)-2-methyl-benzo[h][1,6]naphthyridin-5-yloxy]-acetic acid ethyl ester, 5c

Yellow needles; yield (0.0426 g, 10%); R_f (toluene/ethyl acetate 8:2) 0.53, mp 237 ^{o}C. IR (KBr): ν 2993, 2960, 1731 (C=O), 1664 (C=O), 1533, 1394, 1253, 1126, 786 cm.$^{-1}$ ^{1}H NMR ($CDCl_3$): δ 1.30 (t, J = 6.9 Hz, 3H, OCH_2CH_3), 2.89 (s, 3H, CH_3), 3.46 (t, J = 7.2 Hz, 2H, CH_2CH_2Cl), 3.78 (t, J = 7.2 Hz, 2H, CH_2CH_2Cl), 4.28 (q, J = 6.9 Hz, 2H, OCH_2CH_3), 5.27 (s, 2H, CH_2), 7.29 (t, J = 8.1 Hz, 1H, C_9H), 7.61 (d, J = 8.1 Hz, 1H, C_8H), 8.90 (d, J = 8.1 Hz, 1H, $C_{10}H$). MS: m/z (%): 432 (M+6, 10), 430 (M+4, 15), 428 (M+2, 30), 426 (M+, 100), 391 (30), 381 (50), 341 (60), 91 (50), 85 (90), 77 (40). Analysis Calculated for $C_{19}H_{17}Cl_3N_2O_3$ (427.72): Calcd: C, 53.36; H, 4.01; N, 6.55; Found: C, 53.39; H, 4.07; N, 6.51

3.4 5,7-Dichloro-3-(2-chloroethyl)-4-methoxy-2-methylbenzo[h][1,6]naphthyridine, 5d

4,5,7-trichloro-3-(2-chloroethyl)-2-methylbenzo[h][1,6]naphthyridine **1** (3.60 g, 0.01 mol) was refluxed in sodium methoxide in methanol for about 1 hour. The solvent was removed under reduced pressure. The solid obtained was stirred in cold methanol. The residue was filtered, dried and recrystallized from ethanol. White prisms, yield (0.298 g, 84%); Rf (Toluene) 0.81, mp 180 ^{o}C. IR (KBr): ν 2962, 2837, 1583, 1425, 1321, 1162, 1033, 776 cm.$^{-1}$; ^{1}H NMR ($CDCl_3$): δ 2.89 (s, 3H, CH_3), 3.44 (t, J = 7.6 Hz, 2H, CH_2CH_2Cl), 3.92 (t, J = 7.6 Hz, 2H, CH_2CH_2Cl), 4.19 (s, 3H, OCH_3), 7.54 (t, J = 7.5 Hz, 1H, C_9H), 7.94 (d, J = 7.5 Hz, 1H, C_8H), 8.83 (d, J = 7.5 Hz, 1H, $C_{10}H$).MS: m/s (%): 360 (M+6, 50), 358 (M+4, 60), 356 (M+2, 80), 354 (M, 100), 325 (100), 319 (60), 275 (70), 198 (20), 138 (50), 49 (70). Analysis Calculated for $C_{16}H_{13}Cl_3N_2O$ (355.65): Calcd: C, 54.03; H, 3.68; N, 7.88; Found: C, 55.22; H, 4.11; N, 7.53

3.5. 2-[4,7-Dichloro-3-(2-chloro-ethyl)-2-methyl-5-oxo-5H-benzo[h][1,6]naphthyridine-6-yl]-N-substituted phenyl acetamide 5e

Anhydrous potassium carbonate (0.136 g, 0.01 mmol) was added to the stirred solution of 4,7-dichloro-3-(2-chloroethyl)-2-methylbenzo[h][1,6] naphthyridine-5-(6H)-one **2** (0.341 g, 0.01 mmol) and 2-bromo-N-phenyl-acetamide (0.012 mmol) in DMF at 25^{o}C. The resulting reaction mixture was kept stirring for 2 h. The progress of the reaction was monitored by TLC (toluene/ethyl acetate 8:2). After completion of reaction, the mixture was stirred in cold water (100 mL). The obtained solid was filtered washed with water, dried and purified by column chromatography eluting with gave title compound 6 was purified on silica column eluting with toluene.

