Letters in Organic Chemistry, 2020, *17*, 68-72

RESEARCH ARTICLE

A Scalable Synthesis of Biaryl Unit of the HIV Protease Inhibitor Atazanavir

Chapala Vijayalakshmi[1], Malavattu G. Prasad[1], Naresh K. Katari[1,*] and Pedavenkatagari N. Reddy[1,*]

[1]*Department of Chemistry, School of Technology, Gitam University, Hyderabad (T.S) 502329, India*

ARTICLE HISTORY

Received: January 29, 2019
Revised: April 01, 2019
Accepted: April 19, 2019

DOI:
10.2174/1570178616666190514080155

Abstract: Atazanavir is one of the most prescribed HIV-1 protease inhibitors approved by the FDA. It was the first protease inhibitor approved for once-a-day dosing to treat AIDS due to good oral bioavailability and favorable pharmacokinetic profile. This research aims to develop a new synthetic cost effective process for biaryl-hydrazine unit {*tert*-butyl 2-[4-(2-pyridinyl)benzyl]hydrazinecarboxylate} of atazanavir on a large scale. The synthesis involved palladium catalyzed Suzuki-Miyaura coupling of 2-chloropyridine and (4-cyanophenyl)boronic acid followed by DIBAL-H reduction of cyano group to aldehyde which is then treated with *tert*-butyl carbazate to furnish hydrazone subsequently *in situ* reduction with $NaBH_4$. A large scale synthesis of biaryl-hydrazine unit of atazanavir was accomplished in three steps with 71% overall yield. We have developed a short and efficient synthesis of atazanavir key intermediate biaryl-hydrazine unit. The process does not require the usage of Grignard reagent, expensive catalyst, protection/deprotection of aldehyde moiety and catalytic hydrogenation.

Keywords: Atazanavir, HIV protease inhibitor, Suzuki-Miyaura coupling, *In situ* reduction, grignard reagent, catalytic hydrogenation.

1. INTRODUCTION

Human immunodeficiency virus (HIV), the causative agent for acquired immunodeficiency syndrome (AIDS), is the fifth most common cause of death among humans [1]. In 2016, about 36.7 million people were living with HIV and it resulted in 1 million deaths [2]. AIDS was identified in the early 1980s and from that time to 2017, the disease has caused an estimated 35 million deaths worldwide [3]. HIV-1 protease inhibitors continue to play an important role in the treatment of HIV/AIDS, transforming this deadly ailment into a more manageable chronic infection [4]. Atazanavir (**1**) is a type of anti-HIV protease inhibitor approved by the FDA [5-10]. It was the first protease inhibitor approved for once-a-day dosing to treat AIDS due to good oral bioavailability and favorable pharmacokinetic profile [11-13]. Furthermore, atazanavir (**1**) did not cause large increases in cholesterol, triglycerides or blood sugar levels, which is a problem to various degrees with other protease inhibitors [14]. Few methods have been explored for the synthesis of atazanavir (**1**) [15-17]. A series of inhibitors based on a modified substructure of atazanavir (**1**) have been synthesized and evaluated [18, 19].

The synthesis of atazanavir (**1**) required two chiral intermediates and biaryl-hydrazine unit **2** (Fig. **1**). Generally intermediate **2** was prepared from 4-bromobenzaldehyde or 4-formylphenylboronic acid in three steps [15-17]. However several facets made it impractical for large scale production such as use of Grignard reagent, expensive catalyst and protection and deprotection of aldehyde. Furthermore, isolation of hydrazone intermediate and palladium catalyzed hydrogenation would be unsuitable for scale up. Thus an efficient and cost effective synthesis to biaryl-hydrazine unit **2** of atazanavir (**1**) is of prime importance.

