AN EFFICIENT SYNTHETIC METHOD FOR THE SYNTHESIS OF NOVEL CHIRAL ANALOGOUS OF CILAZAPRIL AND CCKA ANTAGONISTS

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An efficient synthetic method for the synthesis of novel chiral cilazapril and analogous of CCKA_antagonists is desciribed. The reactions proceed *via* acidic deprotection of *tert*-butyl -9 (S)-phthalimido octahydro-6, 10-dioxo- -6H-pyridazo[1,2-a] [1,2] diazepine-1(S)-carboxylate, without isolation, which then coupled with 1-methyl-3-amino-1,3-dihydro-5-phenyl-(2H)-1,4-benzodiazepine-2-one and allylamine using diethyl phosphorocyanidate as a coupling reagent afforded novel peptidomimetics in excellent yield. This sequence of reactions provided a simple four-reaction sequence and efficient synthesis of novel peptidomimetics.

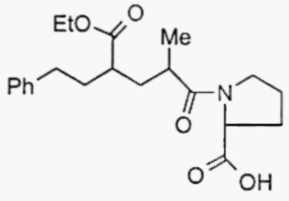
Keywords: Cilazapril, A.C.E inhibitors, cholecystokinin, benzodiazepine

Introduction

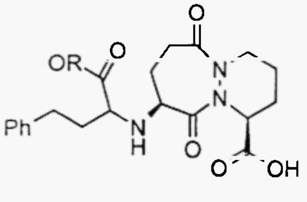
Recently interest has turned to peptide molecules which can be as active and more stable than natural peptide[1] that are expected to have same therapeutic effects as natural peptide counterparts, with the added advantage of metabolic stability[2]. Angiotensin Converting Enzyme (A.C.E.) inhibitors such as enalapril **(1)** and cilazapril **(2)** are effective in the treatment of essential hypertension[3]. A.C.E (E.C. 3.4.15.1) has assumed increasing importance in the therapy of hypertension of congestive heart failure[4]. Cilazapril **(2)**[3,5,6] is one of the most potent of the new generation of antihypertensive drugs. It is an inert prodrug with a high degree of oral bioavaibility and is the monoethyl ester prodrug form of a potent, specific, long-acting antihypertensive inhibitor of Angiotensin Converting Enzyme (A.C.E.). The biochemical and pharmacological properties of this compound has been found most potent and longest - acting compared with those of parent drug enalaptril **(1)**[5]. The dicarboxylic acid (**2**, R=H) is an active A.C.E. inhibitor. The corresponding mono ester (**2**, R=Et, cilazapril) is used for *in vivo* inhibition of A.C.E. This prodrug has better biological characteristics as an antihypertensive in mammals than the corresponding dicarboxylic acid which is formed from cilazapril *in vivo* as a result of the action of esterases.[6]

A substantial amount of novel chemistry[7-9], mainly targeted at the A.C.E inhibitors, has been developed from the parent 9-aminopyrdazino diazepine and t-butyl-9-amino-octahydro-6,10-dioxo-6H-pyridazino[1,2-a] [1,2] diazepine-1-carboxylate and related bicyclic compounds.[6,10]

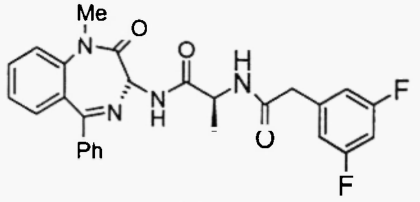
Benzodiazepines have been known to posses important medicinal properties for the last several years. Some benzodiazepines derivatives **(3,4)** have been found to be potent antagonist of the peptide hormones cholecystokinin (CCK) and gastrin.[11-14] The 1,4-benzodiazepines have constitutes a class of widely used anxiolytic and anticonvulsant drug.[15] Recently some amino and succinoylamino benzodiazepines such as **(3)** have been useful in treatment of neurologic disorders related to β-amyloid production such as Alzheimer's disease and Down's Syndrome[16].



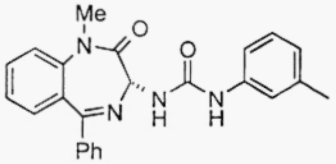
(1)



(2) R = H and Et



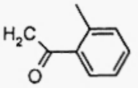
(3)



(4)

