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Synthesis and antibacterial activity of some novel 1,3-dihydro-2*H*-benzimidazol-2-one analogs

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ABSTRACT

1,3-dihydro-2H-benzimidazole-2-one ring system represents the core skeleton of a large number of biologically active, structurally intriguing compounds found in a multitude of pharmaceutically important compounds. The development of efficient and practical methods for construction of this important heterocyclic remains as an active area of synthetic research. The present paper describes the synthesis and antibacterial activity of some novel 1,3-dihydro-2H-benzimidazol-2-one analogs ***6a -6g*** *(****Scheme 1****) from commercially available 1,2-phenylenediamine as starting material. The newly synthesized compounds,* ***6a-6g*** *were screened in-vitro at a concentration of 100 µg/mL for antibacterial activity against two Gram-positive (Staphylococcus aureus and Staphylococcus pyogenes) and two Gram-negative strains (Escherichia coli and Pseudomonas aeruginosa). It was observed that among all the compounds tested, compound* ***6e, 6f*** *and* ***6g*** *showed high activity against all the tested bacterial strains.*

Keywords: 1,2-phenylenediamine, 1,3-dihydro-2H-benzimidazol-2-one, CDI, 2-MeTHF, antibacterial activity

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INTRODUCTION

Emerging infectious diseases and the increasing number of multi-drug resistant microbial pathogens still make the treatment of infectious diseases an important and challenging problem [1]. In spite of the large number of antibiotics and chemotherapeutics available for medical use, the emergence of old and new antibiotic resistant bacterial strains in the last decades constitutes a substantial need for new classes of antibacterial agents [2]. As such, the "last resort for anti-infective diseases, the Vancomycin family of antibiotics, has now been gravely challenged in recent years due to the emergence of Vancomycin resistance in clinical practice [3,4].

In order to overcome these emerging resistance problems, there is an urgent need to discover novel antibacterial agents in structural classes distinct from existing antibiotics. 1,3-dihydro-2H-benzimidazole-2-one ring system **1** represents the core skeleton of a large number of biologically active, structurally intriguing compounds found in a multitude of pharmaceutically important compounds [5]. Both mono- and disubstituted benzimidazol-2-one derivatives **1** have been identified as putative antipsychotic [6], Selective A2B Adenosine Receptor Antagonists [7], as nanomolar inhibitors [8], as potent non-nucleoside HIV-1 reverse transcriptase inhibitors [9], as anti-HIV agents [10], M1 allosteric agonist TBPB [11], as NOP receptor agonists [12], potent NK1 antagonists [13], CGRP receptor antagonists [14], farnesyl transfer inhibitors [15], p38 inhibitors [16], cathepsin S inhibitors [17], 5-HT4 agonists and antagonists [18], progesterone receptor antagonist [19], respiratory syncytial virus (RSU) inhibitors [20], vasopressin 1a receptor antagonists [21]. The development of efficient and practical methods for construction of this

important heterocycle remains as an active area of synthetic research **(Fig 1).** The present paper describes the synthesis and antibacterial activity of some novel 1,3-dihydro-2H-benzimidazol-2-one analogs **6a-6g** (**Scheme 1**).

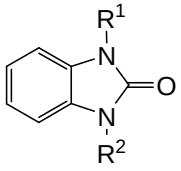


Fig 1.

MATERIALS AND METHODS

Chemical and solvents used were purchased either from Fluka or Merck. All the reagents were of analytical grade. Thin-layer chromatography (TLC) was performed on E.Merck AL silica gel 60 F254 plates and visualized under UV light. The IR spectra were recorded on a Perkin Elmer FT-IR spectrometer. The ^{1}H NMR spectra were recorded in $CDCl_3$ on a Varian EM-360 spectrometer (400MHz). The ^{13}C NMR spectra recorded in $CDCl_3$ on a Varian EM-360 spectrometer operating at 100MHz. All the chemical shifts were reported in δ (ppm) using TMS as an internal standard. The mass spectra were recorded on Agilent ion trap MS. All the reactions were carried out under argon atmosphere.

