ISSN: 0974 - 7516 Volume 8 Issue 8

Trade Science Inc.

Organic CHEMISTRY

An Indian Journal

Full Paper

OCAIJ, 8(8), 2012 [317-322]

Synthesis and biological evaluation of (4-(trifluoromethyl)-hexahydro-4-hydroxy-1-methyl-6-aryl-2-thioxopyrimidin-5-yl)(4-methoxyphenyl)methanone derivatives

Parthiv Kantilal Chaudhari

Shri R.R. Lalan College, Bhuj-Kutch, Gujarat, (INDIA)

E-mail: pkchaudhari6698@gmail.com

Received: 30th January, 2012 ; Accepted: 21st February, 2012

ABSTRACT

The synthesis of (4-(trifluoromethyl)-hexahydro-4-hydroxy-1-methyl-6-aryl-2-thioxopyrimidin-5-yl)(4-methoxyphenyl) methanone can be achieved from a mixture of 4,4,4-trifluoro-1-(4-methylphenyl)butane-1,3-dione, an appropriate aldehyde, *N*-methylthiourea and catalytically amount of concentrated hydrochloric acid in ethanol was heated under reflux condition. Elemental analysis, IR, ^{1}H-NMR, and mass spectral data established identification of the compounds. Products were evaluated for their antimicrobial activity using cup plate method[1]. Some of the obtained compounds showed the interesting antimicrobial activity.

KEYWORDS

Multicomponent reactions;
Begineli reaction;
Antimicrobial activity;
Antimycobacterial activity.

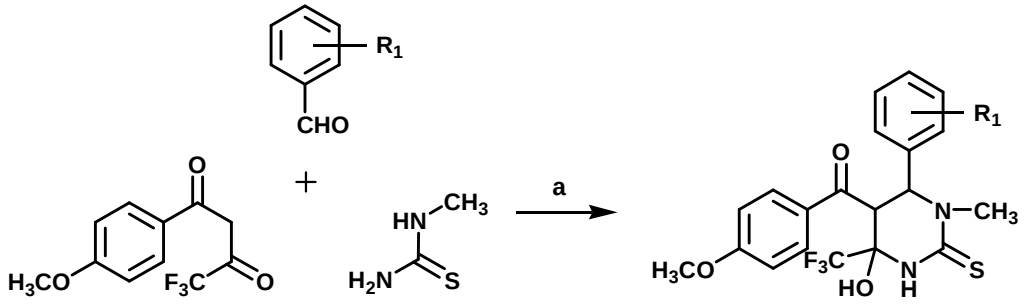
INTRODUCTION

In the past decade, the multicomponent reaction has experienced a remarkable revival, mainly due to the interesting pharmacological properties associated with this dihydropyrimidine scaffold. Biginelli P. reported the synthesis of functionalized 3, 4-dihydropyrimidin-2(1*H*)-ones (DHPMs) via three-component condensation reaction of an aromatic aldehydes, urea and ethyl acetoacetate. Multicomponent reactions (MCRs) occupy an outstanding position in organic and medicinal chemistry for their high degree of atom economy, applications in combinatorial chemistry and diversity-oriented synthesis[1]. The interest in synthesis of dihydropyrimidines - Biginelli compounds stems from their close structural relationship[2] to clinically important 1,4-dihydropyridine calcium channel modulators of the type nifedipine etc. and also because of interesting biological properties of several marine alkaloids[3-5] based upon dihydropyrimidine *viz*. crambine, batzelladine and ptilomycelin A. Derivatization of the dihydropyrimidines especially[6] at C4 has led to the recognition of several lead compounds that show a very similar pharmacological profile[7-9] to 1, 4-dihydropyridine based drugs. C. crambe is a bright red marine sponge, that is the most wide spread in the north-western meditettanean[10]. Extract of C. crambe have been known to be ichthyotoxic and shown various pharmacological activities. A variety of structurally intricate guanidine alkaloids are present in marine sources[11]. Diverse biological activities are associated with many of these alkaloids, likely reflecting the multiple ways that a guanidinium cation can participate in noncovalent interactions. Among the most notable marine alkaloids of