2. RESULTS AND DISCUSSION

Owing to the challenges with the original approach to the biaryl-hydrazine unit **2**, a fundamentally different route was devised. Our synthetic route is summarized in Scheme (**1**). Accordingly, inexpensive and readily available (4-cyanophenyl)-boronic acid (**4**) was selected as the starting material. Suzuki-Miyaura coupling of (4-cyanophenyl)boronic acid (**4**) and 2-chloropyridine (**3**) was investigated first. As indicated in Table **1**, the reaction conditions were optimized in terms of the catalyst, ligand, base, solvent and temperature. Initially, 2-chloropyridine (**3**) (1 equiv) was treated with (4-cyanophenyl)boronic acid (**4**) (1.2 equiv) in the presence of tetrakis(triphenylphosphine)palladium(0) using ligand TPP (triphenylphosphine) (0.2 equiv) and K_2CO_3 (2.2 equiv) as a base in 1,4-dioxane at 100°C. The coupling product **5** was obtained in 74% yield (Table **1**, entry 1). To improve the yield the reaction was screened in different solvents with different bases. After an extensive screening process 0.2 equiv of tetrakis(triphenylphosphine)palladium(0) using ligand TPP (0.2 equiv), 2.2 equiv of K_2CO_3 in DMF at 100°C

*Address correspondence to this author at the Department of Chemistry, GITAM University, Hyderabad, P.O. Box: 502329, India; Tel: +91-9493499396; E-mails: iictpnreddy@gmail.com; dr.n.k.katari@gmail.com

1875-6255/20 $65.00+.00

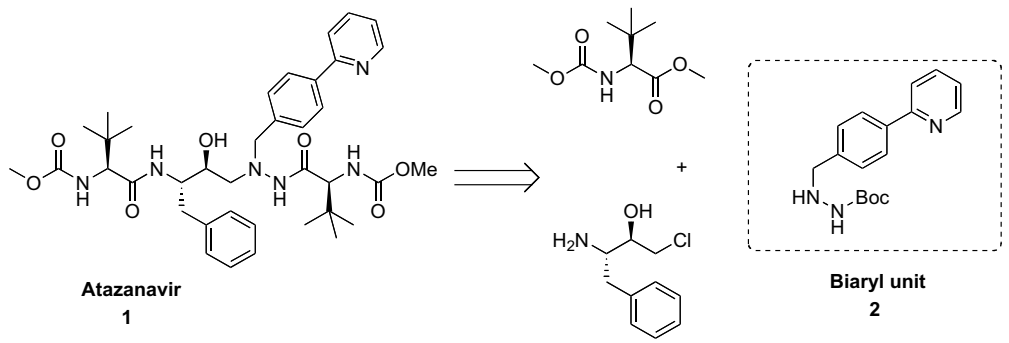
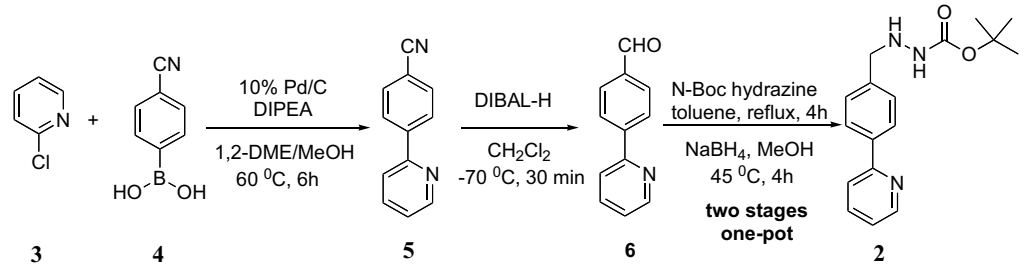


Fig. (1). Chemical structures concerning atazanavir (**1**).



Scheme (1). Synthetic route for biaryl-hydrazine unit **2** of atazanavir (**1**).

were determined to be the most effective coupling conditions (Table **1**, entry 2). Second, the combination of $Pd(OAc)_2$ with different ligands such as TPP, dppe (1,2-(bis(diphenylphosphino)ethane), dppf (1,1'-ferrocenediyl-bis(diphenyphosphine) was tested for the reaction of 2-chloropyridine (**3**) with (4-cyanophenyl)boronic acid (**4**). The products were obtained in good yields ranging from 80 to 89%. As described above, the reaction worked equally well for both tetrakis(triphenylphosphine)palladium(0) and $Pd(OAc)_2$. However, considering the cost of these palladium catalysts, next we tested the reaction with Pd/C which is cheap and commercially available. The reaction of 2-chloropyridine (**3**) and (4-cyanophenyl)boronic acid (**4**) with 10% Pd/C in the presence of TEA (triethylamine) as a base in 1,2-dimethoxyethane/methanol (1,2-DME/MeOH) at 60°C gave 62% yield (Table **1**, entry 12). Further reaction yield was improved to 90% when the reaction was carried out in the presence of DIPEA (diisopropylethylamine) as a base for 6 h (Table **1**, entry 14). We also demonstrated that the reaction could be scaled to 100 g level with similar yield (Table **1**, entry 15). Compared to air-sensitive and expensive homogeneous palladium catalysts, palladium charcoal can be safely handled and removed from the reaction mixture by simple filtration. The recovered palladium charcoal can be purified and reused as palladium metal. These features are great advantages in an industrial process.

