European Journal of Chemistry 3 (3) (2012) 363-366

European Journal of Chemistry

Journal homepage: www.eurjchem.com

# Synthesis and characterization of 1'-benzyl-1,4'-dimethyl-2'propyl-1*H*,1'*H*-2,6'-dibenzimidazole derivatives and their antibacterial activity studies

Doddarasinakere Kempaiah Ravishankara and Paduvalahippe Gowdegowda Chandrashekara*

*Department of Chemistry, Yuvaraja's College, University of Mysore, Mysore, 570005, India*

**Corresponding author at: Department of Chemistry, Yuvaraja's College, University of Mysore, Mysore, 570005, India. Tel.: +91.0821.2342867; fax: +91.0821.2419239. E-mail address: chanduchem@yahoo.com (P.G. Chandrashekara).*

COMMUNICATION INFORMATION

Received: 21 April 2012
Received in revised form: 20 May 2012
Accepted: 25 May 2012
Online: 30 September 2012

KEYWORDS

Ampicillin
*Bacillus subtilis*
*Escherichia coli*
Spectroscopic study
Antibacterial activity
Benzimidazole derivatives

ABSTRACT

A series of 1'-benzyl-1,4'-dimethyl-2'propyl-1*H*,1'*H*-2,6'-dibenzimidazole derivatives have been synthesized and characterized by FT-IR, $^1$H NMR, MS and elemental analyses. Furthermore, these compounds were screened for anti-bacterial study. Ampicillin is the drug used as a standard, for comparision with all the synthesized molecules.

## 1. Introduction

Benzimidazole and its derivatives are of great importance in medicinal chemistry because of their wide variety of biological and pharmacological applications [1, 2]. It is a fused heterocycle, containing a benzene ring attached with one face of the imidazole ring. It is the key structure in numerous compounds of therapeutic importance.

Benzimidazole derivatives have been reported to have various bioactivities, including antiviral [3-6], antihypertensive [7], antimicrobial [8,9], antioxidant [10], anti-inflammatory [11] and anticancer [12–20] activities. There are several marketed benzimidazole based drugs, such as Astemizole (Janssen Pharmaceutica), Micardis (Boehringer Ingelheim), Omepraxole (Astra Zeneca) and Albendazole (Glaxo-SmithKline) [3].In particular, benzimidazole derivatives have been explored as anticancer inhibitors of Topoisomerase I [12], PARP-1 [13,14], kinase Chk2 [15,16], Pgp and DNA synthesis [17], and tyrosine kinases [18-20]. Nonetheless, to the best of our knowledge, although several benzimidazole series have been developed as tyrosine kinase inhibitors, the 2-aryl benzimidazole series have not been explored as multi-target EGFR, VEGFR-2 and PDGFR inhibitors in published reports.

Therefore we designed and synthesized the benzimidazole compounds. Their antimicrobial activities were evaluated, the main purpose of these compounds were to discover possible newantimicrobials.

## 2. Experimental

### *2.1. Materials and methods*

All solvents were dried and distilled according to standard methods before use. NMR spectra were recorded on a BRUKER-AV400 spectrometer in $CDCl_3$ and tetramethylsilane (TMS; δ = 0.00 ppm) served as internal standards for $^1$H NMR. IR spectra were measured using a JASCO FT/IR-4100 spectrophotometer. Mass spectra were measured with Micromass Q-Tof (ESI). Column chromatography was conducted on Silica gel 60-120 mesh (Merck) and thin-layer chromatography was carried out using SILICA GEL GF-254. The melting points (uncorrected) were measured on a SALACO apparatus.

