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Synthesis of (2R,3R,4S)-N-Boc-2,4-Diarylpyrrolidine-3-carboxamides

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A synthesis of (2R,3R,4S)-N-boc-2,4-diarylpyrrolidine-3-carboxylic amides (**i-vii**) *via* HATU, BOP and Mukaiyama mediated coupling of (2R,3R,4S)-1-(*tert*-butoxycarbonyl)-4-(benzo[d][1,3]dioxol-6-yl)-2-(4-methoxyphenyl)pyrrolidine-3-carboxylic acid (**13**) with amine (**a^1-g^1**) has been developed. Under HATU coupling conditions, the products were achieved in good yields comparatively than BOP and Mukaiyama reagent. The structures of compounds **i-vii** were elucidated on the basis of spectral and chemical studies.

Key Words: 2,4-Diarylpyrrolidine-3-carboxylic amides, Mukaiyama reagent, HATU, BOP.

INTRODUCTION

The heterocyclics like pyrrolidines play critical roles as core structures in the design of drugs show different bioactivity. The specific orientation of bioactive motifs in 3D space is pivotal in ligand-receptor and enzyme-inhibitor complexes, which are the underlying mechanism of action for many pharmaceuticals. When one enantiomer provides the efficacy of interest, the other enantiomer may be partially active or inactive, be an antagonist of the active enantiomer or have a different activity that could be desirable or undesirable. More than 50 % of the drugs used in the modern medicine are either synthetic or natural heterocyclic systems. Depending on the substitution pattern and functionalization, pyrrolidines have been shown to be effective antibacterials[1], neuroexcitatory agents[2], potent venom[3], galactosidase inhibitors[4] and fungicides[5].

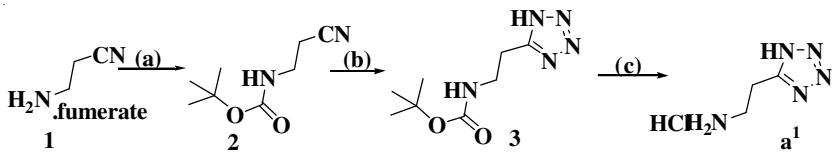
The *trans*, *trans*-2,4-diarylpyrrolidine-3-carboxylates are important class of selective endothelins[6-9] and are most potent peptide vasoconstrictors known. The amide bond is a ubiquitous connection in proteins and peptides and is found in a large number of molecule chemotherapeutics[10]. The preparation of amide bond is most common synthetic transformations in organic chemistry. Most methods employ the dehydrative coupling of carboxylic acids with amines. During present synthesis require high-yielding and reproducible procedure for the coupling of carboxylic acid (**13**) with amine (**a^1-g^1**). When using standard coupling protocols (HATU[11], BOP[12,13], Mukaiyama[14]) with amines (**a^1-g^1**), presumably due to steric hindrance of

the acid especially choice of bonding of neighbour aromatic hydrogen with carbonyl oxygen of acid. Upon further reproducible and applicable to a variety of amine derivatives (**a^1-g^1**).

EXPERIMENTAL

A synthesis of (2R,3R,4S)-N-boc-2,4-diarylpyrrolidine-3-carboxylic amides (**i-vii**) *via* HATU[11], BOP[12,13] and Mukaiyama[14]-mediated coupling of (2R,3R,4S)-1-(*tert*-butoxycarbonyl)-4-(benzo[d][1,3]dioxol-6-yl)-2-(4-methoxyphenyl)-pyrrolidine-3-carboxylic acid (**13**) with amine (**a^1-g^1**) has been developed.

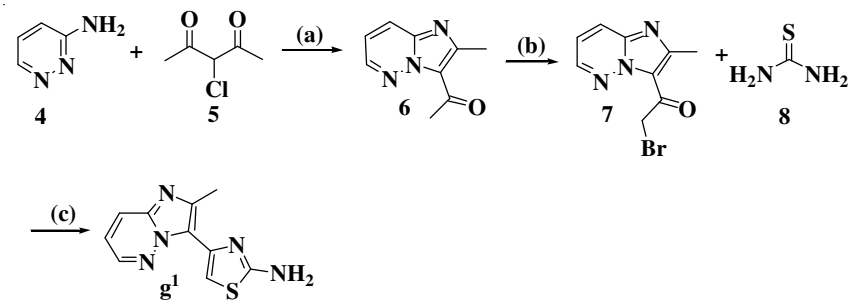
The tetrazole amine (**a^1**) prepared by protecting amine (**1**) with ditertiary butyl di carbonate, 10 % Na_2CO_3 in THF (*ca.* 87 % yield) followed by cyclization with NH_4Cl, NaN_3 in DMF[15] (*ca.* 53 % yield), further deprotected boc in 4 N HCl-dioxane (*ca.* 64 % yield) *via* **Scheme-I**.



