A NEW ENTRY TO ANTIHYPERTENSIVE ACTIVE PHARMACEUTICAL INGREDIENT, IRBESARTAN AND ITS ANALOGUES

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DRL Pub. No. IPDO-IPM 00019

Abstract : A new synthesis of Irbesartan, an antihypertensive active pharmaceutical ingredient and its analogues is reported.

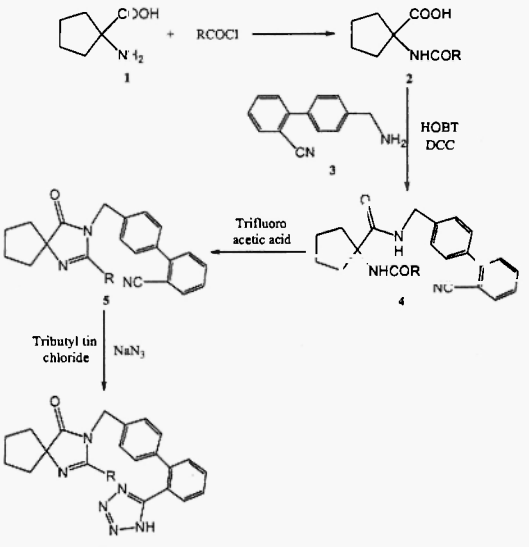
Introduction

Irbesartan, an antihypertensive drug, is one among the class of angiotensin receptor blockers. It functions as a specific and competitive angiotensin I receptor antagonist, thereby blocking the actions of endogenous ligand angiotensin II, [1-3] in turn preventing the increase in blood pressure. Earlier reported synthetic methods [4] of Irbesartan involved elaborate protection and deprotection procedures and column chromatography purifications, which made them less viable for scale up and large scale manufacturing. In continuation of our recently reported synthetic route [5] involving Suzuki coupling, herein we report a high yielding and scalable new synthetic route for the preparation of Irbesartan.

Discussion

Acylation of 1-amino-cyclopentanecarboxylic acid **1**[6] using pentanoyl chloride and subsequent dicyclohexyl carbodiimide (DCC) mediated condensation of the resulted 1-pentanoylamino-cyclopentanecarboxylic acid **2a** with 4'-aminomethyl-biphenyl-2-carbonitrile **3**[7] in dichloromethane in the presence of 1-hydroxybenzotriazole (HOBT) yielded 1-pentanoylamino-cyclopentanecarboxylic acid (2'-cyano-biphenyl-4-ylmethyl)-amide **4a**. Intramolecular dehydrocyclisation of **4a** in the presence of trifluoroacetic acid yielded the corresponding imidazole derivative **5a** as an exclusive product. The cyano group was further elaborated into a tetrazole moiety by reacting with sodium azide and tributyl tin chloride furnishing 2-butyl-3-[2'-(1*H*-tetrazol-5-yl)-biphenyl-4-ylmethyl]-1,3 diaza-spiro [4.4] non-1-en-4-one **(Irbesartan, 6a)** in 95 % yield. Compound **6a** was characterized based on its IR, ^{1}H-NMR, ^{13}C-NMR, Mass spectral data, elemental analysis and also by comparison with an authentic sample.

In order to verify the generality of this synthetic route, the synthetic sequence was extended to four other analogues of Irbesartan and in all the cases, corresponding 2-substituted 3-[2'-(1*H*-tetrazol-5-yl)-biphenyl-4-ylmethyl]-1,3 diaza-spiro [4.4] non-1-en-4-ones **6** were obtained as final products in quantitative yields.



Compounds 2, 4, 5, 6	a	b	c	d	e
R	C_4H_9	C_2H_5	C_3H_7	C_5H_{10}	C_6H_5

Scheme-1

Experimental Section

^{1}H NMR spectra were recorded on a Gemini 200-MHz FTNMR spectrometer, the chemical shifts were reported as δ values in ppm relative to TMS as an internal standard. The IR spectra were recorded in the solid state as KBr dispersion using Perkin Elmer FT-IR spectrophotometer. Mass spectra were recorded on Shimadzu LCMS-QP 8000, LC-MS and AB-4000 Q-trap LC-MS/MS. Melting points were determined on Polmon Model MP 96 capillary melting point apparatus and were uncorrected.