Next, attention was turned to a partial reduction of nitrile group of **5** to aldehyde **6** with 1 equiv DIBAL-H in DCM at 0°C. The reduction provided 4-(2-pyridinyl)benzaldehyde (**6**) in 58% yield (Table **2**, entry 1). We investigated the reaction at various temperatures and observed that reducing the temperature significantly increases the yield. After some optimization, we found that 1.1 equiv of DIBAL-H at -70°C in DCM was the optimum condition for this reaction (Table **2**, entry 8). This procedure was successfully scaled up to 100 g large scale with similar yield (Table **2**, entry 9**)**.

The condensation of aldehyde **6** with *tert*-butyl carbazate was initially carried out by heating in toluene. We then presumed that *in situ* reduction of imine could proceed by the addition of reducing agent to the reaction mixture. Reduction with sodium borohydride is being increasingly used as an alternative for the classical catalytic hydrogenation of organic functional groups, as it offers convenient and simple experimental conditions. Accordingly, after completion of condensation reaction 1 equiv of sodium borohydride was added and then MeOH was added slowly. This procedure afforded a 78% yield of biaryl-hydrazine unit **2** of atazanavir (**1**) (Table **3**, entry 1). We investigated various reducing agents and found that the use of 1.05 equiv of sodium borohydride with the use of solvent mixture of 10:1 toluene/MeOH was ideal for both the condensation and subsequent *in situ* reduction (Table **3**, entry 2). This procedure was scaled up to 100 g of **2** in a single bath (Table **3**, entry 10). The structures of all the compounds were confirmed by spectral analysis. One of the features of this method is that both the condensation and reduction reactions were conducted in one-pot, while in previously reported methods two steps were involved [15-17]. It is worth to mention that this transformation minimizes the side reactions and over reduction byproducts. Further, the method does not require isolation and crystallization of hydrazone intermediate.

3. EXPERIMENTAL SECTION

3.1. General

All chemicals were purchased from Lancaster (Alfa Aesar, Johnson Matthey Co, Ward Hill, MA, USA), Sigma-Aldrich

Table 1. Optimization of reaction conditions for the preparation of 4-(2-pyridinyl)benzonitrile (5).

S. No.	Catalyst	Base	Ligand	Solvent	Temperature (^oC)	Time (h)	Yield[a] (%)
1	$Pd[(C_6H_5)_3P]_4$	K_2CO_3	TPP	1,4-dioxane	100	10	74
2	$Pd[(C_6H_5)_3P]_4$	K_2CO_3	TPP	DMF	100	10	85
3	$Pd[(C_6H_5)_3P]_4$	Cs_2CO_3	TPP	1,4-dioxane	100	10	76
4	$Pd[(C_6H_5)_3P]_4$	Cs_2CO_3	TPP	DMF	100	10	77
6	$Pd(OAc)_2$	K_2CO_3	TPP	1,2-DME	100	6	88
7	$Pd(OAc)_2$	Cs_2CO_3	TPP	1,2-DME	100	6	89
8	$Pd(OAc)_2$	DABCO	dppe	DMF	100	4	84
9	$Pd(OAc)_2$	DABCO	dppe	1,4-dioxane	100	4	80
10	$Pd(OAc)_2$	DABCO	dppf	DMF	100	4	86
11	$Pd(OAc)_2$	DABCO	dppf	1,4-dioxane	100	4	85
12	Pd/C	TEA	-	1,2-DME/MeOH	60	8	62
13	Pd/C	DIPEA	-	1,2-DME/MeOH	60	4	68
14	Pd/C	DIPEA	-	1,2-DME/MeOH	60	6	90
15	Pd/C	DIPEA	-	1,2-DME/MeOH	60	6	92[b]

[a] Isolated yield.
[b] 2-chloropyridine (**3**) (0.88 mol), (4-cyanophenyl)boronic acid (**4**) (1.05 mol), 1,2-DME/MeOH (500:20 mL), 10% Pd/C (wet) (0.05 w/w) at 60^{o}C,

Table 2. Optimization of reaction conditions for the preparation of 4-(2-pyridinyl)benzaldehyde (6).