Reagents& conditions: (a) $(BOC)_2O$;10%Na_2CO_3;THF/RT-5 h; (b) NaN_3; NH_4Cl; DMF, 90 °C; (c) 4N HCl in dioxane/RT-3 h;

Scheme-I

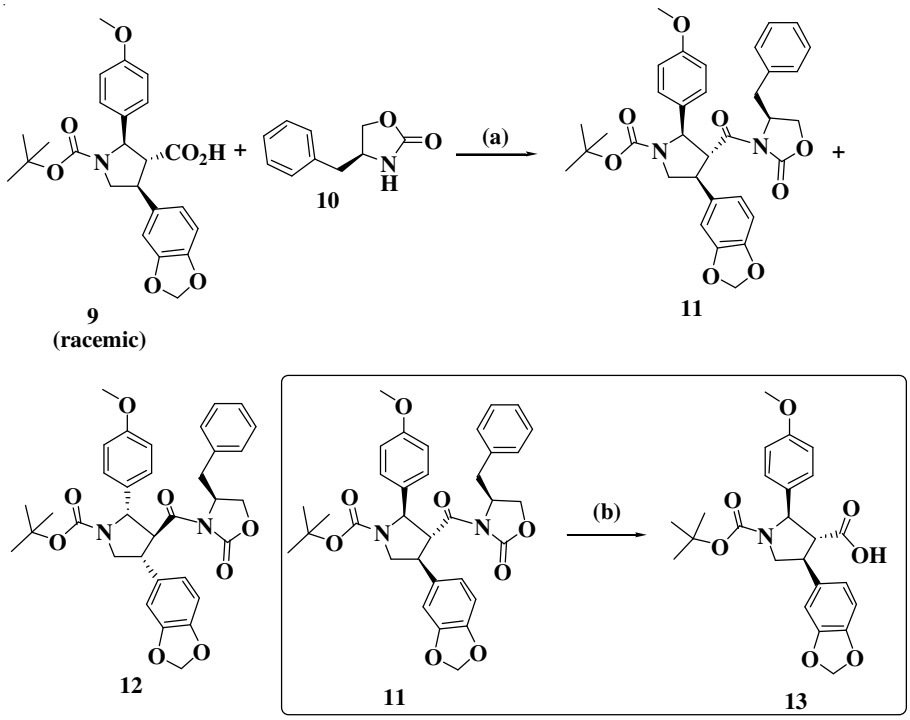
The thiozole amine (**g^1**) prepared by cyclization of pyridazine-3-amine[16] (**4**) with 3-chloropentane-2,4-dione (**5**) in EtOH for 24 h reflux to cyclized keto (**6**) (*ca.* 39 % yield), then prepared α-bromo compound[16] (**7**) by treating with bromine in diethyl ether/dichloromethane at 0 ºC to room temperature (*ca.* 58 % yield) further prepared thiozole amine (**g^1**) by cyclization of α-bromo compound (**7**) with thiourea (**8**) in toluene for 4 h reflux (*ca.* 68 % yield) of **Scheme-II**.



Reagents & Conditions: (a) EtOH; reflux; 24 h (b) Br2; ether; DCM; 0 ºC-RT; 2 h (c) toluene; reflux

Scheme-II

Further prepared chiral acid (**13**) by enantiomeric separation of recemic acid (**9**)[16], by using chiral auxillary (S)-4-benzyloxazolidine-2-one (**10**) to give pure chiral acid (**13**) (*ca.* 32 % yield) *via* **Scheme-III**.



Reagents & Conditons:- (a) n-BuLi; pivalyl chloride (b) LiOH; H_2O_2; THF; H_2O

Scheme-III

***Tert*-butyl-2-cyanoethylcarbamate (2):** To a solution of 3-aminopropanenitrile (**1**) (10 g, 39 mmol) in THF (100 mL) was added 10 % $NaHCO_3$ (20 mL) solution. Ditertiary butyl dicarbonate (9.36 g, 42.9 mmol) was added slowly. The reaction mixture was stirred for 5 h at room temperature. The volatiles were concentrated under reduced pressure, then the residue was diluted with water (50 mL) and extracted product into ethyl acetate (100 mL), dried (anhy. Na_2SO_4), concentrated under reduced pressure to afford *tert*-butyl-2-cyanoethylcarbamate (**2**) (5.8 g, 87 % yield) as solid. ^{1}H NMR (200 MHz, $CDCl_3$): 1.41 (s, 9H), 2.61 (t, 2H), 3.4 (q, 2H), 5.1 (bs, 1H); M^+ (171).