these are the crambescidin[12] and batzelladine[13] alkaloids, which have been isolated primarily from sponges belonging to the orders Poecilosclerida and Axinellida. Diverse biological activities have been reported for these secondary metabolites, including cytotoxicity towards several cancer cell lines, antifungal and antiviral activities and inhibition of HIV-1 fusion. The novel structures of these marine alkaloids have inspired the development of many strategies or assembling polycyclic guanidines that contain the octahydro-5, 6,6a-triazaacenaphthalene and hexahydro-5, 6,6a-triazaacenaphthalene moieties co-mmon to the crambescidin and batzelladine alkaloids[14,15]. More recently, appropriately functionalized DHPMs have emerged as, e.g., orally active antihypertensive agents[16-18] or α_{1a} adrenoceptor-selective antagonists[19]. A family of proteins, termed fatty acid transport proteins (FATPs), that mediate the uptake of fatty acids into cells has been described[20,21]. Earlier studies[22-25] provided evidence that fatty acid transport protein 4 (FATP4) mediates the transport of fatty acids from the gut into enterocytes both *in vitro* and *in vivo*.

The chemistry of pyrimidines and its derivatives has been studied for over a century due to their di-

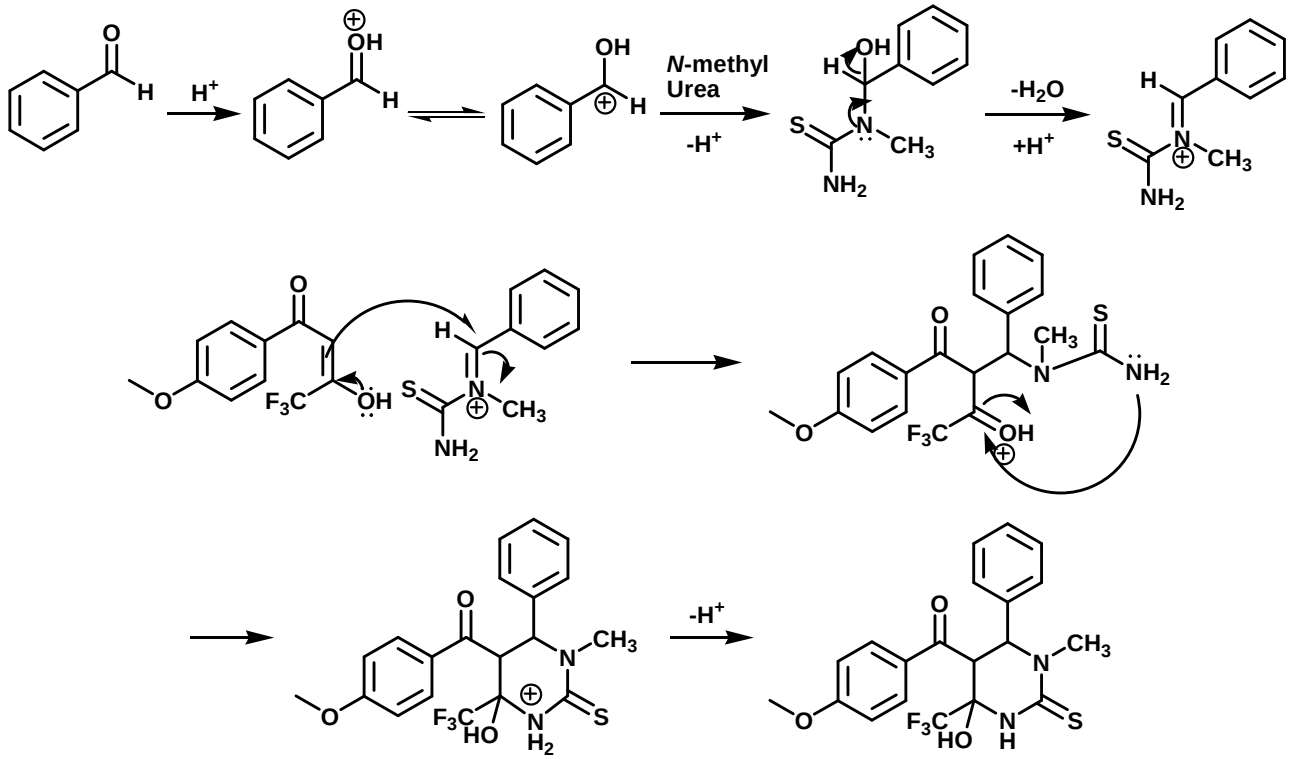
REACTION SCHEME



PK- 11 TO 20

Reagents and conditions: (a) Conc. HCl, MeOH, reflux, 8-10 Hrs

MECHANISM



verse biological activities. The 1, 2, 3, 4-tetrahydropyrimidine ring system is of special biological interest because it has numerous pharmacological and medicinal applications *viz*, antitumour, antiviral, antimalarial, antitubarcular etc. Keeping in mind various biomedical applications and with a view to further assess, the pharmacological profile of these class of compounds, three novel series of 1,2,3,4-tetrahydropyrimidine (PK-11 to PK-20) are