R = Me **L-365,260**

R =

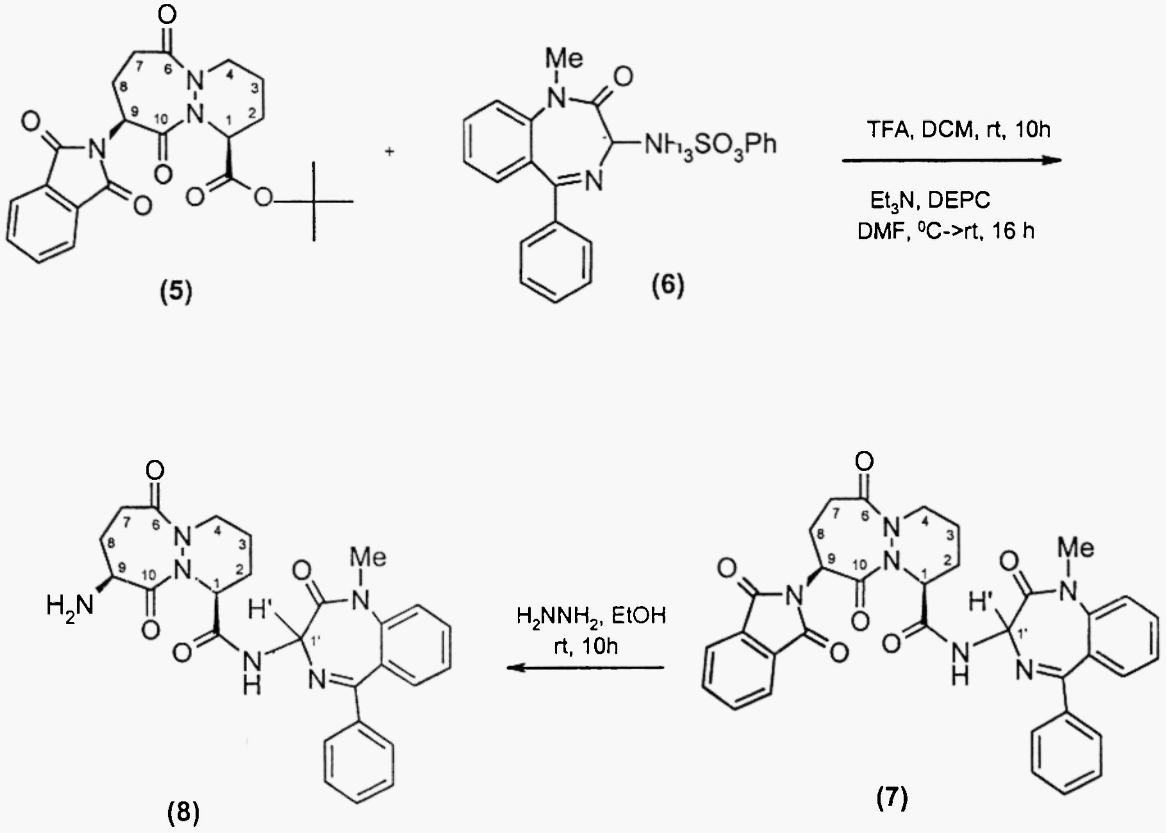


YMO22

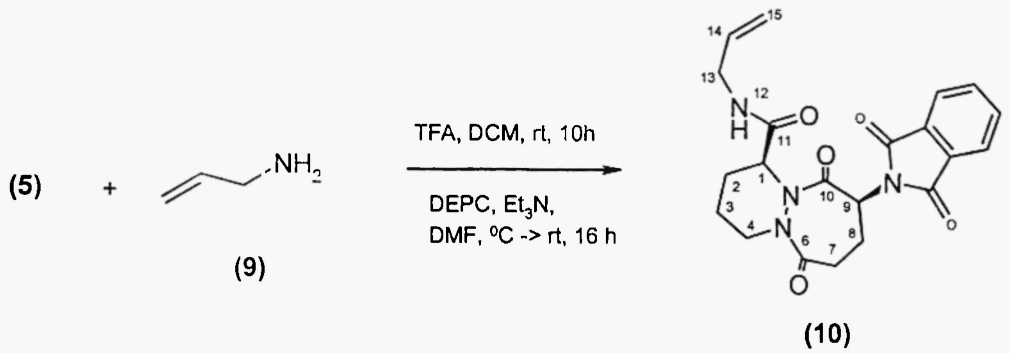
We have previously shown that amines of 1,4-benzodiazepine[17,18] and 9-aminopyrdazino diazepine[20,21] react with aldehydes to generate imines which then gave azomethine ylides *via* thermal and metal catalysed processes. 1,3-Dipolar cycloaddition reactions of which with chiral and achiral dipolarophiles afforded cycloadduct in good to excellent yield.[17-22] Thus imine - azomethine ylide - cycloaddition cascade chemistry has provided a series of spirobenzodiazepines related to MK-329[17-19] and spirocilazapril analogues[20-22] and potentially offers a facile route conformationally restricted analogues of **(2-4)**[17-22].