***Tert*-butyl-2-(2*H*-tetrazol-5-yl)ethylcarbamate (3):** A mixture of *tert*-butyl-2-cyanoethylcarbamate (**2**) (5.5 g, 32 mmol), NaN_3 (10.4 g, 160 mmol) and NH_4Cl (8.5 g, 160 mmol) in DMF (50 mL) was heated to 90 ºC, stirred for 2 days. The reaction mixture was allowed to room temperature and then concentrated volatiles

under reduced pressure. The residue was diluted with water, extracted product into ethyl acetate, dried (anhy. Na_2SO_4), concentrated under reduced pressure to afford *tert*-butyl-2-(2*H*-tetrazol-5-yl)ethylcarbamate (**3**) (3.7 g, 53 % yield) as a white solid. ^{1}H NMR (200 MHz, DMSO-d_6): 1.39 (s, 9H), 2.98 (t, 2H), 3.24 (q, 2H), 7.01 (t, 1H); M^+ (214)

2-(2*H*-Tetrazol-5-yl)ethanamine hydrochloride (a[1]): To a solution of *tert*-butyl-2-(2*H*-tetrazol-5-yl)ethylcarbamate (**3**) (3.2 g, 15 mmol) in methanol (10 mL) was added 4 N HCl in dioxane (10 mL) slowly at 0 ºC. The reaction mixture was stirred for 4 h at room temperature. The volatiles were distilled by using rotavapour and the residue was triturated in diethyl ether. The precipitated solids were filtered, washed with diethyl ether and dried to afford desired product (**a[1]**) (1.1 g, 64 % yield) as a solid. ^{1}H NMR (DMSO-d_6): 2.97 (t, 2H), 3.23 (q, 2H), 7.0(t, 1H); M^+ (114).

1-(2-Methylimidazo[1,2-b]pyridazin-3-yl)ethanone (6): A mixture of pyridazine-3-amine (**4**) (10 g, 105.15 mmol), 3-chloropentane-2,4-dione (**5**) (21.2 g; 157.7 mmol) in ethanol (100 mL) was refluxed at 80 ºC for 24 h. The volatiles were concentrated under reduced pressure. The residue was purified through silica gel column chromatography, eluted product with 80 % ethylaceate/hexanes to afford 1-(2-methylimidazo[1,2-b]pyridazin-3-yl)ethanone (**6**) (7.1 g; 39 % yield) as a solid. ^{1}H NMR (200 MHz, $CDCl_3$): 2.77 (s, 3H), 2.83 (s, 3H), 7.18-7.26 (m, 1H), 7.95-8.0 (dd, 1H), 8.46-8.49(dd, 1H); M^+ (176).

2-Bromo-1-(2-methylimidazo[1,2-b]pyridazin-3-yl)ethanone (7): To a 1-(2-methylimidazo[1,2-b]pyridazin-3-yl)ethanone (**6**) (1 g; 5.71 mmol) in a mixture of diethyl ether (10 mL) and dichloromethane (2 mL) was added slowly dropwise bromine (1.09 g; 6.85 mmol) at 0 ºC. Then warmed reaction mixture to room temperature, stirred for 2 h. The reaction mixture was diluted with diethy ether (50 mL), filtered the precipitated solids. The solids were washed with 10 % ethanol/diethyl ether (20 mL), dried under vacuum to afford 2-bromo-1-(2-methylimidazo-[1,2-b]pyridazin-3-yl)ethanone (**7**) (850 mg; 58 % yield) as a light white solid. ^{1}H NMR (200 MHz, DMSO-d_6): 2.64 (s, 3H), 4.95 (s, 2H), 7.49-7.56 (m, 1H), 8.23-8.28 (dd, 1H), 8.78-8.8 (d, 1H); M^+ (254).