synthesized. The synthesis of these thirty compounds was achieved by the Biginelli reaction of acetoacetanilide, urea derivatives and corresponding aldehydes. The reaction is catalysed by concentrated hydrochloric acid (HCl). The products were characterized by various analytical techniques like FT-IR spectroscopy, mass spectrometry, ^{1}H NMR spectroscopy and elemental analysis. The newly synthesized compounds were subjected to various biological activities *viz*., antimicrobial, antimycobacterial.

EXPERIMENTAL

Materials and methods

Melting points were determined in open capillary tubes and are uncorrected. Formation of the compounds was routinely checked by TLC on silica gel-G plates of 0.5 mm thickness and spots were located by iodine. IR spectra were recorded Shimadzu FT-IR-8400 instrument using KBr pellet method. Mass spectra were recorded on Shimadzu GC-MS-QP-2010 model using Direct Injection Probe technique. ^{1}H NMR was determined in DMSO-d_6 solution on a Bruker Ac 400 MHz spectrometer. Elemental analysis of the all the synthesized compounds was carried out on Elemental Vario EL III Carlo Erba 1108 model and the results are in agreements with the structures assigned.

4, 4, 4-trifluoro-1-(aryl) butane-1, 3-dione

Synthesis of 4, 4, 4-trifluoro-1-(aryl) butane-1, 3-diones was achieved using previously published methods[26].

(4-(trifluoromethyl)-hexahydro-4-hydroxy-1-methyl-6-phenyl-2-thioxopyrimidin-5-yl)(4-methoxyphenyl) methanone [PK 11-20]

A mixture of 4, 4, 4-trifluoro-1-(4-methoxyphenyl) butane-1, 3-dione (0.01 mol), an appropriate aldehyde (0.01 mol), N-methylthiourea (0.015 mol) and catalytical amount of concentrated hydrochloric acid in ethanol (30 ml) was heated under reflux condition for 8 to 10 hrs. The reaction mixture was kept at room temperature for 24 hrs. The product obtained was isolated and recrystallized from ethanol.