S. No.	DIBAL-H (Equiv)	Temperature (^oC)	Solvent	Time (min)	Yield[a] (%)
1	1	0	DCM	30	58
2	1.2	0	DCM	60	61
3	1.1	-10	DCM	30	67
4	1.1	-30	DCM	30	69
5	1.1	-40	DCM	30	74
6	1.1	-50	DCM	30	76
7	1.1	-60	DCM	30	89
8	1.1	-70	DCM	30	92[b]
9	1.1	-70	DCM	30	92[c]

[a] Isolated yield.
[b] 4-(2-Pyridinyl)benzonitrile (**5**) (1.00 mmol), DIBAL-H (1.2 mmol) at -70^{o}C.
[c] 100 g scale.

(St Louis, MO, USA) and Spectrochem Pvt Ltd (Mumbai, India). Reactions were monitored by TLC, performed on silica gel glass plates containing 60 F-254 and visualization on TLC was achieved by UV light or iodine indicator. NMR spectra were recorded on Avance (300 MHz) Bruker, Fallanden, Switzerland instruments. Chemical shifts were reported in ppm, downfield from internal TMS standard. Spectral patterns were designated as s, singlet; d, doublet; m, multiplet. ESI spectra were recorded on Micro mass, Quattro LC using ESI+ software with a capillary voltage of 3.98 kV and ESI mode positive ion trap detector.

3.2. Synthesis of 4-(2-pyridinyl)benzonitrile (5)

To a solution of 2-chloropyridine (**3**) (0.97 mmol, 0.11 g) and **(**4-cyanophenyl)boronic acid (**4**) (1.16 mmol, 0.17 g) in 1,2-DME (10 mL), DIPEA (2.37 mmol, 0.4 mL), MeOH (1 mL), and 10% Pd/C (wet) (0.05 w/w based on 2-chloropyridine) were added at room temperature. The reaction mixture was heated at 60^{o}C for 6 h. Then it was cooled to room temperature, filtered through celite bed, and washed with 1,2-DME. The filtrate was poured into water and precipitated solid was filtered, washed with water, and dried under vacuum at 40°C for 12 h to afford the pure product **5**.

Table 3. Preparation of *tert*-butyl 2-[4-(2-pyridinyl)benzyl]hydrazinecarboxylate (2).

S. No.	Reducing Reagent	Equiv	Temperature (^{o}C)	Solvent	Time (h)	Yield[a] (%)
1	$NaBH_4$	1	45	Toluene: Methanol	4	78
2	$NaBH_4$	1.05	45	Toluene: Methanol	4	86
3	$NaBH_4$	1.1	45	Toluene: Methanol	4	82
4	$NaBH_4$	1.2	45	Toluene: Methanol	4	82
5	$NaBH(OAc)_3$	1.05	45	Toluene: Methanol	4	83
6	$NaBH(OAc)_3$	1.1	45	Toluene: Methanol	4	80
7	$NaBH_3CN$	1.05	45	Toluene: Methanol	6	77
8	$NaBH_3CN$	1.1	45	Toluene: Methanol	6	79
10	$NaBH_4$	1.05	45	Toluene: Methanol	4	85[a]

[a] Isolated yield.

[b] 4-(2-Pyridinyl)benzaldehyde (6) (0.54 mol), *tert*-butyl carbazate (0.65 mol) at reflux in toluene (500 mL), sodium borohydride (0.56 mol) at 30^{o}C.

White solid, m.p. 106-108^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.76-8.71 (m, 1H, ArH), 8.18 (d, 2H, J = 8.4 Hz, ArH), 7.82-7.63 (m, 4H, ArH), 7.36-7.28 (m, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.0 (pyridine C-1'), 149.8 (C-3'), 143.3 (C-4), 137.0 (C-5'), 132.3 (C-2,6), 127.3 (C-3,5), 123.2 (C-4'), 120.9 (C-6'), 118.6 (CN), 112.2 (C-1); ESIMS: *m/z* 181 $(M+H)^+$; HRMS: *m/z* $(M+H)^+$ calcd for $C_{12}H_9N_2$ 181.1725, found 181.1729.