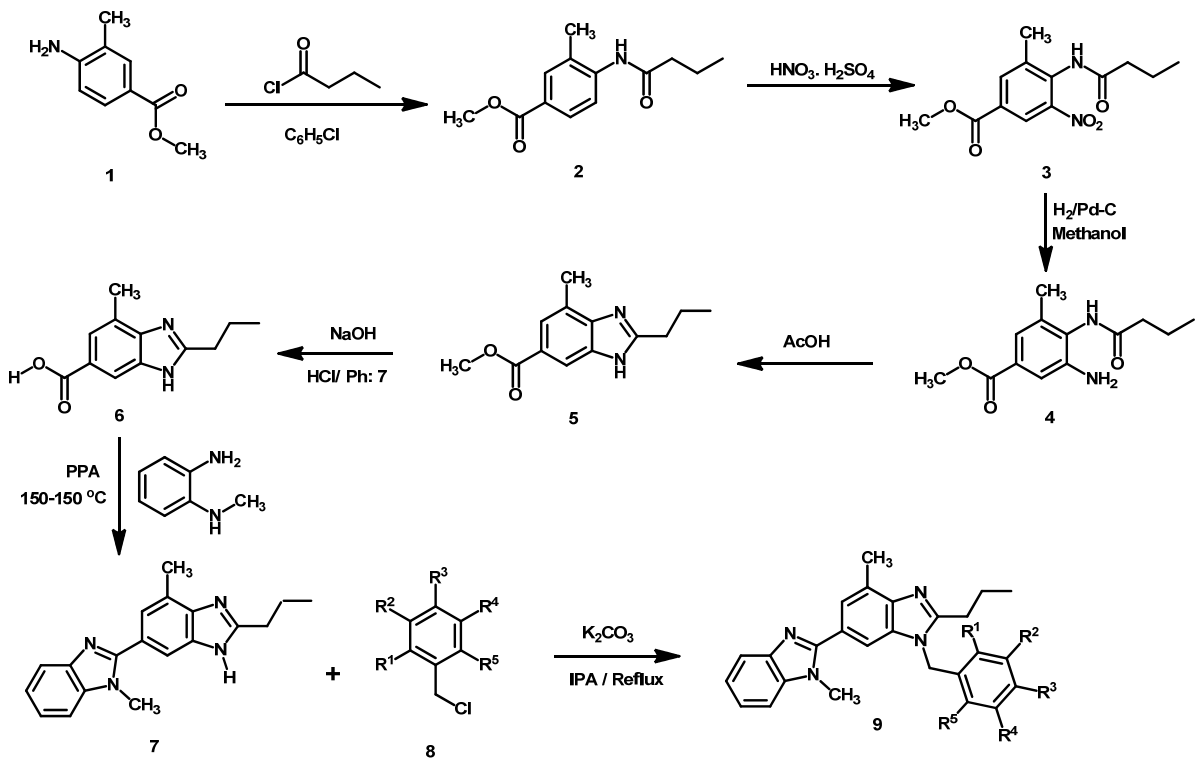
### *2.2. Synthesis*

#### *2.2.1. General procedure for the synthesis of 1'-benzyl-1,4'-dimethyl-2'propyl-1H,1'H-2,6'-dibenzimidazole derivatives (9)*

The compound 7, 1,7'-dimethyl-2'-propyl-1*H*,3'*H*-2,5'-dibenzimidazole have been synthesized as per the procedure given in the reference [21]. The compound 1,7'-dimethyl-2'-propyl-1*H*,3'*H*-2,5'-dibenzimidazole (1.0eq, 0.29g, 0.98mmol), substituted benzyl chloride (0.98mmol) and potassium carbonate (2.9mmol) in 15 mL of isopropyl alcohol was stirred with reflux for 4 hours. Completion of the reaction was monitored by TLC, finally the reaction mixture was distilled completely, then added water and extracted with dichloromethane, the dichloromethane was distilled completely to get crude product, which was purified by column chromatography using ethyl acetate and hexane as eluent, obtained the pure product with good yield (Scheme 1).

*1'-Benzyl-1,4'-dimethyl-2'propyl-1H,1'H-2,6'-dibenzimidazole* (**9a**): Color: Light brown. Yield: 82% (0.22 g). M.p.: 102-104 $^0$C. FT-IR (KBr, cm$^{-1}$): 1511 (aromatic CN stretch.), 1450 (aromatic CC stretch.), 2900 (alkane CH stretch), 3030 (aromatic CH stretch.). $^1$H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.08-1.12 (t, 3H, $CH_3$), 1.65-1.72 (m, 2H, $CH_2$), 1.92 (s, 3H, $ArCH_3$), 2.76-2.81 (q, 2H, $CH_2$), 3.95 (s, 3H, $NCH_3$), 5.46 (s, 2H, $ArCH_2$),