Experimental methods

1H-benzo[α]imidazol-2(3H)-2-one **(2)**

To a stirred solution of 1,2-phenylenediamine (10 g, 92 mmol) in 2-MeTHF (100 mL) was added 1,1'-carbonyldiimidazole (14.99 g, 92 mmol). The resulting solution was stirred at room temperature for 48 h. The solvent was concentrated under reduced pressure, filtered, and washed with dichloromethane to afford compound **2.** White solid; m.p. 100-102 ^{o}C; Yield: 98%; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 6.92 (m, 4 H), 10.2 (s, 2 H); IR (KBr): υ_{max} 3016, 1755, 1629, 1483 cm^{-1}; ^{13}C NMR ($CDCl_3$, 400 MHz): δ 121, 124.6, 129.9, 155.2; ESI-MS: m/z (rel.abund.%) 135.2 (M+, 100).

ethyl 2-oxo-2,3-dihydro-1H-benzimidazole-1-carboxylate (**3)**

To a stirred suspension of 1H-benzo[α]imidazol-2(3H)-2-one **2** (15 g, 0.111 mmol) and K_2CO_3 (18.5 3 g, 0.134 mmol) in 2-MeTHF (150 mL) was added ethylchloroformate (12 g ,0.111 mmole) dropwise over 30 min at room temperature. The reaction mixture was stirried at 90 ^{o}C for 16 h. The mixture was concentrated in *vacuo* and the residue diluted with water. The precipitated solids were filtered, washed with water, dried in air to afford compound **3**. White solid; m.p. 149-150 ^{o}C; Yield: 81%; IR (KBr): υ_{max} 3270, 1780 ,1480 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.48 (t, *J* = 7.0 Hz, 3H), 4.53 (q, *J* = 7.0 Hz, 2 H), 7.0-7.20 (m, 3 H), 7.77 (d, *J* = 7.5 Hz, 1H), 10.27 (s, 1 H), ^{13}C NMR (400 MHz, $CDCl_3$): δ 13.8, 58.3, 121.8, 124.6, 127.3, 129.9, 150.2, 151.4; ESI-MS: m/z (rel.abund.%) 206.9 (M+, 100).

1-[2-(4-bromophenyl)-2-oxoethyl]-1,3-dihydro-2H-benzimidazol-2-one (**4)**

A mixture of compound **3** (1.5 g, 7.28 mmol), compound **3a** (2 g, 7.28 mmol), K_2CO_3 (2 g, 14.56 mmol) in 2-MeTHF (20 mL) was refluxed at 90 ^{0}C for 10 h. The reaction mixture was cooled to room temperature, diluted with water and extracted with isopropyl acetate, organic layer dried over $MgSO_4$, filtered and evaporated in *vacuo* to obtain compound **4.** Off white solid, m.p. 121-122 ^{o}C; Yield: 84%. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 11.0 (br.s, 1H), 8.04 (d, *J* = 11.2 Hz, 2H), 7.83 (d, *J* = 11.2 Hz, 2H), 7.10-690 (m, 4H), 5.40 (s, 2H); IR (KBr): υ_{max} 3377, 3056, 1694, 1586, 1495 cm^{-1}; ESI-MS: m/z (rel.abund.%) 331.1 (M+, 100).

