An Efficient Synthesis of α-Amino-δ-valerolactones by the Ugi Five-Center Three-Component Reaction†

Young Bae Kim,‡ Soo Jung Park, Gyochang Keum, Min Seok Jang, Soon Bang Kang, Duck Hyung Lee,‡ and Youseung Kim*

Biochemicals Research Center, Korea Institute of Science and Technology, P.O. Box 131, Cheongryang, Seoul 130-650, Korea
‡Department of Chemistry, Sogang University, Seoul 121-742, Korea
Received March 27, 2002

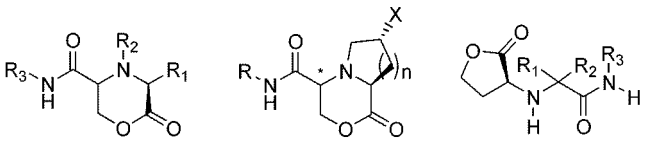
A novel approach to α-amino-δ-valerolactone derivatives **8** by the intramolecular Ugi five-center three-component reaction (U-5C-3CR) using the multifunctional starting material, L-pentahomoserine **5** is described.

Key Words : Multicomponent reactions, Combinatorial chemistry, Ugi reaction, L-Pentahomoserine, Glycolaldehyde dimer

Introduction

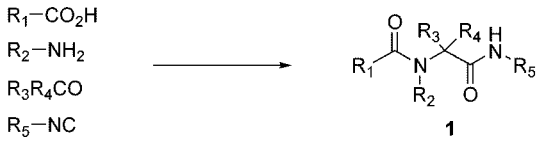
Multicomponent reactions (MCRs) are reactions of three or more reactants combine in a one-pot procedure to produce a single product, which contains at least a part of every reactant. The product is formed by several individual reactions, which occur simultaneously or sequentially in a single reaction step without the intermediates being isolated.[1] MCRs, by virtue of their synthetic potential, their easy performance, and the generation of molecular diversity, have attracted much attention because of the advantages that they offer to the field of combinatorial chemistry. Libraries based on MCRs have far greater constitutional variety than those based on conventional reaction.[2-6] The Ugi four-component reaction (U-4CR), which is the most prominent example among the MCRs, is a condensation reaction of four components, *i.e.*, a carboxylic acid, a primary amine, an aldehyde or ketone, and an isocyanide react in a one-pot manner to afford an *N*-substituted acyl amino amide **1** (Scheme 1), introducing four independently varying R groups in one reaction.[7,8]

Several studies have attempted to broaden the scope of structure that are accessible by the U-4CR, either through postcondensation transformations or by using bifunctional starting materials.[9] Thus easy and effective syntheses of a variety of heterocyclic ring systems including lactams,[9-13] hydantoins,[14,15] tetrazoles,[16] imidazoles,[17] pyrroles,[18-20] diketopiperazines,[21,22] ketopiperazines,[23-25] and benzodiazepines[26,27] have been established. During our extensive work with the Ugi reaction, we were recently able to develop a multicomponent reaction for the synthesis of various new skeleton molpholin-2-one derivatives **2** and **3** by using bifunctional starting material, glycolaldehyde dimer that have an aldehyde functional group and a hydroxy functional group.[28] We were also able to demonstrate that novel α-amino-butyrolactones **4** were successfully synthesized by employing multifunctional starting material, L-homoserine, which has three functional groups (an amine, a carboxylic acid, and a hydroxy group).[29] These syntheses are characterized as a one pot reaction involving five different functional groups and three different components, Ugi five-center three-component reaction (U-5C-3-CR).