General procedure for the preparation of 1-acyl/benzoylamino-cyclopentanecarboxylic acid (2a-e)
1-Amino-cyclopentanecarboxylic acid (**1**, 50.0 g, 0.387 mol) was added to a solution of sodium hydroxide (61.9 g, 1.547 mol) in water (200 mL) at 0-10 ^{0}C and the solution was stirred for 10-15 minutes. To this reaction mixture, acyl chloride / benzoyl chloride (0.775 mol) in toluene (100 mL) was added slowly over a period of 60-90 minutes at 0-10 ^{0}C and was maintained for 2 hours. The reaction mass was quenched with water (250 mL). The organic layer and aqueous layers were separated and the aqueous layer was washed with toluene (50 mL). The aqueous layer pH was adjusted to 2.0-2.5 using HCl and stirred for 15-30 minutes at 25-35 ^{0}C. The isolated solid was filtered and washed with water (50 mL). To the wet compound, cyclohexane (500 mL) was added and stirred for 30-45 minutes at 25-35 ^{0}C. The solid was filtered, washed with cyclohexane (100 mL) and dried to a constant weight at 70-80 ^{0}C to yield 1-acyl/benzoylamino-cyclopentanecarboxylic acid **2a-e**.

1-Pentanoylamino-cyclopentanecarboxylic acid (2a)
White solid; yield: 82 %; mp: 177-178 ^{0}C.
IR (KBr, cm^{-1}): 3332.2 (NH), 1719.9 (C=O), 1699.1 (C=O).
^{1}H NMR (200 MHz, $CDCl_3$, δ ppm): 0.8-1.0 (t, 3H, CH_3), 1.3-1.4 (sext, 2H, CH_2), 1.5-1.7 (p, 2H, CH_2), 1.7-1.9 (m, 4H, CH_2), 1.9-2.0 (m, 4H, CH_2), 2.2-2.3 (t, 2H, CH_2).
MS (EI, 70 eV): m/z = 214 (M^+).
Anal. Calcd. for $C_{11}H_{19}NO_3$ (213.14): C, 61.95; H, 8.98; N, 6.57.
Found: C, 62.11; H, 8.92; N, 6.52.

1-Propionylamino-cyclopentanecarboxylic acid (2b)
White solid; Yield: 85 %; mp: 170-174 ^{0}C.
IR (KBr, cm^{-1}): 3363.2 (NH), 1727.2 (C=O), 1703.1 (C=O).
^{1}H NMR (200 MHz, $CDCl_3$, δ ppm): 1.0-1.2 (t, 3H, CH_3), 1.6-1.8 (m, 4H, CH_2), 1.9-2.1 (m, 4H, CH_2), 2.1-2.3 (q, 2H, CH_2).
MS (EI, 70 eV): m/z = 186 (M^+).
Anal. Calcd. for $C_9H_{15}NO_3$ (185.11): C, 58.36; H, 8.16; N, 7.56.
Found: C, 58.30; H, 8.19; N, 7.60.

1-Butyrylamino-cyclopentanecarboxylic acid (2c)
White solid; yield: 87 %; mp: 173-179 ^{0}C.
IR (KBr, cm^{-1}): 3337.2 (NH), 1715.6 (C=O), 1666.7 (C=O).
^{1}H NMR (200 MHz, $CDCl_3$, δ ppm): 0.8-1.0 (t, 3H, CH_3), 1.5-1.8 (m, 8H, CH_2), 1.9-2.1 (m, 2H, CH_2), 2.1-2.4 (m, 2H, CH_2).
MS (EI, 70 eV): m/z = 200 (M^+).
Anal. Calcd. for $C_{10}H_{17}NO_3$ (199.12): C, 60.28; H, 8.60; N, 7.03.
Found: C, 60.30; H, 8.55; N, 7.11.