4-(2-Methylimidazo[1,2-b]pyridazin-3-yl)thiazol-2-amine (g[1]): A mixture of 2-bromo-1-(2-methylimidazo[1,2-b]pyridazin-3-yl)ethanone (**7**) (500 mg; 1.96 mmol) and thiourea (**8**) (180 mg; 2.36 mmol) in toluene was refluxed for 4 h. Then toluene was decanted. The residue was dissolved in water, adjusted pH to 8 by using sat. $NaHCO_3$ solution. Then filtered the solids, washed with water and dried under vacuum to afford 4-(2-methylimidazo[1,2-b]pyridazin-3-yl)thiazol-2-amine (**9**) (310 mg; 68 % yield) pale green solid. ^{1}H NMR (200 MHz, DMSO-d_6): 2.79 (s, 3H), 7.01 (brs, 2H), 7.19-7.22 (dd, 1H), 7.56 (s, 1H), 8.01-8.05 (dd, 1H), 8.58-8.6 (dd, 1H); M^+ (232).

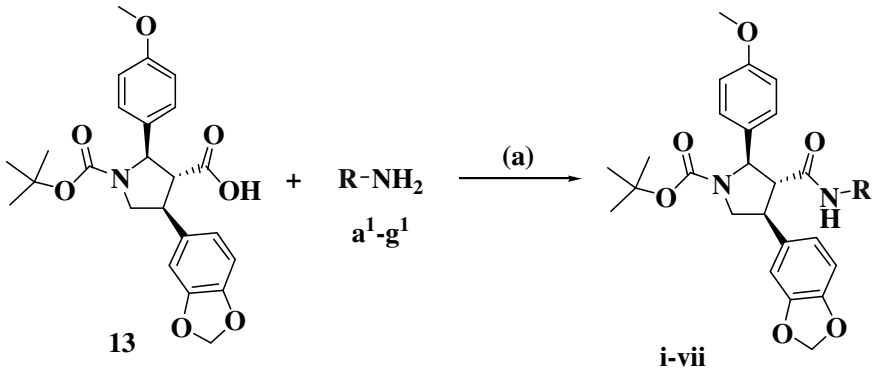
Imides (11) and (12)[6]: To a solution of acid (**9**) (1 g; 2.267 mmol) in THF (10 mL) was added triethyl amine (343 mg; 3.4 mmol) and pivaloyl chloride (301 mg;

2.49 mmol) at -78 ºC, stirred for 15 min. The reaction mixture allowed to 0 ºC and stirred for 40 min and re-cooled to -78 ºC. In a separate flask a solution of (S)-4-benzyl-2-oxazolidinone (601 mg; 3.4 mmol) was added *n*-BuLi (2.5 M in hexanes) (1.36 mL; 3.4 mmol) slowly dropwise at -78 ºC. Then added this solution to above solution slowly drop wise at -78 ºC. The reaction mixture was warmed to room temperature, stirred for overnight. The reaction mixture was quenched with sodium bisulfate, then concentrated reaction mixture under reduced pressure. The residue was diluted with dichloromethane and water. The organic layer was separated, dried (anhy. Na_2SO_4) and concentrated under reduced pressure. The residue was purified through silica gel column chromatography, eluted products with 20 % ethyl acetate/hexanes to afford faster one imide (**11**) (210 mg; 15 % yield) and slowler moving imide (**12**) (200 mg; 14.7 % yield) as a solid. Imide (**11**): ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.15 and 1.41 (brs, 9H), 2.47-2.52 (t, 1H), 3.18 (d, *J* = 4.8 Hz, 1H), 3.64-3.68 (m, 1H), 3.81 (s, 3H) 3.83 (m, 1H), 3.89-3.91 (m, 1H), 4.20-4.24 (m, 1H), 4.51 (m, 1H), 4.90-5.13 (m, 2H), 5.91 (2H), 6.70-6.74 (m, 2H), 6.80 (s, 1H), 6.84 (d, 2H), 7.16 (d, 2H), 7.24-7.26 (m, 5H); M^{+Na} (623) and M^{-boc} (501).

Imide (12): ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.14 and 1.41 (brs, 9H), 2.42-2.46 (t, 1H), 3.01 (d, *J* = 5.6 Hz, 1H), 3.64-3.66 (m, 1H), 3.68-3.74 (m, 1H), 3.81 (s, 3H) 3.83 (m, 1H), 3.85-3.90 (m, 1H), 4.24 (m, 1H), 4.57 (m, 1H), 4.88 (brs, 1H), 5.04 (m, 2H), 5.94 (d, *J* = 7.2 Hz, 2H), 6.72-6.84 (m, 3H), 6.81 (s, 1H), 6.95 (d, 2H), 7.16 (d, 2H), 7.22-7.26 (m, 5H); M^{+Na} (623) and M^{-boc} (501).