RESULT AND DISCUSSION

6-(4-methoxyphenyl)-4-trifluoromethyl-4-hydroxy-1-methyl-5-[(4methoxyphenyl) carbonyl] tetrahydropyrimidin-2(1H)-ones (PK 11)

Yield: 62%; mp 180 ºC; IR(cm^{-1}): 3384cm^{-1}(-OH stretching), 3291 (N-H stretching of pyrimidine ring), 2919 (C-H asymmetrical stretching of CH_3 group), 1682 (C=O stretching of carbonyl), 1500 (N-H deformation of pyrimidine ring), 1385 (C-N-C stretching of pyrimidine ring), 1268 (C-O-C symmetrical stretching of ether linkage), (1173 C-N stretching), 1123 (C-F stretching); ^{1}H NMR (DMSO-d_6) δ ppm: 2.87 (s, 3H, H_a), 3.58 (s, 3H, H_b), 3.75 (s, 3H, H_c), 4.40-4.43 (d, 1H, H_d, J = 10.80 Hz), 4.73-4.75 (d, 1H, H_e, J = 10.80 Hz), 6.66-6.68 (d, 2H, $H_{ff'}$, J = 8.80 Hz), 6.82-6.84 (d, 2H, $H_{gg'}$, J = 8.40 Hz), 7.22-7.24 (d, 2H, $H_{hh'}$, J = 8.80 Hz), 7.32 (s, 1H, H_i), 7.46 (s, 1H, H_j), 7.66-7.68 (d, 2H, $H_{kk'}$, J = 8.80 Hz); MS: m/z 454.46; Anal. Calcd. for $C_{21}H_{21}F_3N_2O_4S$: C, 57.53; H, 4.83; N, 6.39. Found: C, 57.40; H, 4.69; N, 6.30%.

6-(4-fluorophenyl)-4-trifluoromethyl-4-hydroxy-1-methyl-5-[(4-methoxyphenyl) carbonyl] tetrahydropyrimidin-2(1H)-ones (PK 12)

Yield: 54%; mp 182 ºC; IR(cm^{-1}): 3415 (-OH stretching), 3276 (N-H stretching of pyrimidine ring), 3061 (C-H symmetrical stretching of CH_3 group), 2924 (C-H asymmetrical stretching of CH_3 group) 1674 (C=O stretching of carbonyl), 1513 (N-H deformation of pyrimidine ring), 1423 (C-N-C stretching of pyrimidine ring), 1238 (C-O-C symmetrical stretching of ether linkage), (1173 cm^{-1} C-N stretching), 1061 (C-F stretching); ^{1}H NMR (DMSO-d_6) δ ppm: 2.87 (s, 3H, H_a), 3.73 (s, 3H, H_b), 4.42-4.45 (d, 1H, H_c, J = 10.80 Hz), 4.77-4.80 (d, 1H, H_d, J = 11.20 Hz), 6.80-6.82 (d, 2H, $H_{ee'}$, J = 8.80 Hz), 6.90-6.95 (t, 2H, $H_{ff'}$), 7.33-7.37 (t, 2H, $H_{gg'}$), 7.42 (s, 1H, H_h), 7.47 (s, 1H, H_i), 7.65-

7.67 (d, 2H, $H_{jj'}$, J = 8.80 Hz); MS: m/z 442.42; Anal. Calcd. For $C_{20}H_{18}F_4N_2O_3S$: C, 56.34; H, 4.26; N, 6.57. Found: C, 56.22; H, 4.10; N, 6.45%.

6-(4-methylphenyl)-4-trifluoromethyl-4-hydroxy-1-methyl-5-[(4-methoxy phenyl) carbonyl] tetrahydropyrimidin-2(1H)-ones (PK 13)

Yield: 70%; mp 199-201 ºC; IR(cm^{-1}): 3390cm^{-1}(-OH stretching), 3153 (N-H stretching of pyramiding ring), 2920 (C-H symmetrical stretching of CH_3 group) 1670 (C=O stretching of carbonyl), 1557 (N-H deformation of pyrimidine ring), 1439 (C-N-C stretching of pyrimidine ring), (1161 cm^{-1} C-N stretching), 1221 (C-O-C symmetrical stretching of ether linkage), 1114 (C-F stretching); ^{1}H NMR (DMSO-d_6) δ ppm: 2.23 (s, 3H, H_a), 2.46 (s, 3H, H_b), 3.56 (s, 3H, H_c), 4.67-4.70 (d, 1H, H_d, J = 11.20 Hz), 4.98-5.01 (d, 1H, H_e, J = 10.80 Hz), 6.65-6.67 (d, 2H, $H_{ff'}$, J = 8.40 Hz), 7.09-7.11 (d, 2H, $H_{gg'}$, J = 8.40 Hz), 7.32-7.34 (d, 2H, $H_{hh'}$, J = 8.80 Hz), 7.55 (s, 1H, H_i), 7.59-7.61 (d, 2H, $H_{jj'}$, J = 8.40 Hz), 8.32 (s, 1H, H_k); MS: m/z 438.46; Anal. Calcd. For $C_{21}H_{21}F_3N_2O_3S$: C, 59.71; H, 5.01; N, 6.63. Found: C, 59.56; H, 4.90; N, 6.46%.

