ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

New and Improved Synthesis of Valsartan: An Antihypertensive Drug

Hanumantha Rao Penikelapati*, Srinivas Ambati, Maruthikumar TV, Narahari Babu Ambati

Department of Chemistry, Osmania University Campus, Hyderabad, India

ABSTRACT

A highly efficient approach to the synthesis of the angiotensin-II receptor antagonist Valsartan (Diovan), one of the most important agents used in antihypertensive therapy today is described. The key steps are Negishi coupling for the synthesis of key intermediate 2-(4-chloromethyl-biphenyl-2-yl)-4, 4-dimethyl-4, 5-dihydrooxazole of valsartan, *N*-alkylation and oxazoline conversion to nitrile.

Keywords: Valsartan, antihypertensive drug, Negishi coupling, oxazoline

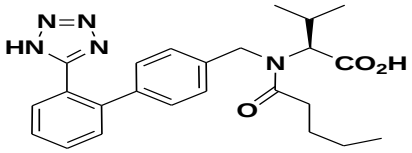
Corresponding author

Email: hanumantharao_penikelapati@rediffmail.com

ISSN: 0975-8585

INTRODUCTION

Hypertension is one of the most prevalent diseases in developed countries with an estimated 1 billion cases worldwide, [1] conferring its treatment an enormous social and economic importance. The therapeutic standard was significantly improved in the 1980s by the introduction of losartan [2] as the first nonpeptidic angiotensin-II-receptor antagonist. An entire therapeutic class, the sartans, has since been developed, among which valsartan (**Figure 1**; Diovan, Novartis: US $4.2 billion sales in 2006) currently holds the largest market share. [3-5]

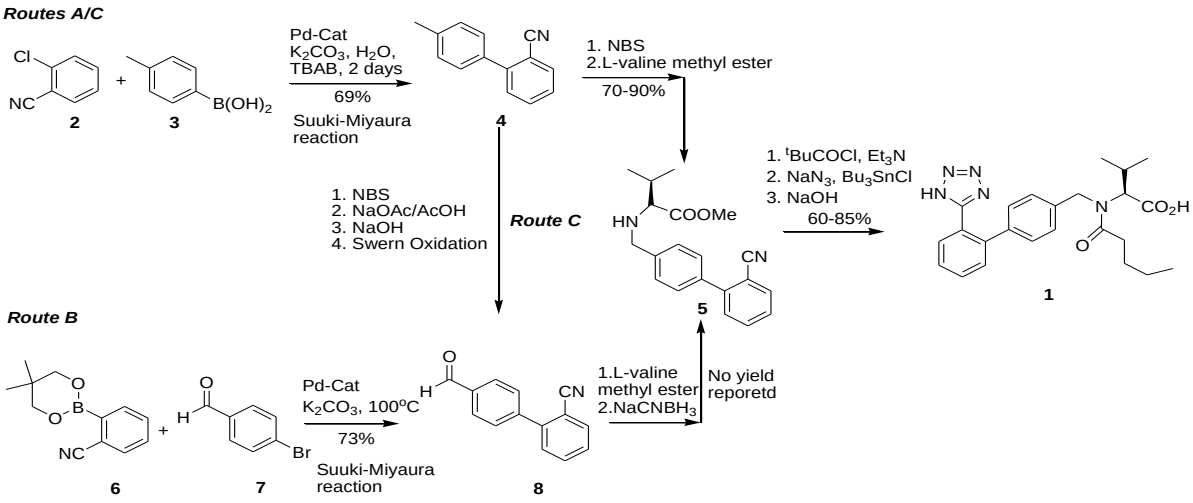


1

Figure1. Valsartan

The common structural element, a biphenyl unit, is essential for the binding affinity to the receptor and for the oral bioavailability. The formation of its aryl-aryl bond represents the key step in the synthesis of sartan and the published methods for the preparation of valsartan involves to make use of Suzuki-Miyaura couplings.[6-10] The principal synthetic pathways leading to valsartan are depicted in **Scheme 1**. In route A, 2-chlorobenzonitrile (**2**) and 4-tolylboronic acid (**3**) are coupled to give 2-cyano-4-methylbiphenyl (**4**), which is then brominated and reacted with L-valine methyl ester to give N-[(2-cyano- biphenyl-4-yl)methyl]-L-valine methyl ester (**5**). Alternatively, **5** can be obtained via the coupling of 4-bromobenzaldehyde (**7**) with a boronic acid derivative (**6**), followed by reductive amination with L-valine methyl ester (route B). Route C results from a combination of both approaches, in which the sensitive formyl group in biaryl **(8)** is generated by oxidation of the more robust derivative (**4)**

SCHEME 1: **Novartis Patent Literature Syntheses of Valsartan via Suzuki-Miyaura Coupling**



Problems with these approaches have been (a) the nonselective and moderately yielding free-radical bromination of 2-cyano-4-methylbiphenyl (**4**) intermediate, (b) the use of expensive boronic acid substrates in the cross coupling step, (c) the use of expensive metallic species that generate extremely dangerous metallic residues not only harmful to human health but also to the environment.