1-(2-bromoethyl)-3-[2-(4-bromophenyl)-2-oxoethyl]-1,3-dihydro-2H-benzimidazol-2-one **(5)**

To a stirred mixture of compound **4** (1.2 g, 3.647 mmol) and K_2CO_3 (1.0 g, 7.294 mmol) in 2-MeTHF 1 5 mL) was added dropwise 1,2-dibromoethane (2.05 g, 10.947 mmol) over 10 min. The reaction mixture was refluxed at reflux for 4 h. The reaction mixture was diluted with water and extracted with isopropyl acetate. The organic layer was washed with water and saturated NaCl, dried over Na_2SO_4, filtered and evaporated in *vacuo* to obtain crude compound **5** which was **p**urified by flash column chromatography using silicagel with hexane-ethyl acetate as eluant to yield **5** as a pale yellow solid. m.p. 116-118 ^{o}C; Yield: 78%; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.68 (t, *J* = 6.9 Hz, 2H), 4.318 (t, *J* = 7.05 Hz, 2H), 5.21 (s, 2H), 7.05-7.21 (m, 3H), 7.77 (d, *J* = 7.5,1H), 6.8 (t, *J* = 8.7 Hz, 1H), 8.1 (s,

1H), 7.92 (t, *J* = 10.8, 1H), 8.91 (s, 1H); IR (KBr): υ_{max} 3058, 2928. 1704, 1498 cm^{-1}; ^{13}C NMR (400 MHz, $CDCl_3$): δ 27.9, 49.7, 55.8, 121.8, 124.6, 121.8, 124.6, 128.3, 130.2, 130.3,133.3, 136.3, 154.6, 195.4; ESI-MS: m/z (rel.abund.%) 425.9 (M+, 100).

General experimental procedure for the preparation of 6a-6g

A mixture of compound **5** (0.2 g, 0.470 mmol), 2^o amines (0.564 mmol), K_2CO_3 (0.940 mmol) in 2-MeTHF (2.5 mL) was reflux for 4h. The reaction mixture was concentrated in *vacuo* and the residue diluted with H_2O and extracted with isopropyl acetate to obtain crude compounds. The crude compounds were purified by column chromatography using silica gel (60-120 mesh). Yields of the products varied between 60 and 85%.

1-[2-(4-bromophenyl)-2-oxoethyl]-3-[2-(dimethylamino)ethyl]-1,3-dihydro-2H-benzimidazol-2-one **6a**:
Yellow syrupy liquid; Yield: 65%; ^1H NMR($CDCl_3$, 400 MHz): δ 2.27 (s, 6 H), 2.62 (t, *J* = 8.2 Hz, 2H), 3.26 (t, *J* = 7.80 Hz, 2H), 5.22 (s, 2H), 6.82 (d, *J* = 9.6 Hz, 1H), 7.13-7.02 (m, 3H), 7.66 (d, *J* = 10.8 Hz, 2H), 7.90 (t, *J* = 10.8 Hz, 2H); ESI-MS: m/z (rel.abund.%) 403 (M+, 100).

1-[2-(4-bromophenyl)-2-oxoethyl]-3-[2-(diethylamino)ethyl]-1,3-dihydro-2H-benzimidazol-2-one **6b**:
Pale yellow solid, m.p. 86-88 ^oC; Yield: 74%; ^1H NMR($CDCl_3$, 400 MHz): δ 1.0 (t, *J* = 7.6 Hz, 6 H), 2.40 (q, *J* = 7.6 Hz, 4 H), 2.62 (t, *J* = 8.2 Hz, 2H), 3.26 (t, *J* = 7.80 Hz, 2H), 5.22 (s, 2H), 6.82 (d, *J* = 9.6 Hz, 1H), 7.13-7.02 (m, 3H), 7.66 (d, *J* = 10.8 Hz, 2H), 7.90 (t, *J* = 10.8 Hz, 2H); ESI-MS: m/z (rel.abund.%) 431.10 (M+, 100).