(2R,3R,4S)-1-(*tert*-Butoxycarbonyl)-4-(benzo[d][1,3]dioxol-6-yl)-2-(4-methoxyphenyl)pyrrolidine-3-carboxylic acid (13): To a stirred solution of imide (**28**) (200 mg; 0.33 mmol) in THF (2 mL); water (2 mL) was added lithium hydroxide (10 mg; 0.4 mmol) and one drop of 30 % H_2O_2 at 0 ºC. The reaction mixture was stirred for 0.5 h at 0 ºC. The solvents were evaporated and residue was dissolved in ether and 0.2 M NaOH. The aqueous layer was separated and then adjusted pH to neutral by using citric acid. Then filtered the precipitated solids, dried under vacuum to afford acid (**30**) (90 mg; 61 % yield) as a solid. ^{1}H NMR (200 MHz, $CDCl_3$): rotamers δ 1.15 and 1.40 (brs, 9H), 3.12 (m, 1H), 3.54-3.59 (m, 2H), 3.79 (s, 3H), 4.20-4.24 (m, 1H), 4.64-4.71 (m, 1H), 4.90-5.01 (m, 1H), 5.91 (2H), 6.71-6.74 (m, 2H), 6.84 (d, 2H), 7.16 (d, 2H); M^+ (442): ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.06 and 1.34 (brs, 9H), 2.81-2.92 (m, 1H), 3.45 (m, 2H), 3.97-4.01(m, 2H), 3.73 (s, 3H), 4.65-4.80 (m, 1H), 5.96 (2H), 6.79-6.88 (m, 3H), 7.01 (s, 1H), 7.20 (d, 2H), 12.41-12.77 (brs, 1H) (**Scheme-IV**).

General amide coupling procedure with HATU reagent[11]: The appropriated Boc-protected carboxylic acid derivative (**13**) (1eq) was added to a solution of the appropriated amines (**a^1-g^1**) (1.2 eq) in dry DMF (0.2 mL/mg) followed by HATU (1.2 eq) and DIPEA (2 eq) at 0 ºC. The reaction mixture was stirred for overnight at 2 h and then reaction mixture poured into water. The precipitated solid was filtered, purified through silica gel column chromatography, eluted product with 5-7 % methanol/dichloromethane to afford carboxamides (**i-vii**) (*ca.* 45-61 % yield).



Reagents & Conditions: (a) HATU; DIPEA; DMF; 2 h (or) BOP; Pyridine;12 h; RT (or) Mukaiyama reagent; THF;12h/RT;

Scheme-IV

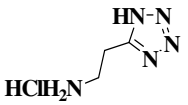
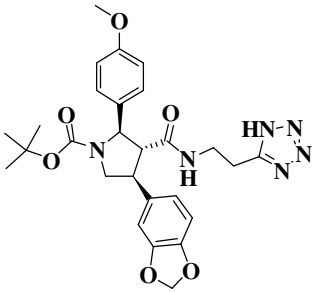
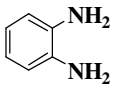
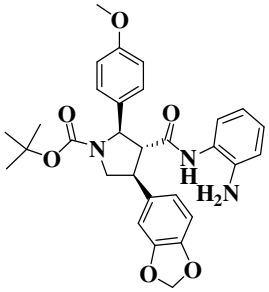
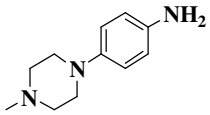
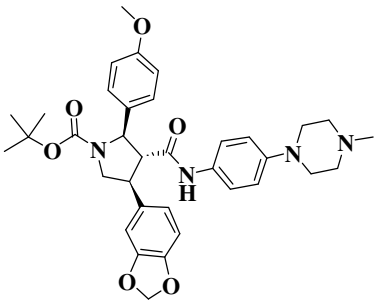
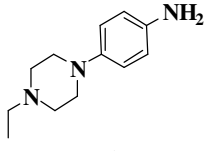
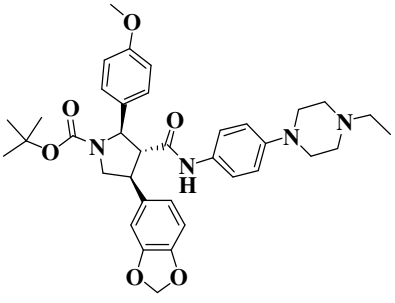
General amide coupling procedure with BOP reagent[12,13,17]: The appropriated Boc-protected carboxylic acid derivative (**13**) (1 eq) was added to a solution of the appropriated amines (**a[1]-g[1]**) (1.2 eq) in dry pyridine (0.2 mL/mg) followed by BOP reagent (1.2 eq) at 0 ºC. The reaction mixture was stirred for 12 h at room temperature and then reaction mixture poured into water. The precipitated solid was filtered, purified through silica gel column chromatography, eluted product with 5-7 % methanol/dichloromethane to afford carboxamides (**i-vii**) (*ca.* 21-51 % yield).