6-(4-nitrophenyl)-4-trifluoromethyl-4-hydroxy-1-methyl-5-[(4-methoxy phenyl) carbonyl] tetrahydropyrimidin-2(1H)-ones (PK 14)

Yield: 71%; mp 170 ºC; IR(cm^{-1}): 3274 (-OH stretching), 3074 (N-H stretching of pyrimidine ring), 2953 (C-H symmetrical stretching of CH_3 group), 1670 (C=O stretching of carbonyl), 1522 (N-H deformation of pyrimidine ring), 1423 (C-N-C stretching of pyrimidine ring), 1267 (C-O-C symmetrical stretching of ether linkage), (1170 cm^{-1} C-N stretching), 1120 (C-F stretching); ^{1}H NMR (DMSO-d_6) δ ppm: 2.88 (s, 3H, H_a), 3.71 (s, 3H, H_b), 4.52-4.55 (d, 1H, H_c, J = 9.60 Hz), 4.93-4.95 (d, 1H, H_d, J = 9.60 Hz), 6.80-6.81 (d, 2H, $H_{ee'}$, J = 7.20 Hz), 7.60-7.69 (m, 6H, $H_{ff'-ii'}$), 7.97-7.99 (d, 2H, $H_{jj'}$, J = 7.60 Hz); MS: m/z 469.43; Anal. Calcd. For $C_{20}H_{18}F_3N_3O_5S$: C, 52.98; H, 4.00; N, 9.27. Found: C, 52.82; H, 3.88; N, 9.18%.

6-(4-chlorophenyl)-4-trifluoromethyl-4-hydroxy-1-methyl-5-[(4-methoxyphenyl) carbonyl] tetrahydropyrimidin-2(1H)-ones (PK 15)

Yield: 77%; mp 225 ºC; IR(cm^{-1}): 3349 (-OH stretching), 3128 (N-H stretching of pyrimidine ring), 3057 (C-H symmetrical stretching of CH_3 group), 2972 (C-H asymmetrical stretching of CH_3 group) 1639 (C=O stretching of carbonyl), 1537 (N-H deformation of pyrimidine ring), 1438 (C-N-C stretching of pyrimidine ring), 1281 (C-O-C symmetrical stretching of ether linkage), (1179 C-N stretching), 1112 (C-F stretching), 756 (C-Cl stretching); ^{1}H NMR (DMSO-d_6) δ ppm: 2.87 (s, 3H, H_a), 3.58-3.60 (s, 3H, H_b), 4.45-4.48 (d, 1H, H_c, J = 10.80 Hz), 4.75-4.77 (d, 1H, H_d, J = 10.80 Hz), 6.67-6.69 (d, 2H, $H_{ee'}$, J = 8.80 Hz), 7.23-7.26 (d, 2H, $H_{ff'}$, J = 8.80 Hz), 7.38-7.40 (d, 3H, $H_{gg'-h}$), 7.61 (s, 1H, H_i), 7.68-7.70 (d, 2H, $H_{jj'}$, J = 8.40 Hz); MS: m/z 458.88; Anal. Calcd. For $C_{20}H_{18}ClF_3N_2O_5S$: C, 54.25; H, 4.10; N, 6.33. Found: C, 54.16; H, 4.00; N, 6.21%

TABLE 1 : Physical and analytical data.