1-[2-(4-bromophenyl)-2-oxoethyl]-3-[2-(pyrrolidin-1-yl)ethyl]-1,3-dihydro-2H-benzimidazol-2-one **6c**:
Yellow solid, m.p. 77-78 ^oC; Yield: 82%; ^1H NMR($CDCl_3$, 400 MHz): δ 1.80-1.72 (m, 4 H), 2.70-2.60 (m, 4 H), 2.84 (t, *J* = 10.0 Hz, 2H), 4.07 (t, *J* = 9.60 Hz, 2H), 5.23 (s, 2H), 6.82 (d, *J* = 9.6 Hz, 1H), 7.13-7.02 (m, 3H), 7.66 (d, *J* = 10.8 Hz, 2H), 7.90 (t, *J* = 10.8 Hz, 2H); IR (KBr): υ_{max} 3373, 1704, 1583, 1498 cm^{-1}; ESI-MS: m/z (rel.abund.%) 428 (M+, 100).

1-[2-(4-bromophenyl)-2-oxoethyl]-3-[2-(piperidin-1-yl)ethyl]-1,3-dihydro-2H-benzimidazol-2-one **6d**:
Pale yellow solid, m.p. 112-113 ^oC; Yield: 79%; ^1H NMR($CDCl_3$, 400 MHz): δ 1.75-1.55 (m, 6 H), 2.52-2.48 (m, 4 H), 2.67 (t, *J* = 9.6 Hz, 2H), 4.05 (t, *J* = 9.60 Hz, 2H), 5.25 (s, 2H), 6.82 (d, *J* = 9.6 Hz, 1H), 7.07-7.01 (m, 3H), 7.65 (d, *J* = 10.8 Hz, 2H), 7.90 (t, *J* = 10.8 Hz, 2H); IR (KBr): υ_{max} 3392, 2933, 1709, 1691, 1496 cm^{-1}; ESI-MS: m/z (rel.abund.%) 443 (M+, 100).

1-[2-(4-bromophenyl)-2-oxoethyl]-3-[2-(morpholinoethyl)]-1,3-dihydro-2H-benzimidazol-2-one **6e**:
Yellow viscous liquid; Yield: 76%; ^1H NMR($CDCl_3$, 400 MHz): δ 2.58 (t, *J* = 6.0 Hz, 4 H), 2.72 (t, *J* = 9.2 Hz, 2 H), 3.68 (t, *J* = 6.0 Hz, 4 H), 4.05 (t, *J* = 9.2 Hz, 2H), 5.24 (s, 2 H), 6.82 (d, *J* = 9.6 Hz, 1H), 7.20-6.85 (m, 3H), 7.65 (d, *J* = 10.8 Hz, 2H), 7.90 (t, *J* = 10.8 Hz, 2H); IR (KBr): υ_{max} 3366, 3061, 1706, 1584, 1495 cm^{-1}; ESI-MS: m/z (rel.abund.%) 445 (M+, 100).

1-[2-(4-bromophenyl)-2-oxoethyl]-3-[2-(piperazin-1-yl)ethyl)]-1,3-dihydro-2H-benzimidazol-2-one **6f**:
Yellow semi solid; Yield: 70%; ^1H NMR($CDCl_3$, 400 MHz): δ 2.55(m, 4H), 2.71 (br.s, 2 H), 2.89 (m, 4H), 4.04 (s, 4H), 5.23 (s, 2 H), 6.82 (d, *J* = 9.2 Hz, 1H), 7.07-7.0 (m, 3H), 7.64 (d, *J* = 9.6 Hz, 2H), 7.91 (d, *J* = 10.0 Hz, 2H); IR (KBr): υ_{max} 3393, 2925, 1697, 1585, 1495 cm^{-1}; ESI-MS: m/z (rel.abund.%) 444 (M+, 100).

1-[2-(4-bromophenyl)-2-oxoethyl]-3-[2-(azepan-1-yl)ethyl)]-1,3-dihydro-2H-benzimidazol-2-one **6g**:
Pale yellow solid; m.p. 94-95 ^oC; ^1H NMR($CDCl_3$, 400 MHz): δ 1.62 – 1.58 (m, 4H), 2.75 (m, 4H), 2.87 (t, *J* = 9.6 Hz, 2H), 4.01(t, J = 9.2 Hz, 2H), 5.22 (s, 4H), 6.82 (d, *J* = 9.6 Hz, 1H), 7.10-7.02 (m, 3H), 7.66 (d, *J* = 11.2 Hz, 2H), 7.91 (d, *J* = 11.2 Hz, 2H); IR (KBr): υ_{max} 3368, 2922, 1702, 1584, 1496 cm^{-1}; ESI-MS: m/z (rel.abund.%) 457 (M+, 100).