1-Hexanoylamino-cyclopentanecarboxylic acid (2d)
White solid; yield: 84 %; mp: 172-176 ^{0}C.
IR (KBr, cm^{-1}): 3334.3 (NH), 1718.4 (C=O), 1698.6 (C=O).
^{1}H NMR (200 MHz, $CDCl_3$, δ ppm): 0.8-1.0 (t, 3H, CH_3), 1.2-1.4 (sext, 2H, CH_2), 1.4-1.7 (m, 2H, CH_2), 1.7-1.8 (m, 2H, CH_2), 1.8-2.0 (m, 8H, CH_2), 2.0-2.3 (t, 2H, CH_2).
MS (EI, 70 eV): m/z = 228 (M^+).
Anal. Calcd. for $C_{12}H_{21}NO_3$ (227.15): C, 63.41; H, 9.31; N, 6.16.
Found: C, 63.30; H, 9.25; N, 6.06.

1-Benzoylamino-cyclopentanecarboxylic acid (2e)
White solid; yield: 89 %; mp: 207-209 ^{0}C.
IR (KBr, cm^{-1}): 3296.8 (NH), 1704.9 (C=O), 1697.7 (C=O).
^{1}H NMR (200 MHz, $CDCl_3$, δ ppm): 1.7-2.0 (m, 4H, CH_2), 2.0-2.2 (m, 2H, CH_2), 2.2-2.4 (m, 2H, CH_2), 7.4-7.5 (m, 3H, Ar-H), 7.8-7.9 (m, 2H, Ar-H).
MS (EI, 70 eV): m/z = 234 (M^+).
Anal. Calcd. for $C_{13}H_{15}NO_3$ (233.11): C, 66.94; H, 6.48; N, 6.00.
Found: C, 66.99; H, 6.58; N, 5.92.

General procedure for the preparation of 1-acyl/benzoylamino-cyclopentanecarboxylic acid (2'-cyano- biphenyl-4-ylmethyl)-amide (4a-e)
To a solution of 4'-aminomethyl-biphenyl-2-carbonitrile (**3**, 50.0 g, 0.240 mol) in dichloromethane (750 mL), 1-acyl/benzoylamino-cyclopentanecarboxylic acid (**2**, 0.234 mol) and 1-hydroxybenzotriazole (5.7 g, 0.042 mol) were added and the reaction mass was stirred at 25-35 °C for 10-15 minutes. To the above mixture, dicyclohexyl carbodiimide (43.8 g, 0.212 mol) in dichloromethane (150 mL) was added slowly for 30-45 minutes and the reaction mass was maintained till reaction completion. The precipitated solid was filtered and washed with dichloromethane (100 mL). The organic layer was washed with saturated sodium bicarbonate solution (250 mL) followed by water (150 mL) and the organic layer was concentrated atmospherically below 50 ^{0}C to get the residue. To the residue, cyclohexane (250mL) was added and stirred for 45-60 minutes at 25-35 ^{0}C. The isolated compound was filtered, washed with cyclohexane (125 mL) and dried to a constant weight at 70-80 ^{0}C to yield 1-acyl/benzoylamino-cyclopentanecarboxylic acid (2'-cyano-biphenyl-4-ylmethyl)-amide **4a-e**.

1-Pentanoylamino-cyclopentanecarboxylic acid (2'-cyano-biphenyl-4-ylmethyl)-amide (4a)
White solid; yield: 96 %; mp: 147-149 ^{0}C.
IR (KBr, cm^{-1}): 3311.7 (NH), 3254.4 (NH), 2220.4 (CN), 1709.6 (C=O), 1650.3 (C=O).
^{1}H NMR (200 MHz, $CDCl_3$, δ ppm): 0.8-1.0 (t, 3H, CH_3), 1.2-1.4 (sext, 2H, CH_2), 1.5-2.0 (m, 10H, CH_2), 2.1-2.2 (t, 2H, CH_2), 4.4-4.6 (s, 2H,Ar- CH_2), 7.4-7.6 (m, 6H, Ar-H), 7.6-7.7 (t, 1H, Ar-H), 7.7-7.8 (d, 1H, Ar-H).
MS (EI, 70 eV): m/z = 404 (M^+).
Anal. Calcd. for $C_{25}H_{29}N_3O_2$ (403.23): C, 74.41; H, 7.24; N, 10.41.
Found: C, 74.31; H, 7.30; N, 10.30.