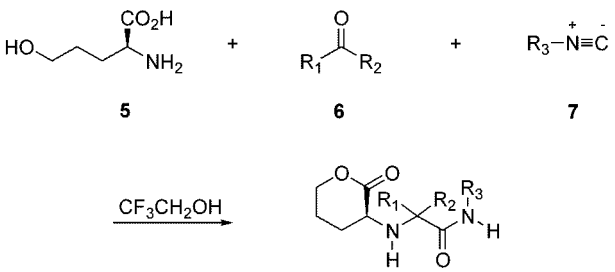
2 **3** **4**

To expand the structural diversity accessible through this type of U-5C-3CR, we have used several functionalized compounds as one component of the multicomponent condensation reaction. In this article, we describe the synthesis of *N*-carbamoylmethyl-α-amino-δ-valerolactone



1

Scheme 1



5 **6** **7**

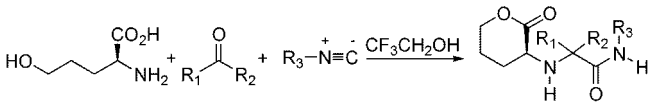
α-amino-δ-valerolactone **8**

Scheme 2

†This paper is dedicated to Professor Sang Chul Shim for his distinguished achievements in chemistry.

*Corresponding Author. e-mail: yosekim@kist.re.kr; Fax: +82-2-958-5189

Table 1. Synthesis of α-Amino-δ-Valerolactones **8** by the Ugi Five-Center Three-Component Reaction Using L-Pentahomoserine **5**



5 **6** **7** **8**

Entry	R_1	R_2	R_3	Time (hr)	Yield (%)	Ratio[a]
1[b]	Me_2CH	H	Me_3C	24	58	6 : 4
2	Me_3C	H	Me_3C	24	93	4 : 6
3	$(CH_2)_5$		Me_3C	5	63	–
4	Ph	H	Me_3C	5	81	7 : 3
5	4-MeOPh	H	Me_3C	5	92	6 : 4
6	3-MeOPh	H	Me_3C	5	59	7 : 3
7	2-MeOPh	H	Me_3C	5	70	6 : 4
8	4-MePh	H	Me_3C	5	89	7 : 3
9	4-*t*-BuPh	H	Me_3C	5	95	7 : 3
10	4-FPh	H	Me_3C	5	66	7 : 3
11	3-FPh	H	Me_3C	5	65	8 : 2
12	4-ClPh	H	Me_3C	5	74	6 : 4
13	3-ClPh	H	Me_3C	5	63	6 : 4
14	2-ClPh	H	Me_3C	5	77	8 : 2
15	3-BrPh	H	Me_3C	5	77	8 : 2
16	2-BrPh	H	Me_3C	5	73	7 : 3
17	4-NCPh	H	Me_3C	5	83	8 : 2
18	3-NCPh	H	Me_3C	5	81	8 : 2
19	4-CF_3Ph	H	Me_3C	5	75	7 : 3
20	2-CF_3Ph	H	Me_3C	5	76	8 : 2
21	4-Pyridyl	H	Me_3C	5	78	7 : 3
22	3-Pyridyl	H	Me_3C	5	78	8 : 2
23	2-Pyridyl	H	Me_3C	5	77	6 : 4
24	1-Naphthyl	H	Me_3C	5	57	5 : 5
25	2-Furyl	H	Me_3C	5	88	7 : 3
26	Me_2CH	H	$PhCH_2$	5	51	5 : 5
27	Me_2CH	H	EtO_2CCH_2	5	69	5 : 5
28	Me_3C	H	$PhCH_2$	5	69	6 : 4
29	Me_3C	H	EtO_2CCH_2	5	46	3 : 7
30	4-MeOPh	H	EtO_2CCH_2	2	58	4 : 6
31	4-FPh	H	$PhCH_2$	5	65	3 : 7
32	4-FPh	H	EtO_2CCH_2	5	58	2 : 8