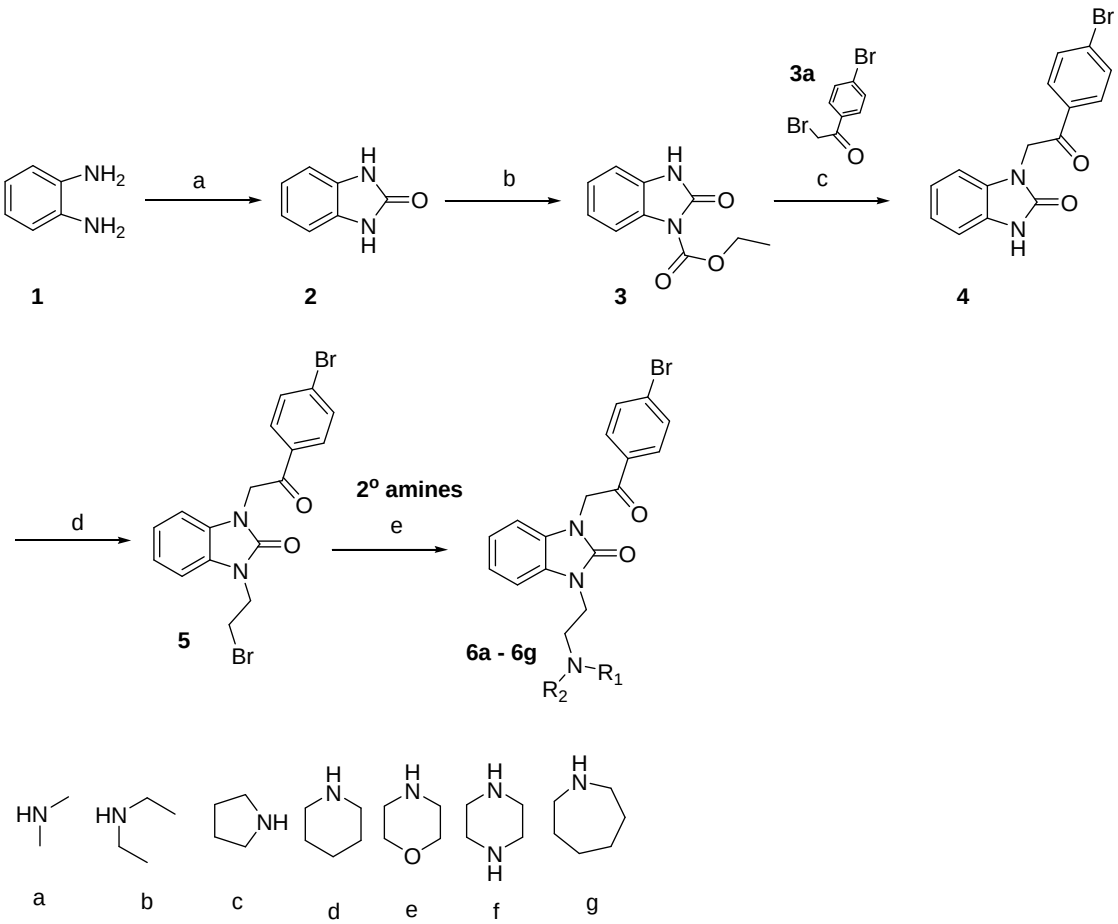
Antimicrobial Activity

The antimicrobial activity was determined using disc diffusion method by measuring zone of inhibition in mm [22]. All the compounds, **6a-6g** were screened *in-vitro* at a concentration of 100 µg/mL for antibacterial activity against two Gram-positive (Staphylococcus aureus and Staphylococcus pyogenes) and two Gram-negative strains (Escherichia coli and Pseudomonas aeruginosa). Standard antibacterial drug ciprofloxacin (100 µg/disc) was also tested under similar conditions against these organisms. Each experiment was done in triplicate and the average reading was taken. The antibacterial activity was classified as highly active (≥28 mm), moderately active (18-25