Code	R_1	M.F.	M.W.	M.P. ºC	Yield %	R_{f1}	R_{f2}
PK-11	4-OCH_3	$C_{21}H_{21}F_3N_2O_3S$	454.46	180	62	0.50	0.61
PK-12	4-F	$C_{20}H_{18}F_4N_2O_3S$	442.42	182	54	0.58	0.67
PK-13	4-CH_3	$C_{21}H_{21}F_3N_2O_3S$	438.46	199	70	0.41	0.74
PK-14	4-NO_2	$C_{20}H_{18}F_3N_3O_5S$	469.43	170	71	0.56	0.66
PK-15	4-Cl	$C_{20}H_{18}ClF_3N_2O_3S$	458.88	225	77	0.53	0.60
PK-16	3-Cl	$C_{20}H_{18}ClF_3N_2O_3S$	458.88	215	65	0.50	0.58
PK-17	3-NO_2	$C_{20}H_{18}F_3N_3O_5S$	469.43	180	53	0.54	0.61
PK-18	2-Cl	$C_{20}H_{18}ClF_3N_2O_3S$	458.88	185	68	0.57	0.64
PK-19	2-NO_2	$C_{20}H_{18}F_3N_3O_5S$	469.43	180	58	0.48	0.57
PK-20	2-OCH_3	$C_{21}H_{21}F_3N_2O_3S$	454.46	195	59	0.58	0.70

TLC Solvent system R_{f1}: Hexane: Ethyl acetate – 6:4; TLC Solvent system R_{f2}: Chloroform: Methanol – 9:1.

TABLE 2 : *In vitro* antimicrobial screening results for PK-11 to 12

Code	Minimal inhibition concentration (μg mL^{-1})						
	Gram-positive		Gram-negative		Fungal species		
	S.a.	*S. p.*	*E.c.*	*P.a.*	*C. a.*	*A. n.*	*A.c.*
VP- 211	200	100	250	62.5	500	500	>1000
VP- 212	100	250	200	200	500	>1000	>1000
VP- 213	150	150	62.5	100	>1000	>1000	>1000
VP- 214	250	500	250	250	500	1000	1000
VP- 215	500	500	200	200	1000	500	1000
VP- 216	100	62.5	250	250	>1000	500	1000
VP- 217	200	100	250	62.5	500	500	>1000
VP- 218	100	250	200	200	500	>1000	>1000
VP- 219	150	150	62.5	100	>1000	>1000	>1000
VP- 220	250	250	100	100	1000	500	1000
Gentamycin	0.25	0.5	0.05	1	-	-	-
Ampicillin	250	100	100	100	-	-	-
Chloramphenicol	50	50	50	50	-	-	-
Iprofloxacin	50	50	25	25	-	-	-
Norfloxacin	10	10	10	10	-	-	-
Nystatin	-	-	-	-	100	100	100
Greseofulvin	-	-	-	-	500	100	100

BIOLOGICAL EVALUATION

Antimicrobial evaluation

All of the synthesized compounds (PK-11to 12) were tested for their antibacterial and antifungal activity (MIC) *in vitro* by broth dilution method with two Gram-positive bacteria *Staphylococcus aureus* MTCC-96, *Streptococcus pyogenes* MTCC 443, two Gram-negative bacteria *Escherichia coli* MTCC 442, *Pseudomonas aeruginosa* MTCC 441 and three fungal strains *Candida albicans* MTCC 227, *Aspergillus Niger* MTCC 282, *Aspergillus clavatus* MTCC 1323 taking gentamycin, ampicillin, chloramphenicol, ciprofloxacin, norfloxacin, nystatin and greseofulvin as standard drugs. The standard strains were procured from the Microbial Type Culture Collection (MTCC), Institute of Microbial Technology, Chandigarh, India.