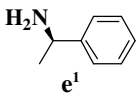
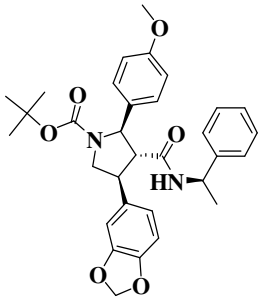
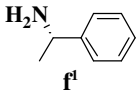
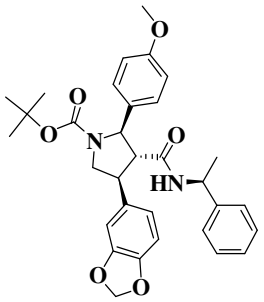
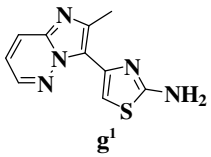
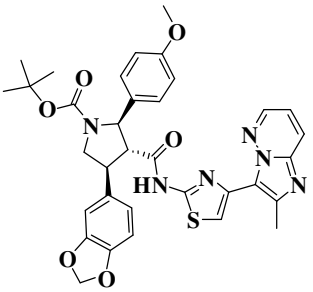
General amide coupling procedure with Mukaiyama reagent[14]: The appropriated Boc-protected carboxylic acid derivative (**13**) (1 eq) was added to a solution of the appropriated amines (**a[1]-g[1]**) (1.2 eq) in dry THF (0.2 mL/mg) followed by Mukaiyama reagent (1.2 eq) and triethyl amine (2 eq) at 0 ºC. The reaction mixture was stirred for 12 h at room temperature and then reaction mixture poured into water, product was extracted into 5 % methanol/dichloromethane, dried (anh. Na_2SO_4), concentrated under pressure. The residue was purified through silica gel column chromatography, eluted product with 5-7 % methanol/dichloromethane to afford carboxamides (**i-vii**) (*ca.* 20-48 % yield).

RESULTS AND DISCUSSION

All of the carboxamides (**i-vii**) in this report were synthesized by direct analogy of acid (**13**) coupled with amines (**a[1]-g[1]**) based on **Scheme-IV**.

(2R,3R,4S)-*tert*-Butyl-3-(2-(2*H*-tetrazol-5-yl)ethylcarbamoyl)-4-(benzo[d]-[1,3]dioxol-6-yl)-2-(4-methoxyphenyl)pyrrolidine-1-carboxylate (i): Pale white solid; ^{1}H NMR (200 MHz, DMSO-d_6)-rotamers 1.15 and 1.40 (brs, 9H), 2.7-2.9 (m, 4H), 3.4-3.5 (m, 2H), 3.7 (s, 3H), 3.98-4.1 (m, 1H), 4.61-4.78 (m, 1H), 5.99 (s, 2H), 6.62-6.8 (m, 2H), 6.82 (d, J = 9 Hz, 2H), 7.1 (d, J = 9 Hz, 2H), 7.9-8.1(m, 1H); M^+ (537).

R	HATU (Yield, %)	BOD (Yield, %)	Mukaiyama (Yield, %)	Product
 **a**[1]	60	51	48	 **(i)**
 **b**[1]	45	21	20	 **(ii)**
 **c**[1]	55	50	40	 **(iii)**
 **d**[1]	52	51	43	 **(iv)**

 **e**[1]	61	48	40	 **(v)**
 **f**[1]	58	50	42	 **(vi)**
 **g**[1]	60	41	32	 **(vii)**

(2R,3R,4S)-*tert*-Butyl 3-(2-aminophenylcarbamoyl)-4-(benzo[d][1,3]dioxol-6-yl)-2-(4-methoxyphenyl)pyrrolidine-1-carboxylate (ii): Pale white solid; ^{1}H NMR (200 MHz, DMSO-d_6)-rotamers 1.15 and 1.40 (brs, 9H), 3.4-3.5 (m, 2H), 3.7 (s, 3H), 3.98-4.1 (m, 1H), 4.4 (brs, 2H), 4.78-4.82 (1H), 5.99 (s, 2H), 6.42 (t, 1H), 6.6 (d, 1H), 6.81-6.97 (m, 4H), 7.1 (s, 1H), 7.2 (d, 2H) 8.99 (s, 1H); M^+ (532).