mm) and least active (<18 mm). The results of antibacterial activity are expressed in terms of zone of inhibition and presented in **Table 1**.

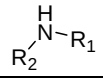
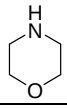
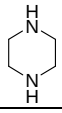
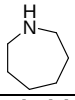
RESULTS AND DISCUSSION

Synthesis of 1,3-dihydro-2H-benzimidazol-2-one analogs **6a–6g** is outlined in (**Scheme 1)**. 1,2-phenylenediamine was reacted with CDI in 2-methyl tetrahydrofuran (2-MeTHF) as a solvent at room temperature for 48 h to afford *1H-benzo[α]imidazol-2(3H)-2-one* **2** in 98 % yield. Compound **2** was treated with ethylchloroformate in presence of K_2CO_3 in 2-MeTHF at 90 ^oC for 16 h to give compound **3** in 81 % yield. Compounds **3** was reacted with 4-brom phenacyl bromide in presence of K_2CO_3 in 2-MeTHF at 90 ^oC to afford compound **4.** Alkylation of compound **4** with 1,2-Dibromoethane in presence K_2CO_3 in 2-MeTHF gave the key intermediate bromide **5**. Reaction of Compounds **5** with various 2^o amines in presence of K_2CO_3 in 2-MeTHF resulted in compounds **6a – 6g**. During the course of the synthesis of **6a – 6g,** 2-Methyl tetrahydrofuran (2-MeTHF) was used as a choice of solvent, since it is derived from renewable resources such as corncobs and bagasse and offers both economical and environmentally friendly advantages over acetonitrile, dimethyl formamide and tetrahydrofuran [23]. The newly synthesized compounds were screened to evaluate their antibacterial activity. Most of the compounds were found to display high to moderate antibacterial activity against different strains of bacteria. From the **Table 1,** it was observed that among all the compounds tested, compound **6e, 6f and 6g** showed high activity against all the tested bacterial strains. Among the other compounds **6c and 6d** showed moderate activity, while compounds **6a** and **6b** showed least activity against all the pathogens.



Scheme 1: Reagent and conditions: a) CDI, 2-MeTHF, r.t., 48 h b) ethylchloroformate, K_2CO_3, 2-MeTHF, 90 ^oC, 16 h; c) 3a, K_2CO_3, 2-MeTHF, 90 ^oC, 10 h; d) 1,2-dibromoethane, K_2CO_3, 2-MeTHF, reflux, 4 h; ef) 2^o amines, K_2CO_3, 2-MeTHF, reflux, 4 h.

Table 1: Antibacterial Activity of Benzimidazolone derivatives 6a-6g

Compound no.		*Gram negative bacteria*		*Gram positive bacteria*	
		E. coli	*P. aeruginosa*	*S.aureus*	*S.pyogenes*
		Zone of inhibitions			
6a		16	15	16	18
6b		18	19	17	18
6c		23	22	19	20
6d		25	24	21	20
6e		29	28	24	24
6f		29	28	23	20
6g		28	26	22	22
Standard drug Ciprofloxacin (Conc. 100 µg /mL)	Standard drug Ciprofloxacin	28	26	21	22

CONCLUSION

Novel 1,3-dihydro-2H-benzimidazol-2-one analogs **6a – 6g** were prepared from commercially available 1,2-phenylenediamine and tested for Gram positive and Gram Negative bacterial cultures. All these compounds were found to display high to moderate antibacterial activity against different strains of bacteria. It was observed that among all the compounds tested, compounds **6e, 6f and 6g** showed high activity against all the tested bacterial strains.