In designing an alternative synthesis of valsartan our goal is to avoid the use of expensive boronic acid substrates, minimize the use of expensive and hazardous metals, circumvent the bromination step, and increase the overall efficiency of the synthesis. This was accomplished by reversing the order of the major bond disconnections. We realized biaryl oxazoline synthesis by Negishi coupling was the key step, and have the potential to overcome the above weaknesses.

MATERIALS AND METHODS

All solvents and reagents were purchased from the commercial suppliers and used without further purification. All non-aqueous reactions were performed in dry glassware under an atmosphere of dry nitrogen. Organic solutions were concentrated under reduced pressure. Thin layer chromatography was performed on Merck precoated Silica-gel $60F_{254}$ plates. ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 and $CDCl_3$ using 400 MHz, on a Varian Gemini 400 MHz FT NMR spectrometer. The chemical shifts were reported in δ ppm relative to TMS (Tetra methyl silane). The mass spectra were recorded on Shimadzu LCMS-QP 800 LC-MS and AB-4000 Q-trap LC-MS/MS. Melting points were obtained by using the open capillary method and are uncorrected.

2-(4, 4-Dimethyl-4, 5-dihydrooxazol-2-yl)-biphenyl-4-carboxylicacid methyl ester (11):

To a stirred solution of 4, 4-dimethyl-2-phenyl-4, 5-dihydrooxazole (**10**, 3.7g, 0.017 mol) in THF (30 mL) at 0 ^{o}C was added 2.5M n-BuLi in hexane (12 mL, 0.02 mol). The mixture was stirred at 0 ^{o}C for 60 mints, and then 1.0 M $ZnCl_2$ in ether (41 mL, 0.03 mol) was added. The reaction mixture was brought to the ambient temperature over a period of 1.0 h, then tetrakis (triphenylphosphine) palladium (0) (0.2 g) and methyl-4-iodobenzoate (**9**, 4.9g, 0.018 mol) was added. The mixture was stirred at 65-70^{o}C for 24 h, poured into saturated ammonium chloride (200 mL) and extracted with ethyl acetate (2x50 mL). The organic extracts were combined, washed with water (2x50 mL), brine (1x50 mL), dried over $MgSO_4$ and concentrated under vacuum to give a brown color oil (**11**, 3.7 g, 70%); ^{1}H NMR (400 MHz, $CDCl_3$) (δ ppm): 7.96 (2H, d, ArH, J = 8.4 Hz), 7.66 (1H, m, ArH, J = 7.4 Hz), 7.57 (1H, m, ArH, J = 7.4 Hz), 7.48-7.44 (2H, m, ArH), 7.42 (2H, d, ArH, J = 8.4 Hz), 3.84 (3H, s, -CH_3), 3.76 (2H, s, -CH_2), 1.13 (6H, s, 2 x -CH_3); ^{13}C NMR (400 MHz, $CDCl_3$) (δ ppm): 24.6, 47.4, 62.8, 74.7, 123.0, 123.1, 123.6, 124.0, 124.5, 125.2, 125.5, 125.8, 135.8, 141.1, 158.3, 162.3.; MS (m/z): 310 [M^{+} + 1].

[2-(4, 4-Dimethyl-4, 5-dihydro-1, 3-oxazol-2-yl) biphenyl-4-yl] methanol (12):