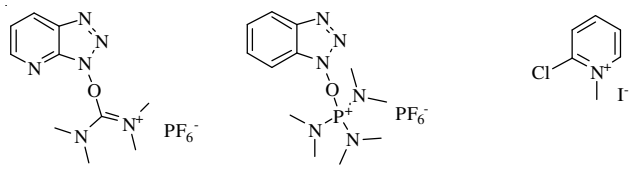
(2R,3R,4S)-*tert*-Butyl-3-(4-(4-methylpiperazin-1-yl)phenylcarbamoyl)-4-(benzo[d][1,3]dioxol-6-yl)-2-(4-methoxyphenyl)pyrrolidine-1-carboxylate (iii): Pale white solid; ^{1}H NMR (200 MHz, DMSO-d_6)-rotamers 1.15 and 1.40 (brs, 9H), 2.21 (s, 3H), 2.32-2.39 (m, 4H), 2.99-3.12 (m, 4H), 3.45-3.61 (m, 2H), 3.7 (s, 3H), 3.98-4.1(m, 1H), 4.78-4.82 (1H), 5.99 (s, 2H), 6.78- 6.88 (m, 6H), 7.01 (s, 1H), 7.15-7.25 (m, 4H), 9.45 (s, 1H); M^+ (615).

(2R,3R,4S)-*tert*-Butyl-3-(4-(4-ethylpiperazin-1-yl)phenylcarbamoyl)-4-(benzo[d][1,3]dioxol-6-yl)-2-(4-methoxyphenyl)pyrrolidine-1-carboxylate (iv): Pale white solid; ^{1}H NMR (200 MHz, DMSO-d_6)-rotamers 1.1 (t, 3H), 1.15 and 1.40 (brs, 9H), 2.21(s, 3H), 2.28 (q, 2H), 2.32-2.39 (m, 4H), 2.99-3.12 (m, 4H), 3.45-3.61 (m, 2H), 3.7 (s, 3H), 3.98-4.1 (m, 1H), 4.78-4.82 (1H), 5.99 (s, 2H), 6.78- 6.88 (m, 6H), 7.01 (s, 1H), 7.15-7.25 (m, 4H), 9.45 (s, 1H); M^+ (629).

(2R,3R,4S)-*tert*-Butyl 3-((R)-1-phenylethylcarbamoyl)-4-(benzo[d][1,3]-dioxol-6-yl)-2-(4-methoxyphenyl)pyrrolidine-1-carboxylate (v): Pale white solid; ^{1}H NMR (200 MHz, DMSO-d_6)-rotamers 1.15-1.40 (m, 12H), 2.92-3.12 (m, 1H), 3.45-3.61 (m, 2H), 3.78 (s, 3H), 3.98-4.1(m, 1H), 4.78-4.83 (m, 2H), 6.11 (s, 2H), 6.62-6.33 (m, 11H), 8.21(t, 1H); M^+ (545).

(2R,3R,4S)-*tert*-Butyl-3-((S)-1-phenylethylcarbamoyl)-4-(benzo[d][1,3]-dioxol-6-yl)-2-(4-methoxyphenyl)pyrrolidine-1-carboxylate (vi): Pale white solid; ^{1}H NMR (200 MHz, DMSO-d_6)-rotamers 1.15-1.40 (m, 12H), 2.92-3.12 (m, 1H), 3.45-3.61 (m, 2H), 3.78 (s, 3H), 3.98-4.1 (m, 1H), 4.78-4.83 (2m, H), 6.11 (s, 2H), 6.62-6.33 (m, 11H), 8.21 (t, 1H); M^+ (545).