3.3. Preparation of 4-(2-pyridinyl)benzaldehyde (6)

4-(2-Pyridinyl)benzonitrile (**5**) (1.00 mmol, 0.18 g) was dissolved in dry DCM (10 mL), cooled to -70^{o}C, and DIBAL-H (1 M solution in DCM, 1.2 equiv, 1.2 mL) was added slowly under nitrogen. The mixture was allowed to stir for 30 min, warmed to 0^{o}C and sodium potassium tartrate solution (saturated) was added (5 mL). The resulting solution was filtered through celite bed and washed with DCM. Organic layer was separated, washed with brine (3 x 20 mL), dried (Na_2SO_4), and solvent removed under vacuum. The resulted solid compound **6** was collected by filtration and subjected to the next step without further purification.

White solid, m.p. 52-54^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.01 (s, 1H, CHO), 8.78-8.68 (m, 1H, ArH), 8.18 (d, 2H, J = 8.4 Hz, ArH), 8.00 (d, 2H, J = 8.4 Hz, ArH), 7.86-7.75 (m, 2H, ArH), 7.35-7.28 (m, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 192.0 (CHO), 156.2 (pyridine C-1'), 150.0 (C-3'), 145.2 (C-4), 137.8 (C-5'), 136.5 (C-1), 130.2 (C-2,6), 127.5 (C-3,5), 123.4 (C-4'), 122.0 (C-6'); ESIMS: *m/z* 184 $(M+H)^+$; HRMS: *m/z* $(M+H)^+$ calcd for $C_{12}H_{10}NO$ 184.1913, found 184.1916.

3.4. Preparation of *tert*-butyl 2-[4-(2-pyridinyl)benzyl] hydrazinecarboxylate (2)

Into a mixture of 4-(2-pyridinyl)benzaldehyde (6) (0.98 mmol, 0.18 g) and *tert*-butyl carbazate (1.13 mmol, 0.15 g) toluene (10 mL) was added. The mixture was heated to reflux for 4 h, cooled to 30^{o}C, and sodium borohydride (1.06 mmol, 0.04 g) was added followed by MeOH (5 mL). Then the reaction mixture was heated to 45^{o}C and stirred at the same temperature. After 4 h, the reaction mixture was cooled to room temperature and water (10 mL) was added. Organic layer was separated, washed with brine (3 x 20 mL), dried (Na_2SO_4), and solvent removed under vacuum. The crude product was crystallized using mixture of ethanol-water, filtered, washed, and dried to afford the product 2.

White solid, m.p. 78-80^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.72-8.63 (m, 1H, ArH), 7.96 (d, 2H, J = 8.0 Hz, ArH), 7.76-7.68 (m, 2H, ArH), 7.45 (d, 2H, J = 8.0 Hz, ArH), 7.22-7.16 (m, 1H, ArH), 6.51 (s, 1H, NH), 4.32 (s, 1H, NH), 4.01 (s, 2H, CH_2), 1.46 [s, 9H, $(CH_3)_3$]; ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.8, 156.5, 150.0, 139.1, 139.0, 137.2, 129.5, 127.3, 122.2, 120.1, 80.1, 55.1, 28.2; IR (KBr pellet, cm^{-1}): 3293, 2982, 2938, 1699, 1457, 1284, 1151, 781; ESIMS: *m/z* 300 $(M+H)^+$; HRMS: *m/z* $(M+H)^+$ calcd for $C_{17}H_{22}N_3O_2$ 300.2236, found 300.2241.

CONCLUSION

We have developed a short and efficient synthesis of atazanavir key intermediate biaryl-hydrazine unit **2**. The method is useful for large scale synthesis and gives excellent yield. The process does not require the usage of Grignard reagent, expensive catalyst, protection/deprotection of aldehyde moiety and catalytic hydrogenation.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

SUPPLEMENTARY MATERIAL

Supplementary material is available on the publisher's web site along with the published article.

REFERENCES

[1] Weiss, R.A. How does HIV cause AIDS? *Science,* **1993**, *260*(5112), 1273-1279.