1-Propionylamino-cyclopentanecarboxylic acid (2'-cyano-biphenyl-4-ylmethyl)-amide (4b)
White solid; yield: 92 %; mp: 136-139 ^{0}C.
IR (KBr, cm^{-1}): 3341.1 (NH), 3279.2 (NH), 2222.1(CN), 1705.0 (C=O), 1646.8 (C=O).
^{1}H NMR (200 MHz, $CDCl_3$, δ ppm): 1.0-1.2 (t, 3H, CH_3), 1.6-2.1 (m, 8H, CH_2), 2.1-2.3 (q, 2H, CH_2), 4.4-4.6 (s, 2H, Ar-CH_2), 7.3-7.6 (m, 6H, Ar-H), 7.6-7.7 (t, 1H, Ar-H), 7.7-7.9 (s, 1H, Ar-H).
MS (EI, 70 eV): m/z = 376 (M^+).
IR (KBr, cm^{-1}): 3341.1 (NH), 3279.1 (NH), 2222.1(CN), 1646.8 (C=O).
Anal. Calcd. for $C_{23}H_{25}N_3O_2$ (375.19): C, 73.57; H, 6.71; N, 11.19.
Found: C, 73.47; H, 6.69; N, 11.08.

1-Butyrylamino-cyclopentanecarboxylic acid (2'-cyano-biphenyl-4-ylmethyl)-amide (4c)
Pale yellow solid; yield: 95 %; mp: 139-143 ^{0}C.
IR (KBr, cm^{-1}): 3311.7 (NH), 3294.5 (NH), 2224.4 (CN), 1699.1 (C=O), 1652.7 (C=O).
^{1}H NMR (200 MHz, $CDCl_3$, δ ppm): 0.8-1.0 (t, 3H, CH_3), 1.5-2.1 (m, 10H, CH_2), 2.1-2.3 (t, 2H, CH_2), 4.4-4.6 (s, 2H, Ar-CH_2), 7.3-7.8 (m, 8H, Ar-H).
MS (EI, 70 eV): m/z = 390 (M^+).
Anal. Calcd. for $C_{24}H_{27}N_3O_2$ (389.21): C, 74.01; H, 6.99; N, 10.79.
Found: C, 73.85; H, 7.05; N, 10.65.

1-Hexanoylamino-cyclopentanecarboxylic acid (2'-cyano-biphenyl-4-ylmethyl)-amide (4d)
White solid; yield: 90 %; mp: 164-166 ^{0}C.
IR (KBr, cm^{-1}): 3264.0 (NH), 3293.5 (NH), 2223.0 (CN), 1703.1 (C=O), 1654.8 (C=O).
^{1}H NMR (200 MHz, $CDCl_3$, δ ppm): 0.8-1.0 (t, 3H, CH_3), 1.2-1.4 (pent, 2H, CH_2), 1.5-2.1 (m, 12H, CH_2), 2.1-2.3 (t, 2H, CH_2), 4.4-4.6 (s, 2H, Ar-CH_2), 7.4-7.6 (m, 4H, Ar-H), 7.6-7.9 (m, 4H, Ar-H).
MS (EI, 70 eV): m/z = 418 (M^+).
Anal. Calcd. for $C_{26}H_{31}N_3O_2$ (417.24): C, 74.79; H, 7.48; N, 10.06.
Found: C, 74.68; H, 7.39; N, 10.11.

N-{1-[(2'-Cyano-biphenyl-4-ylmethyl)-carbamoyl]-cyclopentyl}-benzamide (4e)
White solid; yield: 88 %; mp: 172-175 ^{0}C.
IR (KBr, cm^{-1}): 3309.2 (NH), 3280.0 (NH), 2223.9 (CN), 1704.9 (C=O), 1652.3 (C=O).
^{1}H NMR (200 MHz, $CDCl_3$, δ ppm): 1.7-2.0 (m, 4H, CH_2), 2.1-2.3 (m, 2H, CH_2), 2.3-2.6 (m, 2H, CH_2), 4.5-4.7 (s, 2H, CH_2), 7.3-7.8 (m, 13H, Ar-H).
MS (EI, 70 eV): m/z = 424 (M^+).
Anal. Calcd. for $C_{27}H_{25}N_3O_2$ (423.19): C, 76.57; H, 5.95; N, 9.92.
Found: C, 76.49; H, 5.87; N, 9.81.