3.5.1 2-[4,7-Dichloro-3-(2-chloro-ethyl)-2-methyl-benzo[h][1,6]naphthyridin-5-yloxy]-N-p-tolyl-acetamide (**5f**). Yellow needles; yield (0.374 g, 77%); Rf (toluene/ethyl acetate 8:2) 0.51, mp 218 ^{o}C; IR (KBr): ν 3390 (NH), 2962, 2926, 2854, 1681 (C=O), 1589, 1537, 1300, 1184, 1037 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.34 (s, 3H, CH_3), 2.95 (s, 3H, CH_3), 3.58 (t, J = 7.8 Hz, 2H, CH_2), 3.84 (t, J = 7.8 Hz, 2H, CH_2Cl), 5.35 (s, 2H, CH_2), 7.19 (d, J = 8.7 Hz, 2H, ArH), 7.49-7.52 (m, 3H, C_9H), 7.82 (d, J = 7.5 Hz, 1H, C_8H), 8.82 (s, 1H, NH, D_2O exchangeable), 8.91 (d, J = 7.5 Hz, 1H, $C_{10}H$); MS: m/z (%): 493 (M+6, 10), 491 (M+4, 10), 489 (M+2, 15), 487 (M+, 30), 452 (20), 381 (80), 341 (50), 325 (60), 147 (100), 106 (65), 91 (80), 77 (90). Anal. Calcd for $C_{24}H_{20}Cl_3N_3O_2$ (488.80): C, 58.97; H, 4.12; N, 8.60. Found: C, 59.02; H, 4.11; N, 8.64.

3.5.2 2-[4,7-Dichloro-3-(2-chloro-ethyl)-2-methyl-benzo[h][1,6]naphthyridin-5-yloxy]-N-(4-fluoro-phenyl)-acetamide (**5g**). Yellow needles; yield (0.369 g, 75%); Rf (toluene/ethyl acetate 8:2) 0.80, mp 121 ^{o}C; IR

(KBr): ν 3354 (NH), 3273, 2926, 1670 (C=O), 1595, 1590, 1317, 1224, 833 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.95 (s, 3H, CH_3), 3.57 (t, J = 7.2 Hz, 2H, CH_2l), 3.84 (t, J = 7.2 Hz, 2H, CH_2Cl), 5.35 (s, 2H, CH_2), 7.11 (d, J = 7.2 Hz, 2H, ArH), 7.49 (t, J = 7.2 Hz, 1H, C_9H), 7.61 (d, J = 7.2 Hz, 2H, ArH), 7.85 (d, J = 7.5 Hz, 1H, C_8H), 8.91 (d, J = 7,5 Hz, 1H, $C_{10}H$), 9.21 (s, 1H, NH, D_2O exchangeable). ^{13}C NMR ($CDCl_3$): δ 25.09, 29.66, 41.16, 66.78, 115.67, 115.96, 119.20, 121.66, 122.23, 123.52, 123.98, 125.72, 128.27, 128.80, 129.19, 131.39, 133.33, 143.12, 143.91, 155.14; MS: m/z (%): 497 (M+6, 15), 495 (M+4, 20), 493 (M+2, 30), 491 (M+, 40), 456 (20), 482 (30), 342 (40), 325 (50), 149 (100). 91 (40), 77 (40). Anal. Calcd for $C_{23}H_{17}Cl_3FN_3O_2$ (492.77): C, 56.06; H, 3.48; N, 8.53. Found: C, 56.12; H, 3.42; N, 8.56.

3.5.3 N-(4-Chloro-phenyl)-2-[4,7-dichloro-3-(2-chloro-ethyl)-2-methyl-benzo[h][1,6]naphtha yridin-5-yloxy]-acetamide (**5i**. Yellow needles; yield (0.371 g, 73%); Rf (toluene/ethyl acetate 8:2) 0.82, mp 231-232 ^oC; IR (KBr): ν 3355 (NH), 2926, 2840, 1683 (C=O), 1594, 1510, 1318, 1224, 850 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.72 (s, 3H, CH_3), 3.46 (t, J = 7.6 Hz, 2H, CH_2CH_2Cl), 3.57 (t, J = 7.6 Hz, 2H, CH_2CH_2Cl), 4.41 (s, 2H, CH_2), 7.35 (d, J = 8.3 Hz, 2H, ArH), 7.54 (t, J = 7.8 Hz, 1H, C_7H), 7.61 (d, J = 8.3 Hz, 2H, ArH), 7.83 (d, J = 7.8 Hz, 1H, C_8H), 8.85 (d, J = 7.8 Hz, 1H, C_6H), 9.81 (s, 1H, NH, D_2O exchangeable); MS: m/z (%): 515 (M+8, 10), 513 (M+6, 10), 511 (M+4, 15), 509 (M+2, 20), 507 (M+, 40), 472 (30), 381 (30), 341 (30), 325 (100), 166 (80). Anal. Calcd for $C_{23}H_{17}Cl_4N_3O_2$ (509.22): C, 54.25; H, 3,37; N, 8.25. Found: C, 54.30; H, 3.35; N, 8.27.

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V. REFERENCES

[1]. Roseman K. A.; Maribeth M. G.; Linfield, W. M. and Edwards Ben, E. J. Med. Chem.1969, 13, 230-233.