To a mixture of 2-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)-biphenyl-4-carboxylic acid methyl ester (**11**, 3.0 g, 0.01 mol) in THF and ethanol 1:1 mixture (20.0 mL), sodium borohydride (0.47 g, 0.02 mol) was added portion wise at room temperature under nitrogen atmosphere. The reaction mixture was stirred for 3 hours at room temperature. The reaction mixture was cooled to 5-10 °C and poured into a solution of saturated aqueous ammonium chloride (30 mL). To this was added ethyl acetate (25 mL), and the separated organic layer was washed twice with water (20 mL). Organic layer was dried over sodium sulfate and evaporated under vacuum. The residue was chromatographed on silica gel eluting with hexane / ethyl acetate (50:50) to get a colourless solid (**12,** 2.6g, 95%). Mp: 98-100 °C (lit[11] Mp: 97-100 ^{o}C); ^{1}H NMR (400 MHz, $CDCl_3$) (δ ppm): 7.74 (1H, m, J = 7.4 Hz, ArH), 7.49 (1H, m, J = 7.4 Hz, ArH), 7.40-7.39 (2H, m, ArH), 7.38 (2H, d, J = 8.0 Hz, ArH), 7.35 (2H, d, J = 8.0 Hz, ArH), 4.75 (2H, s, -CH_2), 3.80 (2H, s, -CH_2), 1.30 (6H, s, 2 x -CH_3); ^{13}C NMR (400 MHz, $CDCl_3$) (δ ppm): 32.2, 69.0, 71.6, 83.7, 130.7, 131.3, 131.9, 132.6, 134.3, 134.4, 134.7, 144.2, 144.5, 145.4, 168.0; MS (m/z): 282 [M^+ + 1].

2-(4-Chloromethyl-biphenyl-2-yl)-4, 4-dimethyl-4, 5-dihydrooxazole (13):

To a solution of [2-(4,4-dimethyl-4,5-dihydro-1,3-oxazol-2-yl)biphenyl-4-yl]methanol (**12**, 4.0 g, 0.014 mol) in methylene chloride (40 mL), was added thionyl chloride (2 g, 0.017 mol) drop wisely at 0-5 ^{o}C and maintained for 2 h. The reaction mixture was poured into an aqueous solution of 20 % of sodium hydrogen carbonate solution (40 mL). The Separated organic layer was washed twice with water (50 mL) and the organic layer was concentrated under pressure to get the title compound as a colorless solid (**13**, 4.2 g, 99%). Mp: 73-75 °C; ^{1}H NMR (400 MHz, $CDCl_3$) (δ ppm): 7.75 (1H, d, J = 7.4 Hz, ArH), 7.62 (1H, m, ArH), 7.43-7.27 (6H, m, ArH), 4.64 (2H, s, -CH_2), 3.81 (2H, s, -CH_2), 1.29 (6H, s, 2 x -CH_3); ^{13}C NMR (400 MHz, $CDCl_3$) (δ ppm): 32.1, 50.2, 71.7, 83.6, 131.4, 132.0, 132.4, 132.9, 134.2, 134.3, 134.6, 140.5, 145.1, 145.4, 167.7. MS (m/z): 300 [M^+ + 1].

Methyl-N-pentanoyl-L-valinate (15):

To a suspension of L-valine methyl ester hydrochloride (**14**, 5.0 g, 0.03 mol) in dichloromethane (50 mL) was added Et_3N (8.33 mL, 0.06 mol) followed by valeryl chloride (3.9g, 0.032mol) at 0ºC temperature. The mixture was stirred at 25 ºC temperature for 1 h. To the reaction mixture water (50 mL) was added and the organic layer was separated and concentrated. The solid compound that obtained was triturated with heptane (50 mL) to give a colourless solid (**15**, 6.1g, 95%), ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.01 (s, 1H), 4.12 (m, 1H), 3.59 (s, 3H), 2.48 (m, 2H), 2.13 (m, 2H), 1.95 (m, 1H), 1.45 (m, 3H), 1.25 (m, 5H), 0.86 (d, J = 4.4 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 173.2, 77.4, 56.8, 52.0, 36.2, 34.9, 31.2, 27.7, 22.2, 18.8; ESIMS: m/z calcd [M+]: 215; found: 216 [M+1].

ISSN: 0975-8585

Methyl-N-{[2'-(4, 4-dimethyl-4, 5-dihydro-1, 3-oxazol-2-yl) biphenyl-4-yl] methyl}-N-pentanoyl-L-valinate (16):