ISSN 2153-2249 (Print) / ISSN 2153-2257 (Online) 
DOI:10.5155/eurjchem.3.3.363-366.616




a. $R_1$=H, $R_2$=H, $R_3$=H, $R_4$=H, $R_5$=H.
b. $R_1$=H, $R_2$=$CH_3$, $R_3$=H, $R_4$=H, $R_5$=H.
c. $R_1$=H, $R_2$=Cl, $R_3$=H, $R_4$=H, $R_5$=H.
d. $R_1$=H, $R_2$=H, $R_3$=F, $R_4$=H, $R_5$=H.
e. $R_1$=H, $R_2$=F, $R_3$=F, $R_4$=H, $R_5$=H.
f. $R_1$=H, $R_2$=$NO_2$, $R_3$=H, $R_4$=H, $R_5$=H.
g. $R_1$=H, $R_2$=H, $R_3$=Cl, $R_4$=H, $R_5$=H.
h. $R_1$=H, $R_2$=$OCH_3$, $R_3$=H, $R_4$=H, $R_5$=H.
i. $R_1$=H, $R_2$=Cl, $R_3$=Cl, $R_4$=H, $R_5$=H.
j. $R_1$=H, $R_2$=F, $R_3$=H, $R_4$=H, $R_5$=H.

**Scheme 1**

6.90-7.25 (m, 7H, ArH), 7.59 (d, *J* = 8 Hz, 2H, ArH), 7.73 (s, 1H, Ar). Anal. calcd. for $C_{26}H_{26}N_4$: C, 79.16; H, 6.64; N, 14.20. Found: C, 79.09; H, 6.59; N, 14.16 %. MS (ESI, *m/z*): 395.70 (M+1).

*1'-3-methylbenzyl-1,4'-dimethyl-2'propyl-1H,1'H-2,6'-dibenzimidazole* (**9b**): Color: Brown. Yield: 77% (0.17 g). M.p.: 122-124 $^0$C. FT-IR (KBr, cm$^{-1}$): 1495 (aromatic CN stretch.), 1445 (aromatic CC stretch.), 2855 (alkane CH stretch.), 3045 (aromatic CH stretch.). $^1$H NMR (400 MHz, $CDCl_3$, δ, ppm): 0.93-1.11 (t, 3H, $CH_3$), 1.62-1.70 (m, 2H, $CH_2$), 1.91 (s, 3H, $ArCH_3$), 2.33 (s, 3H, $ArCH_3$), 2.81-2.86 (q, 2H, $CH_2$), 3.96 (s, 3H, $NCH_3$), 5.48 (s, 2H, $ArCH_2$), 6.99-7.29 (m, 7H, ArH), 7.68 (d, *J* = 8 Hz, 2H, ArH), 7.75(s, 1H, Ar). Anal. calcd. for $C_{27}H_{28}N_4$: C, 79.38; H, 6.91; N, 13.71. Found: C, 79.31; H, 6.90; N, 13.68%. MS (ESI, *m/z*): 409.5 (M+1).

*1'-3-Chlorobenzyl-1,4'-dimethyl-2'propyl-1H,1'H-2,6'-dibenzimidazole* (**9c**): Color: Light brown. Yield: 66% (0.16 g). M.p.: 92-94 $^0$C. FT-IR (KBr, cm$^{-1}$): 750 (CCl stretch.), 1510 (aromatic CN stretch.), 1500 (aromatic CC stretch.), 3000 (alkane CH stretch.), 3137 (aromatic CH stretch.). $^1$H NMR (400 MHz, $CDCl_3$, δ, ppm): 0.96-1.11 (t, 3H, $CH_3$), 1.62-1.73 (m, 2H, $CH_2$), 1.93 (s, 3H, $ArCH_3$), 2.71-2.79 (q, 2H, $CH_2$), 3.92 (s, 3H, $NCH_3$), 5.45 (s, 2H, $ArCH_2$), 7.28-7.45 (m, 4H, ArH), 7.59 (d, *J* = 8 Hz, 2H, ArH), 7.60-7.68 (d, *J* = 8.2 Hz, 2H, ArH), 7.67-7.72 (d, *J* = 8.2, 2H, ArH), 7.73 (s, 1H, Ar). Anal. calcd. for $C_{26}H_{25}ClN_4$: C, 72.80; H, 5.87; N, 13.06. Found: C, 72.59; H, 5.70; N, 12.87%. MS (ESI, *m/z*): 429.82 (M+1).