(2R,3R,4S)-*tert*-Butyl-3-(4-(2-methylimidazo[1,2-b]pyridazin-3-yl)thiazol-2-ylcarbamoyl)-4-(benzo[d][1,3]dioxol-6-yl)-2-(4-methoxyphenyl)pyrrolidine-1-carboxylate (vii): ^{1}H NMR (200 MHz, DMSO-d_6): rotamers δ 1.06 and 1.36 (brs, 9H), 2.63 (s, 3H), 2.81-2.92 (m, 1H), 3.45 (m, 2H), 3.97-4.01 (m, 2H), 3.73 (s, 3H), 4.80-4.84 (m, 1H), 5.98 (2H), 6.79-6.88 (m, 3H), 7.01 (s, 1H), 7.20 (m, 3H), 7.99 (s, 1H), 8.04 (d, 1H), 8.59 (d, 1H), 12.05 (brs, 1H); M^+ (655).



HATU **BOP** **MUKAIYAMA REAGENT**

O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU) is aminium based coupling reagent given good yields (*ca.* 45-61 % yield) comparatively with phasphonium based (benzotriazol-1-yloxy)*tris*(dimethylamino)-phosphonium hexafluorophosphate (BOP) (*ca.* 21-51 % yield) and Mukaiyama reagent (2-chloro-1-methyl pyridinium iodide) (*ca.* 20- 48 % yield). Based on our work aminium based (HATU) coupling reagent better for good yield and we are not observed any epimerization product.

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REFERENCES

1. J.M. Domagal, S.E. Hagen, T. Joannides, J.S. Kiely, E. Laborde, M.C. Schroeder, J.A. Sesnie, M.A. Shapiro and M.J. Suto and S. Vanderroest, *J. Med. Chem.*, **36**, 871 (1993).
2. A. Ruck, S. Kramer, J. Metz and M.W. Brennan, *Nature*, **287**, 852 (1980).
3. D.J. Pedder, H.M. Fales, T. Jaouni, M. Blum and J. MacConnell, *Tetrahedron*, **32**, 19, 2275 (1976).
4. M.J. Blanco and F.J. Sardina, *Tetrahedron Lett.*, **35**, 8493 (1994).
5. J.W. Eckert, M.L. Rahm and M.J. Kolbezen, *J. Agric. Food Chem.*, **20**, 104 (1972).
6. M. Winn, T.W. von Geldern, T.J. Opgenorth, H.-S. Jae, A.S. Taskar, S.A. Boyd, J.A. Kester, R. Bal, B.K. Sorensen, R. Jinshyun, W.-Wong, W.J. Chiou, D.B. Dixon, E.I.L. Hernandez and K.C. Marsh, *J. Med. Chem.*, **39**, 1039 (1996).
7. T.W. von Geldern, A.S. Tasker, B.K. Sorensen, M. Winn, B.G. Szczepankiewicz, D.B. Dixon, W.J. Chiou, L. Wang, J.L. Wessale, A. Adler, K.C. Marsh, B. Nguyen and T.J. Opgenorth, *J. Med. Chem.*, **42**, 3668 (1999).
8. G. Liu, N.S. Kozmina, M. Winn, T.W. von Geldern, W.J. Chiou, D.B. Dixon, B. Nguyen, K.C. Marsh and T.J. Opgenorth, *J. Med. Chem.*, **42**, 3679 (1999).
9. S.J. Wittenberger and M.A. McLaughlin, *Tetrahedron Lett.*, **40**, 7175 (1999).
10. A.T. Londregan, G. Storer, C. Wooten, X. Yang and J. Warmus, *Tetrahedron Lett.*, **50**, 1986 (2009).
11. C.P. Balado and A.R. de Lera, *Org. Lett.*, **10**, 3701 (2008).
12. S. Kin and T. Lee, Bull. Korean Soc., 9, 189 (1998).
13. L.V. Dubey, I. Ya. Dubey, *Ukrain. Bioorgan. Acta*, **1**, 13 (2005).
14. S.-Y. Han and Y.-A. Kim, *Tetrahedron*, **60**, 2447 (2004).
15. D.T. Ross, H. Sauer, G.S. Hamilton and J.P. Steiner, Patent WO/2000/00910217 (2000).
16. L.S. Melvin Jr., M. Graupe and C. Venkataramani, Patent WO/2009/002534 (2008).
17. J.B. Thomas, R.N. Atkinson, N.A. Vinson, J.L. Catanzaro, C.L. Perretta, S.E. Fix, S.W. Mascarella, R.B. Rothman, H. Xu, C.M. Dersch, B.E. Cantrell, D.M. Zimmerman and F.I. Carroll, *J. Med. Chem.*, **46**, 3127 (2003).

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