The minimal inhibitory concentration (MIC) values for all the newly synthesized compounds, defined as the lowest concentration of the compound preventing the visible growth, were determined by using micro dilution broth method according to NCCLS standards.

CONCLUSION

It was interesting to note that the reaction occurred immediately. This work demonstrates a very simple and efficient method for the synthesis of a well functionalized tetrahydropyrimidin derivative of biological importance in excellent yields.

ACKNOWLEDGEMENTS

The author's wish to thanks to Principal, Shree R.R. Lalan College, Bhuj for providing research facilities.

REFERENCES

[1] **(a)** D.J.Ramo´n, M.Yus; Angew.Chem., Int.Ed., **44**, 1602 **(2005)**; **(b)** D.B.Ramachary, C.F.Barbas III; Chem.Eur.J., **10**, 5323 **(2004)**; **(c)** S.E.Denmark, Y.Fan; J.Am.Chem.Soc., **125**, 7825 **(2003)**; **(d)** P.R.Andreana, C.C.Liu, S.L.Schreiber; Org.Lett., **6**, 4231 **(2004)**; **(e)** P.G.Cozzi, E.Rivalta; Angew. Chem., Int.Ed., **44**, 3600 **(2005)**.

[2] K.S.Atwal, B.N.Swanson, S.E.Unger, D.M.Floyd, S.Moreland, A.Hedberg, B.C.O'Reilly; J.Med. Chem., **341**, 806 **(1991)**.

[3] A.D.Patil, N.V.Kumar, W.C.Kokke, M.F.Bean, A.J.Freyer, C.Debrosse, S.Mai, A.Trunch, D.J.Faulkner, B.Carte, A.L.Breen, R.P.Hertzberg, R.K.Johnson, J.W.Westley, B.C.Potts; J.Org. Chem., **60**, 1182 **(1995)**.

[4] B.B.Sinder, Z.Shi; J.Org.Chem., **58**, 3828 **(1993)**.

[5] L.E.Overman, M.H.Rabinowitz, P.A.Renhowe; J.Am.Chem.Soc., **117**, 2675 **(1995)**.

[6] C.O.Kappe, M.F.Fabian; Tetrahedron, **53(8)**, 2803 **(1997)**.

[7] E.W.Hurst, R.Hull; J.Med.Pharm.Chem., **3**, 215 **(1961)**.

[8] G.C.Rovnyak, K.S.Atwal, A.Hedberg, S.D.Kimball, S.Moreland, J.Z.Gougoutas, B.C.O'Reilly, J.Schwartz, M.F.Malley; J.Med.Chem., **46**, 3433 **(1981)**.

[9] H.Cho, M.Ueda, K.Shima, A.Mizuno, M.Hayashi-matsu, Y.Ohnaka, M.Hamaguchi, K.Aisaka, T.Hidaka, M.Kawai, M.Takeda, T.Ishihara, K.Funahashi, F.Satoh, M.Morita, T.Noguchi; J.Med.Chem., **32**, 2399 **(1989)**.

[10] M.A.Becerro, M.J.Uriz, X.Turon; Mar.Biol., **121**, 301-307 **(1994)**.

[11] R.G.S.Berlinck; Nat.Prod.Rep., **19**, 617 **(2002)**.

[12] **(a)** Y.Kashman, S.Hirsh, O.J.McConnell, I.Ohtani, T.Kusumi, H.Kakisawa; J.Am.Chem.Soc., **111**, 8925 **(1989)**; **(b)** E.A.Jares-Erijman, R.Sakai, K.L.Rinehart; J.Org.Chem., **56**, 5712 **(1991)**.

[13] **(a)** A.D.Patil, N.V.Kumar, W.C.Kokke, M.F.Bean, A.J.Freyer, C.De Brosse, S.Mai, A.Truneh, D.J.Faulkner, B.Carte, A.L.Breen, R.P.Hertzberg, R.K.Johnson, J.W.Westley, B.C.M.Potts; J.Org. Chem., **60**, 1182 **(1995)**; **(b)** A.D.Patil, A.J.Freyer, P.B.Taylor, B.Carte, G.Zuber, R.K.Johnson, D.J.Faulkner; J.Org.Chem., **62**, 1814 **(1997)**.