General procedure for the preparation of 4'-(2-alkyl/phenyl-4-oxo-1, 3 diaza-spiro [4.4] non-1-en-3-ylmethyl)-biphenyl-2-carbonitrile (5a-e)
A mixture of 1-acyl/benzoylamino cyclopentanecarboxylic acid (2'-cyano-biphenyl-4-ylmethyl)-amide (**4**, 0.124 mol), toluene (500 mL) and trifluoro acetic acid (21.2 g, 0.186 mol) was refluxed azeotropically till reaction completion. To the reaction mass water (150 mL) was added and stirred for 15-30 minutes at 25-35 ^{0}C. The organic and aqueous layers were separated. To the organic layer, 30 % hydrochloric acid (78 mL) in water (290 mL) was added slowly and stirred for 1-2 hours at 25-35 ^{0}C. The reaction mass was further cooled to 0-5 ^{0}C and stirred for 1-2 hours. The isolated salt was filtered and washed with toluene (50 mL). The wet product was added to a solution of ammonia (20.6 mL) in water (250 mL) and stirred for 10-15 minutes at 25-35 ^{0}C. To the reaction mass, toluene (150 mL) was added and stirred for 30-45 minutes. The organic and aqueous layers were separated. The organic layer was washed with water (50 mL) and concentrated under reduced pressure at 50-60 ^{0}C. The residue was cooled to 25-35 ^{0}C, cyclohexane (100 mL) was added, further cooled to 0-5 ^{0}C and stirred for solid isolation. The isolated solid was filtered, washed with cyclohexane (25 mL) and dried to a constant weight to yield 4'-(2-alkyl/phenyl-4-oxo-1,3 diaza spiro [4.4] non-1-en-3-ylmethyl)-biphenyl-2-carbonitrile **5a-e**.

4'-(2-Butyl-4-oxo-1,3 diaza-spiro [4.4] non-1-en-3-ylmethyl)-biphenyl-2-carbonitrile (5a)
White solid; yield: 81 %; mp: 92-95 ^{0}C.
IR (KBr, cm^{-1}): 2225.2 (CN), 1765.3 (C=O).
^{1}H NMR (200 MHz, $CDCl_3$, δ ppm): 0.8-1.0 (t, 3H, CH_3), 1.2-1.5 (sext, 2H, CH_2), 1.5-1.7 (m, 2H, CH_2), 1.7-2.2 (m, 8H, CH_2), 2.3-2.5 (t, 2H, CH_2), 4.7-4.9 (s, 2H, Ar-CH_2), 7.2-7.8 (m, 8H, Ar-H).
MS (EI, 70 eV): m/z = 386 (M^+).
Anal. Calcd. for $C_{25}H_{27}N_3O$ (385.22): C, 77.89; H, 7.06; N, 10.90.
Found: C, 77.92; H, 7.10; N, 10.95.

4'-(2-Ethyl-4-oxo-1,3 diaza-spiro [4.4] non-1-en-3-ylmethyl)-biphenyl-2-carbonitrile (5b)
White powder; yield: 78 %; mp: 90-95 ^{0}C.
IR (KBr, cm^{-1}): 2221.2 (CN), 1719.7 (C=O).
^{1}H NMR (200 MHz, $CDCl_3$, δ ppm): 1.1-1.3 (t, 3H, CH_3), 1.6-2.1 (m, 8H, CH_2), 2.3-2.5 (q, 2H, CH_2), 4.7-4.8 (s, 2H, Ar-H), 7.2-7.4 (m, 2H, Ar-H), 7.4-7.6 (m, 4H, Ar-H), 7.6-7.7 (t, 1H, Ar-H), 7.7-7.8 (d, 1H, Ar-H).
MS (EI, 70 eV): m/z =358 (M^+).
Anal. Calcd. for $C_{23}H_{23}N_3O$ (357.18): C, 77.28; H, 6.49; N, 11.76.
Found: C, 77.18; H, 6.37; N, 11.64.