[2]. Hinschberger, A.; Butt, s.; Lelong, V.; Boulouard, M.; Dumuis, A.; Dauphin, F.;Bureau, R.; Pfeiffer, B.; Renard P.; Rault, S. J. Med. Chem. 2003, 46, 138-147.

[3]. Gorlitzer, K.; Bode, M.; Jones, P.G.; Jomaa, H.; Wiesner, J. Pharmazie, 2007, 62, 15-26.

[4]. Gorlitzer, K.; Bode, M.; Jones, P.G.; Jomaa, H. Pharmazie, 2005, 60, 172-174.

[5]. Chrzastek, L.; Mianowska, B.; Sliwa, W. Aus, J. Chem. 1994, 47, 2129-2133.

[6]. (a) Coatney, G. R. Survey of Antimalarial Agents. Public Health Service Monograph

[7]. No. 9; U. S. Government Printing Office: Washington DC. 1952; (b) Sliwa, W. Heterocycles

[8]. 1979, 12, 1207-1237; c) Matusiak, G.; Sliwa, W. Acta Chimica Hungarica. 1988, 125, 267-274.

[9]. Martindale, R. J. The exta parmacopoeia. 30th ed.; Royal Pharm Soc Great Britain,Pharmaceutical: London, 1993; p 460.

[10]. Hoyer, D.; Clarke, D. E.; Fozard, J. R.; Hartig, P. R.; Martin, G. R.; Mylecharane, E. J.;Saxena, P. R.; Humphrey, P. P. Pharmacol. Rev. 1994, 46, 157-203.

[11]. (a) Eglen, R. M.; Wong, E. H. F.; Dumuis, A.; Bockaert, J. Trends Pharmacol. Sci. 1995, 16,391-398; (b) Eglen, R. M.; Hegde, S. S. Exp. Opin. Invest. Drugs, 1996, 5, 373-388.

[12]. Bureau, R.; Daveu, C.; Lemaitre, S.; Dauohin, F.; Landelle, H.; Lancelot, J. C.; Rault, S. J.Chem. Inf. Comput. Sci. 2002, 42, 962-967.

[13]. Schaus, J. M.; Thompson, D. C.; Bloomquist, W. E.; Susemichel, A. D.; Calligaro, D. O.;Cohen, M. L. J. Med. Chem. 1998, 41, 19-1955.

[14]. Curtet, S.; Soulier, J. L.; Zahradnick, I.; Giner, M.; Berque-Bestel, Fischmeister, R.;Langlois, M. J. Med. Chem. 2000, 43, 3761-3769.

[15]. Lopez-Rodriguez, M. L.; Benhamu, B.; Viso, A.; Morcillo, M. J.; Murcia, M.; Orensanz, L.;Alfaro, M. J.; Martin, M. I. Bioorg. Med. Chem. 1999, 7, 2271-2281.

[16]. Salama, H. M.; Labouta, I. A.; Moustafa M. A.; Moustafa. Alex. J. Pharm. Sci. 1990, 4, 44-46.

[17]. Bonde, C. G.; Gaikwad, N. J. Bioorg. Med. Chem. 2004, 12, 2151-2161.

[18]. Kucukguzel, S. G.; Oruc, E. E.; Rollas, S.; Sahin, F.; Ozbek, A. Eur. J. Med. Chem. 2002,37, 197-206.

[19]. Capan, G.; Ulusoy, N.; Ergenc, N.; Kiraz, M. Monatsh. Chem. 1999, 130, 1399-1407.

[20]. Ergenc, N.; Capan, G. II Farmaco. 1994, 49, 133-135.

[21]. Bhatt, J. J.; Shah, B. R.; Shah, H. P.; Trivedi, P. B.; Undavia, N. K.; Desai, N. C. Indian J.Chem. 1994, 33B, 189-192.

[22]. Bukowski, L.; Janowiec, M.; Zwolska-Kwiek, Z.; Andrezejczyk, Z. Pharmazie 1998, 53,373-376.

[23]. Barreca, M. L.; Chimirri, A.; Luca, L. D.; Monforte, A.; Monforte, P.; Rao, A.; Zappala, M.;
[24]. Balzarini, J.; De Clercq, E.; Pannecouque, C.; Witvrouw, M. Bioorg. Med. Chem. Lett. 2001,11, 1793-1796.
[25]. Andres, C. J.; Bronson, J. J.; Andrea, S. V. D.; Deshpande, M. S.; Falk, P. J.; Grant-Young,
[26]. K.A.; Harte, W. E.; Ho, H. T.; Misco, P. F.; Robertson, J. G.; Stock, D.; Sun, Y.; Walsh, A.W. Bioorg. Med. Chem. Lett. 2000, 10, 715-717.