*1'-4-Fluorobenzyl-1,4'-dimethyl-2'propyl-1H,1'H-2,6'-dibenzimidazole* (**9d**): Color: Orange. Yield: 72% (0.19 g). M.p.: 111-114 $^0$C. FT-IR (KBr, cm$^{-1}$): 1497 (aromatic CN stretch.), 1200 (CF stretch.), 1447 (aromatic CC stretch.), 2887 (alkane CH stretch.), 3107 (aromatic CH stretch.). $^1$H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.08-1.12 (t, 3H, $CH_3$), 1.65-1.72 (m, 2H, $CH_2$), 1.92 (s, 3H, $ArCH_3$), 2.76-2.81 (q, 2H, $CH_2$), 3.95 (s, 3H, $NCH_3$), 5.46 (s, 2H, $ArCH_2$), 6.90-7.25 (m, 7H, ArH), 7.59 (d, *J* = 8 Hz, 2H, ArH), 7.73 (s, 1H, Ar). Anal. calcd. for $C_{26}H_{25}FN_4$: C, 75.70; H, 6.11; N, 13.58. Found: C, 75.62; H, 6.05; N, 13.49%. MS (ESI, *m/z*): 413.9 (M+1).

*1'-3,4-Difluorobenzyl-1,4'-dimethyl-2'propyl-1H,1'H-2,6'-dibenzimidazole* (**9e**): Color: Light brown. Yield: 86% (0.22 g). M.p.: 127-130 $^0$C. FT-IR (KBr, cm$^{-1}$): 1510 (aromatic CN stretch.), 1225 (CF stretch.), 1501 (aromatic CC stretch.), 3006 (alkane CH stretch.), 2999 (aromatic CH stretch.). $^1$H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.11-1.13 (t, 3H, $CH_3$), 1.68-1.73 (m, 2H, $CH_2$), 1.93 (s, 3H, $ArCH_3$), 2.75-2.80 (q, 2H, $CH_2$), 3.95 (s, 3H, $NCH_3$), 5.45 (s, 2H, $ArCH_2$), 7.01-7.62 (m, 9H, ArH). Anal. calcd. for $C_{26}H_{24}F_2N_4$: C, 72.54; H, 5.62; N, 13.01. Found: C, 72.49; H, 5.59; N, 12.88%. MS (ESI, *m/z*): 431.49 (M+1).

**Table 1.** Antimicrobial studies of compounds **9a-j**.

| Compound | Zone of Inhibition (mm)* | | | |
|---|---|---|---|---|
| | *Escherichia coli* | | *Bacillus subtilis* | |
| | 400 µg | 800 µg | 400 µg | 800 µg |
| 9a | 11 | 19 | 13 | 19 |
| 9b | 11 | 16 | - | 10 |
| 9c | - | 9 | - | 9 |
| 9d | - | 9 | - | - |
| 9e | - | 10 | - | 11 |
| 9f | 9 | 13 | - | 12 |
| 9g | 13 | 18 | 10 | 16 |
| 9h | 12 | 23 | 15 | 21 |
| 9i | 13 | 18 | 13 | 19 |
| 9j | 9 | 10 | - | - |
| Ampicillin | 30 | 32 | - | 31 |

*: Inhibition zones including cup borer (8.5 mm) diameter; Positive control zone is 30 to 35 mm in 200 µg; '-' = Not active.

*1'-3-Nitrobenzyl-1,4'-dimethyl-2'propyl-1H,1'H-2,6'-dibenzimidazole* (**9f**): Color: Yellow. Yield: 77% (0.20 g). M.p.: 87-89 $^0$C. FT-IR (KBr, cm$^{-1}$): 1492 (aromatic CN stretch.), 1150 (CO stretch.), 1385 (NO stretch.), 1456 (aromatic CC stretch.), 3030 (alkane CH stretch.), 3107 (aromatic CH stretch.). $^1$H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.12-1.16 (t, 3H, $CH_3$), 1.63-1.68 (m, 2H, $CH_2$), 1.93 (s, 3H, $ArCH_3$), 2.77-2.82 (q, 2H, $CH_2$), 3.95 (s, 3H, $NCH_3$), 5.46 (s, 2H, $ArCH_2$), 6.89-7.23 (m, 7H, ArH), 7.59 (d, *J* = 8 Hz, 2H, ArH), 7.74 (s, 1H, ArH). Anal. calcd. for $C_{26}H_{25}N_5O_2$: C, 71.05; H, 5.73; N, 15.93. Found: C, 70.93; H, 5.69; N, 15.87%. MS (ESI, *m/z*): 440.32 (M+1).