REFERENCES

[1] A.K. Zafer, T.Z. Gulhan, O. Ahmet, R. Gilbert, *Eur. J. Med. Chem.*, **2008**, 43, 155-159.
[2] I. Chopra, C. Schofield, M. Everett, A. O'Neill, K. Miller, M. Wilcox, J.M. Fre` re, M. Dawson, L. Czaplewski, U. Urleb, P. Courvalin, *Lancet Infect. Dis.*, **2008**, 8, 133–139.
[3] T.M. Perl, *Am J Med*, **1999**, 106, 26S.
[4] V.L. Healy, I. A.D. Lessard , D.I. Roper, J.R. Knox , C.T. Walsh, *Chem Biol.*, **2000**, 7, R109.
[5] R.M. Preston, *Chemistry of Heterocyclic Compounds*, Preston P M Ed, Wiley Interscience, New York, NY, 40, **1980**, Part 2, Chapter 10, pp 531–542.
[6] Anette Graven Sams, Krestian Larsen, Gitte Kobberøe Mikkelsen, Morten Hentzer, Claus Tornby Christoffersen, Klaus Gjervig Jensen, Kristen Frederiksen, Benny Bang-Andersen *Bioorg.Med.Chem.Lett.*, **2012**, 22, 5134-5140.
[7] Sabrina Taliani, Isabella Pugliesi, Elisabetta Barresi, Francesca Simorini, Silvia Salerno, Concettina La Motta, Anna Maria Marini, Barbara Cosimelli, Sandro Cosconati, Salvatore Di Maro, Luciana Marinelli, Simona Daniele, Maria Letizia Trincavelli, Giovanni Greco, Ettore Novellino, Claudia Martini, and Federico Da Settimo *J. Med. Chem.*, **2012**, 55 (4), 1490–1499.
[8] Sharmila Sivendran, Victoria Jones, Dianqing Sun, Yi Wang, Anna E. Grzegorzewicz, Michael S. Scherman, Andrew D. Napper, J. Andrew McCammon, Richard E. Lee, Scott L. Diamond, Michael McNeil, *Bioorg Med Chem Lett.*, 2010, 18,896-908.
[9] Anna-Maria Monforte, Patrizia Logoteta, Laura De Luca, Nunzio Iraci, Stefania Ferro, Giovanni Maga, Erik De Clercq, Christophe Pannecouque, Alba Chimirri, *Bioorg Med Chem Lett.*, **2010**,18, 1702-1710.