Results and Discussion: We now report a study of efficient synthetic method for the synthesis of novel chiral cilazapril and analogous of CCKA antagonists. The reaction proceeds *via* coupling reaction of tert-butyl-octahydro-6, 10-dioxo-9 (S)-phthalimido-6H-pyridazo[1,2-a] [1,2] diazepine-1(S)-carboxylate **(5)** with *p*-toluene sulphonic acid salt of 1-methyl-3-amino-1,3-dihidro-5-phenyl-(2H)-1,4-benzodiazepine-2-one **(6)** and allyl amine. This substrate allows the influence of the new stereocentre on the cascade to be assessed with respect to the configuration of (6). Thus reaction of **(5)** with **(6)** afforded compound **(7)** which then gave **(8)** *via* hyrazinolysis. The reactions proceed *via* acidic deprotection of *tert*-butyl moiety of (5) employing

TFA(DCM, rt, 10h)) under an argon atmosphere afforded 9 (S)-phthalimido octahydro-6, 10-dioxo- -6H-pyridazo[1,2-a] [1,2] diazepine-1(S)-carboxylic acid. Without isolation, the acid was coupled with 1-methyl-3-amino-1,3-dihidro-5-phenyl-(2H)-1,4-benzodiazepine-2-one using diethyl phosphorocyanidate (DEPC) as a coupling reagent in anhydrous DMF at 0 °C for 30 min and room temperature for 16h gave **(7)**. The free amine **(8)** of that was liberated from its phthalimido **(7)** by treatment with hydrazine hydrate and trituration - filtration. The chiral compound **(8)** were obtained in 95% yield as a 1:1 mixture of diastereoisomer. The reaction proceeds under mild condition in excellent yield. This sequence of reactions provided a simple four – reaction sequence and efficient synthesis of novel peptide molecules. In a similar manner as outlined in scheme 2 an example of N-allyl substituted cilazapril analogous **(10)** were obtained from **(5)** in the presence of allylamine in 89% yield as a single stereoisomer. The structure of **(7-10)** were assigned on the basis of ^{1}H and ^{13}C NMR spectra, ^{2}D COSY, DEPT and HETCOR studies (see experimental) and conforms to that previous studies.[17-22]



Scheme 1



Scheme 2

In conclusion, an efficient method for the synthesis of novel chiral cilazapril and cholecystokinin analogues have been developed *via* a simple four-reaction sequence in one-pot reaction. Similar methodology should provide a general route to other biologically important cilazapril and benzodiazepine analogues.

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Experimental

Microanalyses were obtained using a Carlo - Erba Model 1106 instrument. Mass spectra were recorded at 70 ev on a VG Autospec mass spectrometer. Melting points were determined on a Kofler hot stage apparatus and are uncorrected. Nuclear magnetic resonance spectra and decoupling experiments were determined at 250 MHz. on a Q.E 250 instrument and at 500 MHz on a Bruker AM500 spectrometer as specified. Chemical shifts are given in parts per million (δ) downfield from tetramethylsilane as internal standard. Spectra were determined in deuteriochloroform except where otherwise stated. The following abbreviations are used; s= singlet, d= doublet, t= triplet, q= quartet, m= multiplet, br= broad and brs= broad singlet. Flash column chromatography was performed using silica gel 60 (230-400 mesh). Kieselgel columns were packed with silica gel GF_{254} (Merck 7730). Petroleum ether refers the fraction with b.p 40-60 °C unless otherwise specified. Optical rotations were determined on an Optical Activity Ltd., AA1000 polarimeter. TFA were purchased from Aldrich and used as received.

Compound 7. To a solution of (5) (0.25g, 0.583 mmol) in dichloromethane (DCM) (20 ml) in 50 ml round-bottom flask flushed with argon was added TFA (2.25 ml). The mixture was stirred for 10h, the solvents were removed under reduced pressure, TFA was azeotropically removed with benzene and the resulting residue was dried in *vacuo*. To a suspension of the residue and salt of (6) (0.382 g, 0.874 mmol) in 4 ml of dimethylformamide(DMF) was added to a solution of diethyl phosphorocyanidate (DEPC) (0.104g, 0.641 mmol) in 4 ml of DMF and Et_3N (0.294g, 2.91 mmol) in 4 ml of DMF. After the mixture were stirred at 0 °C for 30 min and room temperature for 16 h, the solvent was removed *in vacuo*. Purification by colum chromatography 1% MeOH/DCM gave pale pink amorphous solid. mp 172-174 °C. $[\alpha]_D$= -98.3 (c, 0.1, EtOH). HRMS (ES): Found 641.2115, $C_{34}H_{30}N_6O_6Na$ requires: 641.2125. *m/z* (%) (FAB): 6.19 (M+1, 100), 298 (15), 249 (13), 221 (28), 186 (25). δ_H (500 MHz, $CDCl_3$): 7.86 (m, 2H, ArH), 7.84 (m, 2H, ArH), 7.72-7.62 (m, 3H, ArH and NH), 7.59-7.28 (m, 7H, ArH), 5.52-5.50 (m, 2H, 1-H and 1'-H), 5.33 (m, 1H, 9-H), 4.70 (m, 1H, 4β), 3.66 (m, 1H, 7β), 3.47 (s, 3H, NMe), 3.40 (m, 1H, 8α), 3.0 (m, 1H, 4α), 2.48-2.31 (m, 3H, 7α, 8β, 2α), 2.04-1.96 (m, 2H, 2β and 3α), 1.78 (m, 1H, 3β).