*1'-4-Chlorobenzyl-1,4'-dimethyl-2'propyl-1H,1'H-2,6'-dibenzimidazole* (**9g**): Color: Brown red. Yield: 79% (0.26 g). M.p.: 118-120 $^0$C. FT-IR (KBr, cm$^{-1}$): 745 (CCl stretch.), 1520 (aromatic CN stretch.), 1555 (aromatic CC stretch.), 2999 (alkane CH stretch.), 3122 (aromatic CH stretch.). $^1$H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.09-1.13 (t, 3H, $CH_3$), 1.64-1.72 (m, 2H, $CH_2$), 1.94 (s, 3H, $ArCH_3$), 2.76-2.80 (q, 2H, $CH_2$), 3.95 (s, 3H, $NCH_3$), 5.46 (s, 2H, $ArCH_2$), 6.98-7.25 (m, 4H, ArH), 7.59 (d, *J* = 8 Hz, 2H, ArH), 7.72 (d, *J* = 8 Hz, 2H, Ar), 7.74 (s, 1H, Ar), 7.78 (s, 1H, Ar). Anal. calcd. for $C_{26}H_{25}ClN_4$: C, 72.80; H, 5.87; N, 13.06. Found: C, 72.79; H, 5.81; N, 12.90%. MS (ESI, *m/z*): 429.95 (M+1).

*1'-3-Methoxybenzyl-1,4'-dimethyl-2'propyl-1H,1'H-2,6'-dibenzimidazole* (**9h**): Color: Orange. Yield: 69% (0.15 g). M.p.: 137-139 $^0$C. FT-IR (KBr, cm$^{-1}$): 755 (CCl stretch.), 1490 (aromatic CN stretch.), 1550 (aromatic CC stretch.), 2987 (alkane CH stretch.), 3100 (aromatic CH stretch.). $^1$H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.08-1.12 (t, 3H, $CH_3$), 1.64-1.68 (m, 2H, $CH_2$), 1.93 (s, 3H, $ArCH_3$), 2.74-2.83 (q, 2H, $CH_2$), 3.83 (s, 3H, $OCH_3$), 3.94 (s, 3H, $NCH_3$), 5.45 (s, 2H, $ArCH_2$), 6.89-7.23 (m, 7H, ArH), 7.59 (d, *J* = 8 Hz, 2H, ArH), 7.74 (s, 1H, ArH). Anal. calcd. For $C_{27}H_{28}N_4O$: C, 76.39; H, 6.65;N, 13.20. Found: C, 76.28; H, 6.60; N, 13.11%. MS (ESI, *m/z*): 425.37 (M+1).

*1'-3,4-Dichlorobenzyl-1,4'-dimethyl-2'propyl-1H,1'H-2,6'-dibenzimidazole* (**9i**):Color: Yellow. Yield: 75% (0.19 g). M.p.: 120-122 $^0$C. FT-IR (KBr, cm$^{-1}$): 799 (CCl stretch.), 1492 (aromatic CN stretch.), 1399 (aromatic CC stretch.), 2899 (alkane CH stretch.), 3037 (aromatic CH stretch.). $^1$H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.08-1.12 (t, 3H, $CH_3$), 1.67-1.73 (m, 2H, $CH_2$), 1.89 (s, 3H, $ArCH_3$), 2.74-2.76 (q, 2H, $CH_2$), 3.93 (s, 3H, $NCH_3$), 5.44 (s, 2H, $ArCH_2$), 7.01-7.64 (m, 9H, ArH). Anal. calcd. for $C_{26}H_{24}Cl_2N_4$: C, 67.39; H, 5.22; N, 12.09. Found: C, 67.31; H, 5.21; N, 11.98%. MS (ESI, *m/z*): 464.48 (M+1).