[2] **2017**. Fact sheet-latest statistics on the status of the AIDS epidemic www.unaids.org UNAIDS

[3] **2018**. Fact sheet-latest statistics on the status of the AIDS epidemic www.unaids.org UNAIDS

[4] Ghosh, A.K.; Osswald, H.L.; Prato, G. *J. Med. Chem.,* **2016**, *59*(11), 5172-5208.

[5] Piliero, P.J. Atazanavir: a novel HIV-1 protease inhibitor. *Expert Opin. Investig. Drugs,* **2002**, *11*(9), 1295-1301.

[6] Fässler, A.; Bold, G.; Capraro, H-G.; Cozens, R.; Mestan, J.; Poncioni, B.; Rösel, J.; Tintelnot-Blomley, M.; Lang, M. *J. Med. Chem.,* **1996**, *39*(16), 3203-3216.

[7] Gong, Y-F.; Robinson, B.S.; Rose, R.E.; Deminie, C.; Spicer, T.P.; Stock, D.; Colonno, R.J.; Lin, P-F. *Antimicrob. Agents Chemother.,* **2000**, *44*(9), 2319-2326.

[8] Drusano, G.L.; Bilello, J.A.; Preston, S.L.; O'Mara, E.; Kaul, S.; Schnittman, S.; Echols, R. *J. Infect. Dis.,* **2001**, *183*(7), 1126-1129.

[9] Robinson, B.S.; Riccardi, K.A.; Gong, Y.F.; Guo, Q.; Stock, D.A.; Blair, W.S.; Terry, B.J.; Deminie, C.A.; Djang, F.; Colonno, R.J.; Lin, P.F. *Antimicrob. Agents Chemother.,* **2000**, *44*(8), 2093-2099.

[10] Rabasseda, X.; Silvestre, J.; Castaner, J. *Drugs Future,* **1999**, *24*, 375-380.

[11] Croom, K.F.; Dhillon, S.; Keam, S.J. Atazanavir: a review of its use in the management of HIV-1 infection. *Drugs,* **2009**, *69*(8), 1107-1140.

[12] Wensing, A.M.J.; van Maarseveen, N.M.; Nijhuis, M. *Antiviral Res.,* **2010**, *85*(1), 59-74.

[13] Pinheiro, E.D.S. Antunes, O.A.C.; Fortunak. *J.M.D. Antiviral Res.,* **2008**, *79*, 143-165.

[14] Sanne, I.; Piliero, P.; Squires, K.; Thiry, A.; Schnittman, S. *J. Acquir. Immune Defic. Syndr.,* **2003**, *32*(1), 18-29.

[15] Xu, Z.; Singh, J.; Schwinden, M.D.; Zheng, B.; Kissick, T.P.; Patel, B.; Humora, M.J.; Quiroz, F.; Dong, L.; Hsieh, D-M.; Heikes, J.E.; Pudipeddi, M.; Lindrud, M.D.; Srivastava, S.K.; Kronenthal, D.R.; Mueller, R.H. *Org. Process Res. Dev.,* **2002**, *6*, 323-328.

[16] Dalla-Vechia, L.; Reichart, B.; Glasnov, T.; Miranda, L.S.M.; Kappe, C.O.; de Souza, R.O.M.A. *Org. Biomol. Chem.,* **2013**, *11*(39), 6806-6813.

[17] Fan, X.; Song, Y-L.; Long, Y-Q. *Org. Process Res. Dev.,* **2008**, *12*, 69-75.

[18] Bold, G.; Fässler, A.; Capraro, H-G.; Cozens, R.; Klimkait, T.; Lazdins, J.; Mestan, J.; Poncioni, B.; Rösel, J.; Stover, D.; Tintelnot-Blomley, M.; Acemoglu, F.; Beck, W.; Boss, E.; Eschbach, M.; Hürlimann, T.; Masso, E.; Roussel, S.; Ucci-Stoll, K.; Wyss, D.; Lang, M. *J. Med. Chem.,* **1998**, *41*(18), 3387-3401.

[19] Singh, R.K.; Gottumukkala, N.; Khanna, M.S.; Thaper, R.K.; Prasad, M.; Arora, S.K. PCT Int. Appl. WO 2013014633 A1 20130131, 2013.