Sodium hydride (60%) dispersion in mineral oil (1.8g, 0.046 mol) was added to a solution of compound **15**, (5.0 g, 0.023 mol) and 2-(4-chloromethyl-biphenyl-2-yl)-4,4-dimethyl-4,5-dihydrooxazole (**13**, 7.7g, 0.025 mol) in tetrahydrofuran (80 mL) and the reaction mixture was refluxed for 1h. After cooling, the mixture was diluted with ether (100 mL) and washed successively with saturated aq. NH_4Cl (50 mL) and water (100 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuum. The residue was chromatographed on silica gel and elution with a mixture of heptane and ethyl acetate (70:30) yielded the title compound **16**, **(**6.25 g, 70 %) as colourless oil. ^{1}H NMR (400 MHz,DMSO-d_6) δ 7.09-7.59 (m, 8H), 4.52-4.74 (m, 2H), 4.18-4.20 (d, 1H) 3.71-3.77 (q, 2H); 3.31-3.36 (d, 3H), 2.25-2.33 (m, 2H), 1.90-2.20 (m, 2H), 1.55-1.6 (m, 1H), 1.40-1.45 (2H, m), 1.00-1.20 (6H, m), 0.88-0.91 (3H, t), 0.76-0.80 (6H, m) ^{13}C NMR (DMSO-d_6) δ 14.14, 18.63, 19.69, 22.20, 27.35, 27.67, 28.12, 32.76, 48.52, 51.81, 62.25, 67.91, 78.91, 126.18, 127.58, 128.17, 128.68, 130.28, 130.47, 130.97, 137.23, 139.59, 141.05, 162.37, 170.96, 173.81; ESIMS: m/z calcd [M+]: 478; found: 479 [M+H+].

Methyl-N-[(2'-cyanobiphenyl-4-yl) methyl]-N-pentanoyl-L-valinate (17):

To a solution of methyl N-{[2'-(4, 4-dimethyl-4, 5-dihydro-1, 3-oxazol-2-yl) biphenyl-4-yl] methyl}-N-pentanoyl-L-valinate (**16**, 1 g, 2.09 mmol) in dry pyridine (5 mL), phosphorus oxychloride (0.64 g, 4.18 mmol) was added dropwise at 0 °C. The resulting solution was stirred at 85 °C (bath temperature) under nitrogen for 14 h and cooled to 25 °C, was poured onto a cold saturated solution of sodium carbonate (100 mL). After being cooled to 25 °C the mixture was quenched by addition of water (20 mL) and the resulting emulsion was extracted with ethyl acetate (50 X 2 mL). The combined organic phases were washed with water (50 mL), 10% aqueous cupric sulfate solution (80 mL) and brine solution (100 mL). The solution was then dried over anhydrous magnesium sulfate, filtered, concentrated under vacuum and purified by column chromatography (SiO_2, ethyl acetate /hexane 3:7), to yield methyl N-[(2-cyanobiphenyl-4-yl)methyl]-N-pentanoyl-L-valinate as a yellow oil (**17**, 0.75 g, 90%), ^{1}H NMR (400 MHz,DMSO-d_6) δ 7.17-7.86 (m, 8H), 4.53-4.87 (m, 2H), 4.13-4.18 (m, 1H), 3.25-3.33 (d, 3H), 2.24-2.35 (m, 2H), 2.00-2.13 (m, 1H), 1.41-1.53 (2H, m), 1.10-1.31 (2H, m), 0.86-1.08 (3H, m), 0.68-0.79 (6H, m) ^{13}C NMR (DMSO-d_6) δ 14.16, 18.45, 19.59, 22.21, 27.56, 32,76, 48.39, 52.07, 62.17, 65.09, 110.46, 119.03, 126.72, 127.54, 128.51, 128.63, 130.66, 134.22, 136.86, 139.19, 144.72, 170.59, 174.13; ESIMS: m/z calcd [M+]: 406; found: 407 [M+H+], 429 [M+ +Na].