4'-(2-Propyl-4-oxo-1,3 diaza-spiro [4.4] non-1-en-3-ylmethyl)-biphenyl-2-carbonitrile (5c)
White powder; yield: 75 %; mp: 92-98 ^{0}C.
IR (KBr, cm^{-1}): 2222.7 (CN), 1724.6 (C=O).
^{1}H NMR (200 MHz, $CDCl_3$, δ ppm): 0.8-1.0 (t, 3H, CH_3), 1.6-2.2 (m, 10H, CH_2), 2.3-2.5 (t, 2H, CH_2), 4.7-4.9 (s, 2H, Ar-CH_2), 7.2-7.3 (s, 2H, Ar-H), 7.3-7.4 (s, 2H, Ar-H), 7.4-7.7 (m, 3H, Ar-H), 7.7-7.9 (d, 1H, Ar-H).
MS (EI, 70 eV): m/z = 372 (M^+).
Anal. Calcd. for $C_{24}H_{25}N_3O$ (371.2): C, 77.60; H, 6.78; N, 11.31.
Found: C, 77.50; H, 6.81; N, 11.21.

4'-(2-Pentyl-4-oxo-1,3 diaza-spiro [4.4] non-1-en-3-ylmethyl)-biphenyl-2-carbonitrile (5d)
White solid; yield: 79 %; mp: 88-93 ^{0}C.
IR (KBr, cm^{-1}): 2224.7 (CN), 1724.0 (C=O).
^{1}H NMR (200 MHz, $CDCl_3$, δ ppm): 0.8-1.0 (t, 3H, CH_3), 1.2-1.4 (m, 2H, CH_2), 1.4-1.6 (m, 2H, CH_2), 1.7-2.1 (m, 10H, CH_2), 2.2-2.4 (t, 2H, CH_2), 4.8-5.0 (s, 2H, Ar-CH_2), 7.2-7.3 (s, 1H, Ar-H), 7.3-7.4 (d, 1H, Ar-H), 7.4-7.9 (m, 6H, Ar-H).
MS (EI, 70 eV): m/z = 400 (M^+).
Anal. Calcd. for $C_{26}H_{29}N_3O$ (399.23): C, 78.16; H, 7.32; N, 10.52.
Found: C, 78.10; H, 7.28; N, 10.43.

4'-(4'-Oxo-2-phenyl-1,3-diaza-spiro [4.4] non-1-en-3-ylmethyl)-biphenyl-2-carbonitrile (5e)
White powder; yield: 71 %; mp: 139-143 ^{0}C.
IR (KBr, cm^{-1}): 2224.7 (CN), 1698.6 (C=O).
^{1}H NMR (200 MHz, $CDCl_3$, δ ppm): 1.9-2.3 (m, 8H, CH_2), 4.7-4.9 (s, 2H, CH_2), 7.0-7.1 (s, 1H, Ar-H), 7.1-7.2 (s, 1H, Ar-H), 7.3-7.5 (m, 8H, Ar-H), 7.6-7.8 (m, 3H, Ar-H).
MS (EI, 70 eV): m/z = 406 (M^+).
Anal. Calcd. for $C_{27}H_{23}N_3O$ (405.18): C, 79.97; H, 5.72; N, 10.36.
Found: C, 79.87; H, 5.68; N, 10.29.

General procedure for the preparation of 2-alkyl/phenyl-3-[2'-(1*H*-tetrazol-5-yl)-biphenyl-4-ylmethyl]-1,3-diaza-spiro [4.4] non-1-en-4-one (6a-e)
A mixture of 4'-(2-alkyl/phenyl-4-oxo-1,3 diaza-spiro [4.4] non-1-en-3-yl methyl)-biphenyl-2-carbonitrile (5, 0.129 mol), o-xylene (50 mL), tributyl tin chloride (62.9 g, 0.193 mol) and sodium azide (12.65 g, 0.193) was refluxed till reaction completion. To the reaction mass at 25-35 ^{0}C, acetone (400 mL) and water (500 mL) were added and stirred. pH of the reaction mass was adjusted to 4.0-4.5 using acetic acid. To this solution cyclohexane (500 mL) was added and stirred for solid isolation. The isolated solid was filtered, washed with cyclohexane (150 mL) and dried to a constant weight at 80-90 ^{0}C to yield 2-alkyl/phenyl-3-[2'-(1*H*-tetrazol-5-yl)-biphenyl-4-ylmethyl]-1,3-diaza-spiro [4.4] non-1-en-4-one **6a-e**.