*1'-3-Fluorobenzyl-1,4'-dimethyl-2'propyl-1H,1'H-2,6'-dibenzimidazole*(**9j**): Color: Orange. Yield: 72% (0.28 g).M.p.: 108-110 $^0$C. FT-IR (KBr, cm$^{-1}$): 1515 (aromatic CN stretch.), 1400 (CF stretch.), 1555 (aromatic CC stretch.), 2899 (alkane CH stretch.), 3128 (aromatic CH stretch.). $^1$H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.99-1.12 (t, 3H, $CH_3$), 1.67-1.74 (m, 2H, $CH_2$), 1.94 (s, 3H, $ArCH_3$), 2.72-2.78 (q, 2H, $CH_2$), 3.93 (s, 3H, $NCH_3$), 5.44 (s, 2H, $ArCH_2$), 7.28-7.45 (m, 4H, ArH), 7.59 (d, *J* = 8 Hz, 2H, ArH), 7.60-7.68 (d, *J* = 8.2 Hz, 2H, ArH), 7.73(s, 1H, Ar). Anal. calcd. for $C_{26}H_{25}FN_4$: C, 75.70; H, 6.11; N, 13.58. Found: C, 75.61; H, 6.07; N, 13.49%. MS (ESI, *m/z*): 413.50 (M+1).

### *2.3. Biological evaluation*

#### *2.3.1. Antibacterial Activity*

The screening of the compounds **9a-j**for antibacterial action is performed by Well diffusion method [22] with modification in concentration of prepared compounds. The synthesized compounds were tested against one strain of gram +ve bacteria (*Bacillus subtilis*), and gram–ve bacteria (*Escherichia coli*). 25 mL of nutrient agar medium was poured into petri plate and after cooling; agar plates were swabbed with 100 µL of bacterial suspension containing $10^6$ cells/mL. Wells were made in the seeded plates with the help of a cup-borer (8.5 mm) and 20 µL, 40 µL (10 mg/1mL) of each test compound dissolved in DMSO was loaded into the wells. Ampicillin and DMSO as positive control and negative control respectively were used as for all the test compounds.

## 3. Results and discussion

We have synthesized a series of 1'-benzyl-1,4'-dimethyl-2'propyl-1*H*,1'*H*-2,6'-dibenzimidazole derivatives by using a known procedure and obtained products with good yield.

The structures of all the synthesized compounds were characterized by spectroscopic data, and subjected these molecules for study of antibacterial activities (Table 1). Benzimidazole derivatives have shown very good antibacterial activities, we compared the synthesized new benzimidazole derivatives with the ampicillin which is a known antibacterial drug [22]. In the present study compound **9h** shows good bacterial activity, in which the methoxy group is attached, which is electron releasing group, The compound **9a** shows a next highest antibacterial activity, none of electron withdrawing and electron releasing group is attached. The remaining molecules showed moderate antibacterial activity.

## 4. Conclusion

We have synthesized 1'-benzyl-1,4'-dimethyl-2'propyl-1*H*,1'*H*-2,6'-dibenzimidazole derivatives and structure proposed to the synthesized compound is well supported by spectroscopic data. From the data of antibacterial activity, it may be concluded that all the synthesized compounds showed good to moderate activity.

### *Acknowledgements*

Our work was financially supported by Sri Mahadeshwara Government First Grade College, Kollegal.