Compound 8 was obtained (95%) as a 1:1 mixture of diastereoisomer pale yellow prism, mp 128-131 °C. $[\alpha]_D$= -102.2 (c, 0.1, EtOH). HRMS (ES): Found 511.2047, $C_{26}H_{28}N_6O_6Na$ requires: 511.2070. *m/z* (%)(FAB): 489 (M+1, 100), 311 (12), 266 (15), 249 (25), 221 (58), 168 (24), 149 (18). Found: C, 56.3; H, 5.85; N, 15.55; $C_{26}H_{28}N_6O_4$. $4H_2O$ required: C, 55.7; H, 6.40; N, 15.0%. δ(250 MHz, $CDCl_3$): 7.89 (br, 1H, CONH), 7.58-7.55 (m, 2H, ArH), 7.52-7.25 (m, 7H, ArH), 5.42-5.30 (m, 2H, 1-H and 1'-H), 4.58 (m, 1H, 4β), 3.81 (m, 1H, 7β), 3.79 (m, 1H, 8α), 3.51 (br, 2H, NH_2), 3.46 and 3.44 (2xs, 3H, N-Me isomer), 2.94 (m, 1H, 4α), 2.50 (m, 1H, 7α), 2.25-2.20 (m, 2H, 8β and 2α), 2.10-1.77 (m, 4H, 2β, 3α, 3β, 9α).

Compound (10). To a solution of (5) (0.25 g, 0.583 mmol) in dichloromethane (DCM) (15 ml) in 50 ml round-bottom flask flushed with argon was added TFA (4.5 ml). The mixture was stirred for 10 h, the solvent were removed under reduced pressure. TFA was azeotropically removed with benzene and the resulting residue dried at 70 °C in vacue. To a suspension of the residue and allyl amine (**9**) (0.033 g, 1 eq) in 3 ml of DMF was added a solution of DEPC (diethyl phosphorocyanidate) (0.104 g, 0.641 mmol) in 3 ml DMF and Et_3N (0.07 g, 1.2 eq) in 3 ml of DMF. After the mixture were stirred at 0 °C for 30 min and room temperature for 6 h, the solvent was removed in *vacuo*. Purification by column chromatography 1% MeOH/DCM gave colourless prisms in 89% yield. mp 179-181 °C. $[\alpha]_D$= -90.3 (c, 0.1, EtOH). Found: C, 61.35; H, 5.5; N, 13.45; $C_{21}H_{22}N_4O_5$ required: C, 61.45; H, 5.35; N, 13.65 %. *m/z* (%) (ES): 433 (M^++Na, 100). *m/z* (%) (EI): 411 (M^++1, 20), 355 (50), 326 (75), 298 (98), 186 (100), 104 (27) and 85 (57). δ_H(500 MHz, $CDCl_3$) 7.90-7.84 (m, 2H, Ar-H), 7.86-7.84 (m, 2H, Ar-H), 6.0 (br, 1H, NH), 5.83 (m, 1H, CH=CH_2), 5.26 (t, 1H, 1-CHCONH), 5.16-5.13 (m, 2H, 15-CH_2) 5.10 (m, 1H, 9-CHN), 4.67 (m, 1H, 4-$CH_{2\alpha}$), 3.95-3.90 (m, 2H, CH_2NH), 3.50 (m, 1H, 2-CH_2), 3.20 (m, 1H, 7-CH_2), 3.02 (m, 1H, 4-$CH_{2\beta}$), 2.60 (m, 1H, 2'-CH_2), 2.56 (m, 1H, 7'-CH_2), 2.11 (m, 1H, 8-CH_2), 2.05 (m, 1H, 3-CH_2), 1.98 (m, 1H, 8'-CH_2), 1.88 (m, 1H, 3'-CH_2). δ_C (500 MHz, $CDCl_3$): 19.17 (CH_2), 24.49 (CH_2), 26.33 (CH_2), 30.38 (CH_2), 41.95 (CH_2), 42.03 (CH_2), 42.90 (CH), 53.08 (CH), 117.09 (CH), 123.59 (2C, CH), 133.43 (CH), 134.33 (2C, CH), 167.96 (2C, q), 168.42 (2C, q), 168.57 (q), 172.0 (2C, q).

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