2-Butyl-3-[2'-(1*H*-tetrazol-5-yl)-biphenyl-4-yl-methyl]-1,3-diaza-spiro [4.4] non-1-en-4-one (6a)
White powder; yield: 95 %; mp: 180-183 ^{0}C.
IR (KBr, cm^{-1}): 3441.7 (NH), 1732.9 (C=O).
^{1}H NMR (200 MHz, $CDCl_3$, δ ppm): 0.7-0.9 (t, 3H, CH_3), 1.2-1.4 (sextet, 2H, CH_2), 1.4-1.6 (quintet, 2H, CH_2), 1.6-2.0 (m, 8H, CH_2), 2.2-2.4 (t, 2H, CH_2), 3.2-3.6 (br, 1H, N-H), 4.6-4.8 (s, 2H, Ar-CH_2), 7.5-7.8 (m, 8H, Ar-H).
^{13}C NMR (200 MHz, $CDCl_3$, δ ppm): 185.6, 161.1, 155.0, 141.0, 138.4, 136.3, 131.0, 130.5, 129.2, 127.7, 126.2, 123.5, 75.8, 42.2, 40.3, 39.9, 39.5, 39.0, 38.7, 36.8, 27.5, 26.6, 25.4, 21.5, 13.6.
MS (EI, 70 eV): m/z = 429 (M^+).
Anal. Calcd. for $C_{25}H_{28}N_6O$ (428.23): C, 70.07; H, 6.59; N, 19.61.
Found: C, 70.17; H, 6.49; N, 19.62.

2-Ethyl-3-[2'-(1*H*-tetrazol-5-yl)-biphenyl-4-ylmethyl]-1,3-diaza-spiro [4.4] non-1-en-4-one (6b)
White powder; yield: 94 %; mp: 192-197 ^{0}C.
IR (KBr, cm^{-1}): 3451.1 (N-H), 1737.5 (C=O).
^{1}H NMR (200 MHz, $CDCl_3$, δ ppm): 1.0-1.1 (t, 3H, CH_3), 1.3-1.9 (m, 8H, CH_2), 2.2-2.4 (q, 2H, CH_2); 3.5-3.9 (br, 1H, N-H), 4.6-4.8 (s, 2H, Ar-CH_2), 7.0-7.1 (d, 2H, Ar-H), 7.1-7.2 (d, 2H, Ar-H), 7.4-7.5 (d, 1H, Ar-H), 7.5-7.7 (m, 2H, Ar-H), 7.9-8.0 (d, 1H, Ar-H).
^{13}C NMR (200 MHz, $CDCl_3$, δ ppm): 185.7, 164.3, 156.4, 140.8, 139.2, 135.2, 130.5, 129.5, 127.7, 126.4, 123.8, 122.1, 77.6, 77.0, 76.4, 75.8, 42.9, 37.1, 26.6, 25.8, 22.0, 13.4, 9.4.
MS (EI, 70 eV): m/z = 401 (M^+).
Anal. Calcd. for $C_{23}H_{24}N_6O$ (400.20): C, 68.98; H, 6.04; N, 20.99.
Found: C, 69.05; H, 6.10; N, 21.12.

2-Propyl-3-[2'-(1*H*-tetrazol-5-yl)-biphenyl-4-ylmethyl]-1,3-diaza-spiro [4.4] non-1-en-4-one (6c)
White solid; yield: 92 %; mp: 190-194 ^{0}C.
IR (KBr, cm^{-1}): 3450.6 (NH); 1733.7 (C=O).
^{1}H NMR (200 MHz, $CDCl_3$, δ ppm): 0.8-1.0 (t, 3H, CH_3), 1.4-1.6 (m, 2H, CH_2), 1.6-2.0 (m, 8H, CH_2), 2.0-2.2 (t, 2H, CH_2), 3.2-3.6 (br, 1H, N-H), 4.5-4.7 (s, 2H, Ar-CH_2), 7.0-7.3 (m, 4H, Ar-H), 7.4-7.7 (m, 3H, Ar-H), 7.8-8.0 (d, 1H, Ar-H).
^{13}C NMR (200 MHz, $CDCl_3$, δ ppm): 186.26, 162.51, 155.25, 140.82, 138.65, 135.25, 130.80, 129.24, 127.56, 126.26, 122.77, 77.63, 77.00, 76.35, 75.92, 42.91, 36.98, 30.18, 29.85, 25.61, 24.34, 18.50, 18.44, 12.93.
MS (EI, 70 eV): m/z = 415 (M^+).
Anal. Calcd. for $C_{24}H_{26}N_6O$ (414.22): C, 69.54; H, 6.22; N, 20.27.
Found: C, 69.65; H, 6.42; N, 20.35.