## References


[1]. Goker, H.; Kus, C.; Abbasoglu, U. *Arch Pharm (Weinheim)* **1995**, *328*, 425-430.
[2]. Garuti, L.; Roberti, M.; Gentilomi, G. *Il Farmaco* **2000**, *55*, 35-39.
[3]. Tonelli, M.; Simone, M.; Tasso, B.; Novelli, F.; Boido, V.; Sparatore, F.; Paglietti, G.; Pricl, S.; Giliberti, G.; Blois, S.; Ibba, C.; Sanna, G.; Loddo, R.; La Colla, P. *Bioorg. Med. Chem.* **2010**, *18*, 2937-2953.
[4]. Tonelli, M.; Boido, V.; La Colla, P.; Loddo, R.; Posocco, P.; Paneni, M. S.; Fermeglia, M.; Pricl, S. *Bioorg. Med. Chem*. **2010**, *18*, 2304-2316.
[5]. Keurulainen, L.; Salin, O.; Siiskonen, A.; Kern, J. M.; Alvesalo, J.; Kiuru, P.; Maass, M.; Yli-Kauhaluoma, J.; Vuorela, P. *J. Med. Chem.* **2010**, *53*, 7664-7674.
[6]. Lyakhova, E. A.; Gusyeva, Y. A.; Nekhoroshkova, J. V.; Shafran, L. M.; Lyakhov, S. A. *Eur. J. Med. Chem.* **2009**, *44*, 3305-3312.
[7]. Navarrete-Vazquez, G.; Hidalgo-Figueroa, S.; Torres-Piedra, M.; Vergara-Galicia, J.; Rivera-Leyva, J. C.; Estrada-Soto, S.; Leon-Rivera, I.; Aguilar-Guardarrama, B.; Rios-Gomez, Y.; Villalobos-Molina, R.; Ibarra-Barajas, M. *Bioorg. Med. Chem*. **2010**, *18*, 3985-3991.
[8]. Rohini, R.; Shanker, K.; Reddy, P. M.; Ho, Y. P.; Ravinder, V. *Eur. J. Med. Chem.* **2009**, *44*, 3330-3339.
[9]. Sharma, D.; Narasimhan, B.; Kumar, P.; Jalbout, A. *Eur. J. Med. Chem.* **2009**, *44*, 1119-1127.
[10]. Kus, C.; Ayhan-Kilcigil, G.; Ozbey, S.; Kaynak, F. B.; Kaya, M.; Coban, T.; Can-Eke, B. *Bioorg. Med. Chem.* **2008**, *16*, 4294-4303.
[11]. Savall, B. M.; Edwards, J. P.; Venable, J. D.; Buzard, D. J.; Thurmond, R.; Hack, M.; McGovern, P. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 3367-3371.
[12]. Kim, J. S.; Gatto, B.; Yu, C.; Liu, A.; Liu, L. F.; LaVoie, E. J. *J. Med. Chem.* **1996**, *39*, 992-998.
[13]. White, A. W.; Curtin, N. J.; Eastman, B. W.; Golding, B. T.; Hostomsky, Z.; Kyle, S.; Li, J.; Maegley, K. A.; Skalitzky, D. J.; Webber, S. E.; Yu, X. H.; Griffin, R. J. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2433-2437.
[14]. White, A. W.; Almassy, R.; Calvert, A. H.; Curtin, N. J.; Griffin, R. J.; Hostomsky, Z.; Maegley, K.; Newell, D. R.; Srinivasan, S.; Golding, B. T. *J. Med. Chem.* **2000**, *43*, 4084-4097.
[15]. Neff, D. K.; Lee-Dutra, A.; Blevitt, J. M.; Axe, F. U.; Hack, M. D.; Buma, J. C.; Rynberg, R.; Brunmark, A.; Karlsson, L.; Breitenbucher, J. G. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6467-6471.
[16]. Arienti, K. L.; Brunmark, A.; Axe, F. U.; McClure, K.; Lee, A.; Blevitt, J.; Neff, D. K.; Huang, L.; Crawford, S.; Pandit, C. R.; Karlsson, L.; Breitenbucher, J. G. *J. Med. Chem.* **2005**, *48*, 1873-1885.
[17]. Vock, C. A.; Ang, W. H.; Scolaro, C.; Phillips, A. D.; Lagopoulos, L.; Juillerat-Jeanneret, L.; Sava, G.; Scopelliti, R.; Dyson, P. J. *J. Med. Chem.* **2007**, *50*, 2166-2175.
[18]. McBride, C. M.; Renhowe, P. A.; Heise, C.; Jansen, J. M.; Lapointe, G.; Ma, S.; Pineda, R.; Vora, J.; Wiesmann, M.; Shafer, C. M. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3595-3599.
[19]. Hasegawa, M.; Nishigaki, N.; Washio, Y.; Kano, K.; Harris, P. A.; Sato, H.; Mori, I.; West, R. I.; Shibahara, M.; Toyoda, H.; Wang, L.; Nolte, R. T.; Veal, J. M.; Cheung, M. *J. Med. Chem.* **2007**, *50*, 4453-4470.
[20]. Hubbard, R. D.; Bamaung, N. Y.; Fidanze, S. D.; Erickson, S. A.; Palazzo, F.; Wilsbacher, J. L.; Zhang, Q.; Tucker, L. A.; Hu, X.; Kovar, P.; Osterling, D. J.; Johnson, E. F.; Bouska, J.; Wang, J.; Davidsen, S. K.; Bell, R. L.; Sheppard, G. S. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1718-1721.
[21]. Reddy, K. S.; Srinivasan, N.; Reddy, C. R.; Kolla, N.; Anjaneyulu, Y.; Venkatraman, S.; Bhattacharya, A.; Mathad, V. T. *Org. Process Res. Dev*. **2007**, *11*, 81-85.
[22]. Kumar, R.; Nair, R. R.; Dhiman, S. S.; Sharma, J.; Prakash, O. *Eur. J. Med. Chem.* **2009**, *44(5)*, 2260-2264.