[14] **(a)** K.Nagasawa, A.Georgeiva, H.Koshino, T.Nakata, T.Kita, Y.Hashimoto; Org.Lett., **4**, 177 **(2002)**; **(b)** T.Ishiwata, T.Hino, H.Koshino, Y.Hashimoto, T.Nakata, K.Nagasawa; Org.Lett., **4**, 2921 **(2002)**; **(c)** K.Nagasawa, Y.Ishiwata, Y.Hasimoto, T.Nakata; Tetrahedron Lett., **43**, 6383 **(2002)**; **(d)** C.G.Moore, P.J.Murphy, H.L.Williams, A.T.McGown, N.K.Smith; Tetrahedron Lett., **44**, 251 **(2003)**.

[15] **(a)** D.S.Coffey, A.I.McDonald, L.E.Overman, M.H.Rabinowitz, P.A.Renhowe; J.Am.Chem.Soc., **122**, 4893 **(2000)**; **(b)** D.S.Coffey, L.E.Overman, F.Stappenbeck; J.Am.Chem.Soc., **122**, 4094 **(2000)**.

[16] K.S.Atwal, B.N.Swanson, S.E.Unger, D.M.Floyd, S.Moreland, A.Hedberg, B.C.O'Reilly; J.Med. Chem., **34**, 806-811 **(1991)**.

[17] G.C.Rovnyak, K.S.Atwal, A.Hedberg, S.D.Kimball, S.Moreland, J.Z.Gougoutas, B.C.O'Reilly, J.Schwartz, M.F.Malley; J.Med.Chem., **35**, 3254-3263 **(1992)**.

[18] G.J.Grover, S.Dzwonczyk, D.M.McMullen, D.E.Normandin, C.S.Parham, P.G.Sleph, S.Moreland; J.Cardiovasc.Pharmacol., **26**, 289-294 **(1995)**.

[19] J.C.Barrow, P.G.Nantermet, H.G.Selnick, K.L.Glass, K.E.Rittle, K.F.Gilbert, T.G.Steele, C.F.Homnick, R.M.Freidinger; J.Med.Chem., **43**, 2703-2718 **(2000)**.

[20] J.E.Schaffer, H.Lodish; Cell, **79**, 427 **(1994)**.

[21] D.Hirsch, A.Stahl, H.F.Lodish; Proc.Natl.Acad.Sci. U.S.A, **95**, 8625 **(1998)**.

[22] **(a)** N.Abumrad, C.Coburn, A.Ibrahimi; Biochim. Biophys.Acta, **1441**, 4 **(1999)**; **(b)** G.M.Hatch; J.Lipid Res., **43**, 1380 **(2002)**; **(c)** J.E.Schaffer; Am.J. Physiol.Endocrinol.Metab., **282**, E239 **(2002)**.

[23] A.Stahl, D.J.Hirsch, R.E.Gimeno, S.Punreddy, P.Ge, N.Watson, S.Patel, M.Kotler, A.Raimondi, L.A.Tartaglia, H.F.Lodish; Mol.Cells, **4**, 299 **(1999)**.

[24] R.E.Gimeno, D.J.Hirsch, S.Punreddy, Y.Sun, A.M.Ortegon, H.Wu, T.Daniels, A.Stricker-Krongrad, H.F.Lodish, A.Stahl; J.Biol.Chem., **278**, 49512 **(2003)**.

[25] S.M.Stuhlsatz-Krouper, N.E.Bennett, J.E.Schaffer; J.Biol.Chem., **273**, 28642 **(1998)**.

[26] S.L.Jeon, D.H.Kim, J.B.Son, I.H.Jeong; Bulletin of the Korean Chemical Society, **27(12)**, 1961 **(2006)**.