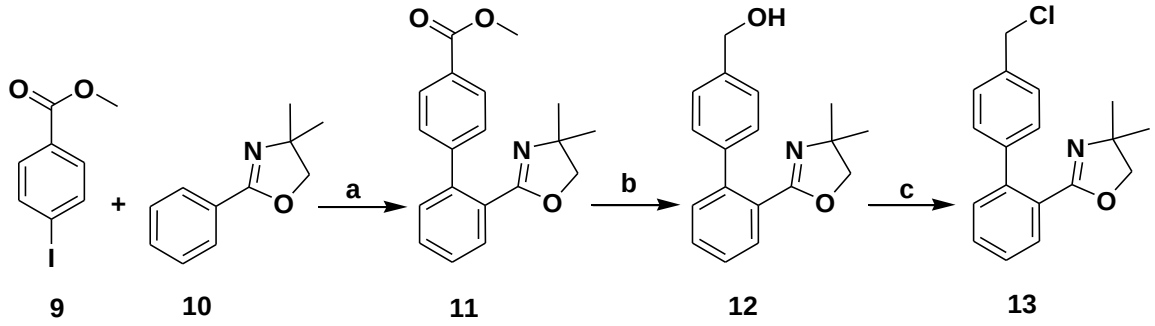
RESULTS AND DISCUSSION

Our approach involved the directed metalation of an appropriate carboxy protecting group followed by transmetalation with zinc chloride then transition metal catalysed cross coupling with aryl iodides. We initially chose the oxazoline moiety as a carboxy synthon because of its excellent ortho-metalating properties, its stability in common reaction conditions, its use as a versatile synthetic intermediate and ease of converting into nitrile under

ISSN: 0975-8585

mild conditions. We chose to explore Negishi cross couplings because of great tolerance of zinc-based organometallics to a wide range of sensitive functionalities.

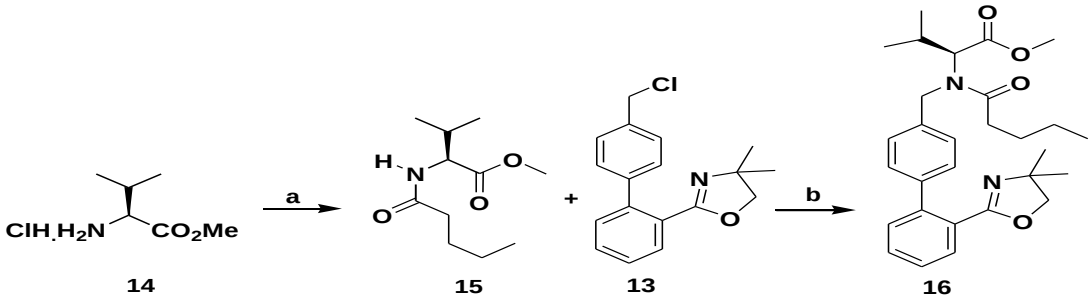
The first segment in our synthesis involves the construction of the 2-(4-chloromethyl-biphenyl-2-yl)-4,4-dimethyl-4,5-dihydrooxazole (**13, Scheme 2**) starting from inexpensive and commercially available 4,4-dimethy-2-phenyl-4,5-dihydro oxazole (**10**).The Oxazole was metalated with 2.5M n-BuLi at 0 ^{o}C for 60 mints and transmetalated with $ZnCl_2$ in THF solvent. The methyl-4-iodobenzoate (**9**) was then added with tetrakis- (triphenylphosphine) palladium (0) and the mixture was stirred for 24 h at 65-70^{o}C to give the 2-(4, 4-Dimethyl-4, 5-dihydrooxazol-2-yl)-biphenyl-4-carboxylic acidmethyl ester (**11**). Reduction of **(11) with** sodium borohydride gave the crystalline hydroxy methyl intermediate (**12**). Which with thionyl chloride afforded the crystalline chloromethyl biphenyl oxazoline (**13**) in 99% yield. [11]



9 10 11 12 13

Scheme 2: (a) n-BuLi, $ZnCl_2$, Pd $(PPh_3)_4$, THF, 65-70 ^{o}C, 24 h (70%) (b) $NaBH_4$, EtOH, THF, 20-25^{o}C, 3 h (95%) (c) $SOCl_2$, DCM, 0-5^{o}C, 2 h (99%).

The second segment in our synthesis (**Scheme 3**) the construction of the compound **16,** first N-Acetylation has been carried out from the commercially available valeryl chloride with L-valine methyl ester hydrochloride (**14**) in dichloromethane the presence of triethyl amine in at 0°C to get methyl N–pentanoyl-L-valinate (**15**) in 95 % yield Then N-alkylation of (**15**) with 2-(4-chloromethyl-biphenyl-2-yl)-4,4-dimethyl-4,5-dihydrooxazole (**13**) in tetrahydrofuran in the presence of Sodiumhydride in tetrahydrofuran gave N-{[2-(4, 4-dimethyl-4,5-dihydro-1,3-oxazol-2-yl)bi-
phenyl-4-yl] methyl}-N-pentanoyl-L-valinate (16) in 70% yield