2-Pentyl-3-[2'-(1*H*-tetrazol-5-yl)-biphenyl-4-yl methyl]-1,3-diaza-spiro [4.4] non-1-en-4-one (6d)
White solid; yield: 90 %; mp: 189-192 ^{0}C.
IR (KBr, cm^{-1}): 3449.9 (N-H), 1733.4 (C=O).
^{1}H NMR (200 MHz, $CDCl_3$, δ ppm): 0.8-1.0 (t, 3H, CH_3), 1.2-1.4 (m, 2H, CH_2), 1.5-1.7 (m, 2H, CH_2), 1.7-2.2 (m, 10H, CH_2), 2.2-2.4 (t, 2H, CH_2), 3.0-3.6 (br, 1H, N-H), 4.6-4.8 (s, 2H, Ar-CH_2), 7.0-7.2 (m, 3H, Ar-H), 7.3-7.7 (m, 4H, Ar-H), 7.7-7.8 (d, 1H, Ar-H).
^{13}C NMR (200 MHz, $CDCl_3$, δ ppm): 186.1, 162.8, 155.2, 140.8, 138.6, 135.2, 130.7, 130.3, 130.1, 129.2, 127.5, 126.2, 122.7, 77.6, 77.0, 76.4, 75.8, 42.9, 36.9, 30.6, 28.3, 25.5, 24.7, 24.6, 21.7, 13.2.
MS (EI, 70 eV): m/z = 443 (M^+).
Anal. Calcd. for $C_{26}H_{30}N_6O$ (442.25): C, 70.56; H, 6.83; N, 18.99.
Found: C, 70.62; H, 6.72; N, 19.0.

2-Phenyl-3-[2'-(1*H*-tetrazol-5-yl)-biphenyl-4-ylmethyl]-1,3-diaza-spiro [4.4] non-1-en-4-one (6e)
White solid; yield: 88 %; mp: 243-245 ^{0}C.
IR (KBr, cm^{-1}): 3473.2 (NH); 1746.9 (C=O).
^{1}H NMR (200 MHz, $CDCl_3$, δ ppm): 1.9-2.2 (m, 8H, CH_3), 3.3-3.6 (br, 1H, N-H), 4.7-4.8 (s, 2H, Ar-CH_2), 6.9-7.0 (s, 2H, Ar-H), 7.0-7.1 (s, 2H, Ar-H), 7.3-7.6 (m, 7H, Ar-H), 7.6-7.7 (t, 1H, Ar-H), 7.7-7.9 (d, 1H, Ar-H).
^{13}C NMR (200 MHz, $CDCl_3$, δ ppm): 187.6, 163.3, 142.3, 139.6, 136.8, 132.0, 131.4, 131.2, 130.1, 129.9, 129.6, 128.8, 128.7, 127.7, 123.8, 79.2, 75.5, 77.9, 49.9, 49.4, 49.0, 48.6, 48.2, 45.2, 38.3, 26.7, 25.1.
MS (EI, 70 eV): m/z = 449 (M^+).
Anal. Calcd. for $C_{27}H_{24}N_6O$ (448.20): C, 72.30; H, 5.39; N, 18.74.
Found: C, 72.20; H, 5.40; N, 18.80.

Conclusions

A new, simple and industrially scalable synthetic route for the preparation of Irbesartan and its analogues has been provided.

Acknowledgements

The authors wish to thank the management of Dr. Reddy's Laboratories Ltd., Bulk Actives Unit IV for supporting this work.

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Received on February 14, 2006