[10] Anna-Maria Monforte, Patrizia Logoteta, Stefania Ferro, Laura De Luca, Nunzio Iraci, Giovanni Maga, Erik De Clercq, Christophe Pannecouque, Alba Chimirri, *Bioorg Med Chem Lett.*, **2009**, 17, 5962 – 5967.
[11] Thomas M. Bridges, Ashley E. Brady, J. Phillip Kennedy, R. Nathan Daniels, Nicole R. Miller, Kwango Kim, Micah L. Breininger, Patrick R. Gentry, John T. Brogan, Carrie K. Jones, P. Jeffrey Conn, Craig W. Lindsley, *Bioorg Med Chem Lett.*, **2008**, 18, 5439-5442.
[12] Ronald Palin, John K. Clark, Louise Evans, Andrea K. Houghton, Philip S. Jones, Alan Prosser, Grant Wishart, Kazuya Yoshiizumi, *Bioorg Med Chem.*, **2008,** 16, 2829-285.
[13] G. Remond ,B. Portevin, J. Bonnet, E. Cnaet, D. Regoli, G. Denanteuil, *Eur J Med Chem*, **1997,** 32,843-868. .
[14] D. Zuev, J.A. Michne, H. Huang, B.R. Beno , D. Wu, Q. Gao, J. R.Torrente, C. Xu, C.M. Conway, J.E. Macor, G.M.Dobowchik, *Org Lett.*, **2005,** 7, 2465–2468.
[15] T. Li Q, K.W. Woods, W.Z. Gu, J. Cohen, V.S. Stoll, T. Galicia, C. Hutchins, D. Frost, S. H. osenberg, H. L. Sham, *Bioorg Med Chem Let.t*, 15, **2005**, 2918–2922.
[16] a) M.A. Dombroski, M.A. Letavic, K.F. McClure, J. T. Barberia, T.J. Carty, S. R. Cortina, C. Csiki, A.J. Dipesa, N.C. Elliott, C.A Gabel, C.K. Jordan, J.M. Labasi , W.H. Martin, K.M. Pesse, I.A. Stock, L. Svensson, F.J. Sweeney, C.H. Yu, *Bioorg Med Chem Let.t*, **2004**, 14, 919–923. b) K.F. McClure, Y.A. Abramos, E.R.Laird, J.T. Barberia , W. Cai, T.J. Carty, S.R. Cortina, D.E. Danley, A.J. Dipesa, K.M. Donahue, M.A. Dombroski, N.C. Elliot, C.A. Gabel, S. Han, T.R. Hynes, .K. LeMotte, M.N. Mansour, E.S. Marr, M.A. Letavic, J. Pandit, D.B. Ripin, F.J. Sweeney, D. Tan , Y. Tao, *J Med Chem.*, **2005**, 48, 5728–5737.
[17] D.J. Gustin, C.A. Sehon, J. Wei, H. Cai, S.P. Meduna, H. Khatuya, S. Sun S, Y. Gu, W. Jiang, R.L. Thurmond, L. Karlsson, J.P. Edwards, *Bioorg Med Chem Lett.*, **2005**, 15, 1687–1691.
[18] I. Tapia, L. Alonso-Cires, P.L. Lopes-Tudanca, R. Mosquera,L. Labeaga, A. Innerarity, A. Orjales, *J Med Chem.*, **1999,** 42, 2870–2880.
[19] a) P. Zhang, E.A. Terefenko , J. Wrobel, Z. Zhang, Y. Zhu, J. Cohen, K.B. Marschke,D. Mais, *Bioorg Med. Chem Lett.*, **2001**, 11, 2747–2750; b) E.A. Terefenko, J. Kern, A. Fensome, J. Wrobel, Y. Zhu, J. Cohen, R. Winneker, Z. Zhang, P. Zhang, *Bioorg Med Chem Lett.*, **2005**, 15, 3600–3603.
[20] a) K.L. Yu, Y. Zhang, R.L. Civiello, A.K. Trehan , B.C. Pearce, Z. Yin, K.D. Combrink, H.B. Gulgeze, X.A.Wang, K.F. Kadow , C.W. Cianci, M. Krystal, N.A. Meanwell, *Bioorg Med Chem Lett*, **2004**, 14, 1133– 1137; b) K.L. Yu, X.A. Wang , R.L. Civiello, A.K. Trehan, B.C. Pearce B C, Z. Yin, K.D. Combrink, H. Gulgeze, Y. Zhang , K.F. Kadow, C.W. Cianci, J. Clarke, E.V. Genovesi, I. Medina, L. Lamb,P.R. Wyde, M. Krystal, N.A. Meanwell., *Bioorg Med Chem.*, **2006**, 16, 1115–1122.
[21] M. Guillaume, *Org Process Res Dev*, **2006**, 10, 1227–1230.
[22] A. N. Bauer, W. N. M. Kirby, J. C. Sherries, M. Truck, *Am. J. Clin. Pathol.*, **1996**, 45, 493.
[23] Ponnapali Veerabhadra Swamy, Bhaskara Venkata Prasad B, Balram B, Ram B, Taara B, *Der Pharma Chemica.*, **2012,** 4(5):2050-2054.