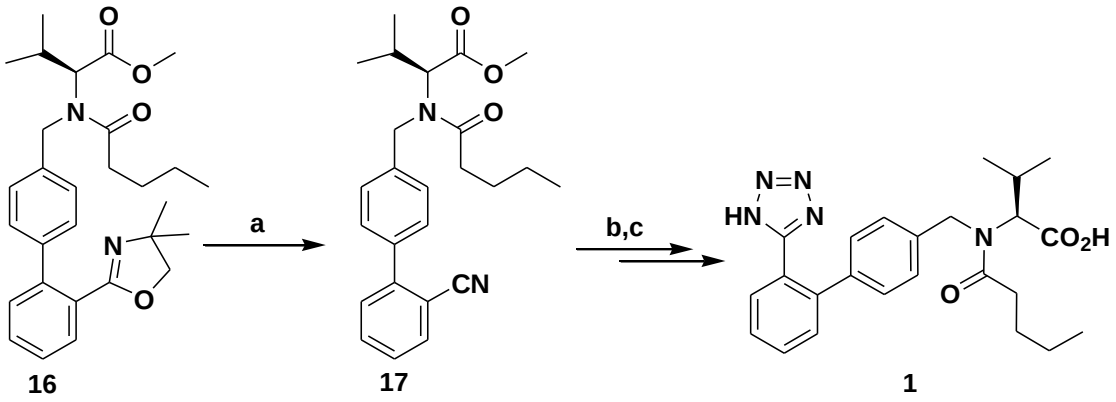


14 15 13 16

Scheme 3: (a) Valeryl Chloride, Et_3N, CH_2Cl_2, 0°C, 95%; (b) NaH, THF, 70%

ISSN: 0975-8585

In the last part (**Scheme 4**) oxazoline (16) is converted into nitrile (**17**), On treatment with phosphorous oxychloride in pyridine at 0-5°C by raising the temperature to 85 °C to get methyl-N-[(2-cyanobiphenyl-4-yl)methyl]-N-pentanoyl-L-valinate (**17**) in 90% yield. The conversion of compound (**17**) to compound (**1**) has already been reported in literature. [12]



16 17 1

Scheme 4: (a) $POCl_3$, Pyridine, 85°C, 14 h, 90%; (b) NaN_3, Bu_3SnCl, TBAB, Toluene, 110°C, 60%; (c) NaOH, Aqueous MeOH, 25°C, 95%.

CONCLUSION

In summary, an improved and convergent approach to the biphenyl oxazoline structure of valsartan has been developed by employing a combination of the ortho directed metalation and Negishi coupling methodologies for the synthesis of the key intermediate 2-[4-(chloromethyl)biphenyl-2-yl]-4,4-dimethyl-4,5-dihydro-1,3-oxazole.This methodology overcomes many drawbacks previously associated with the reported syntheses.

ACKNOWLEDGEMENT

We are grateful to Osmania University Campus, Hyderabad for supporting this work.

REFERENCES

[1] U.S. Department of Health and Human Services; National Heart, Lung, and Blood Institute; National High Blood Pressure Education Program, NIH Publication No. 03-5233, December 2003.
[2] Duncia JV, Chiu AT, Carini DJ, Gregory GB, Johnson AL, Price WA, Wells GJ, Wong PC, Calabrese JC, Timmermans PBMWM. J Med Chem 1990; 33:1312-1329.
[3] For sales figures, see: Novartis Annual Report 2006; Novartis International AG: Basel, Switzerland, 2007.
[4] Bühlmayer P, Furet P, Criscione L, Gasparo M, Whitebread S, Chmidlin T, Lattmann R, Wood J. J Bioorg Med Chem Lett 1994; 4:29-34.
[5] For clinical trial results, see: Novartis Pharma Schweiz, AG. Health & Science 2005; 2:8-9.

[6] Carini DJ, Duncia JV, Aldrich PE, Chiu AT, Johnson AL, Pierce ME, Price WA, Santella JB, Wells GJ, Wexler RR, Wong PC, Yoo SE, Timmermans, PBWM. J Med Chem 1991; 34:2525–2547.
[7] Kohler B, Langer M, Mosandl T. Ger Pat Appl DE19632643C1, 1998.
[8] Amatore C, Jutand A, Negri S. J Organomet Chem 1990; 390:389–398.
[9] Sharp MJ, Snieckus V. Tetrahedron Lett 1985; 26:5997–6000.
[10] Copar A, Antoncic L, Antoncic MT. Int Pat Appl WO 2006/103068A1, 2006.
[11] Urawa Y, Furukawa K, Shimizu T, Yamagishi Y, Tsurugi T, Ichino T. US Patent 5,557,002, 1996.
[12] Sanjeev AK, Samir G; Mehta GN. J Chem Res 2010; 191-193.