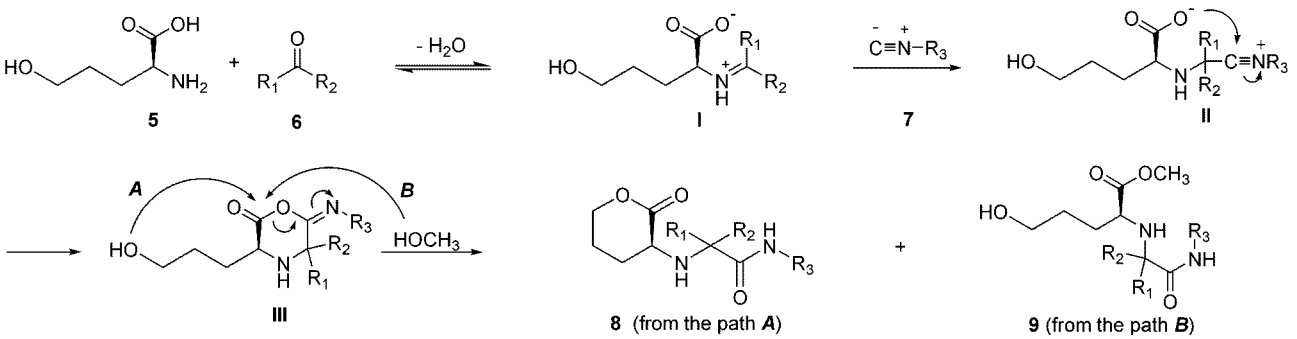
[a]The diastereomeric ratio was determined either by ^{1}H NMR or by GC of the crude mixture. [b]All new compounds were characterized by IR, ^{1}H and ^{13}C NMR, and HRMS data.

8, one carbon extended lactone compared with **4**, through U-5C-3CR using appropriate an aldehydes or ketones **6**, an isocyanides **7**, and a L-pentahomoserine **5** bearing an amine, a carboxylic acid, and an alcohol functional group as a functionalized starting material (Scheme 2). The compound **8** of the general structure is of interest due to certain biological activities such as immuno suppressant, anti-allergy, asthma, and antineoplastic agents.[30,31]

Results and Discussion

In our initial experiment, the starting material L-pentahomoserine **5** was prepared from the L-glutamic acid 5-methyl ester in high yield in three steps following known procedures.[32-34] The reaction in 2,2,2,-trifluoroethanol expectedly provided the desired α-amino-δ-valerolactones **8** in moderate to excellent yields as a mixture of diastereomers in varying ratios as shown in the Table 1. It is necessary to use 2,2,2,-triflulorethanol as a solvent for the formation of 6-membered cyclic lactone **8** in order to generate the desired sole product and obtain better yields. Results obtained by using solvents other than 2,2,2,-triflulorethanol such as THF, CH_3CN, and DMF were unsatisfactory. The reaction yields largely depend on the chosen aldehydes and isocyanides. In spite of various substrates used, however, the 6-membered lactone derivatives **8** showed poor diastereoselectivity compared with the previously reported 5-membered lactones **4**.[27]

The proposed reaction mechanism for the formation of **8** through the U-5C-3CR is summarized in Scheme 3. The addition of the isocyanide **7** to the imine **I** derived from condensation of the amino function of **5** with **6** produced the intermediate **II**. The attack of the carboxylate on the nitrilium carbon of **II** followed by the internal hydroxy addition on the carboxylate carbon of **III** resulted in the formation of **8** by the double intramolecular attacks through path ***A***. When methanol was used as a solvent, the ring opening compound **9** was formed as a major product by the extenal methanol attack to the carboxylate carbon of the intermediate **III** through path ***B***. In this reaction, a new chiral center was created in the initially quaternary carbon atom of the aldehyde. The relative stereochemistry of the obtained diastereoisomers **8** has not yet been determined.



Scheme 3

In summary, an efficient Ugi five-center-three-component reaction for preparation of the α-amino-δ-valerolactone derivatives **8** has been reported. These new structures broaden the scaffolds that are accessible through the Ugi reaction. This synthesis is characterized as a one pot reaction involving five different functional groups such as a carboxylic acid, an amine, an alcohol, an aldehyde or ketone, and an isocyanide. This intramolecular Ugi condensation reaction will be an excellent tool for a library synthesis of interesting pharmacophores. Further investigations in this area are in progress.

Experimental Section

All reactions were performed under nitrogen atmosphere. Infrared spectra (IR) were recorded on a Perkin Elmer 16F PC FT-IR spectrophotometer and frequencies are given in reciprocal centimeters. NMR spectra were obtained through Varian Gemini 300 MHz and 500 MHz instruments. Chemical Shifts are given in δ scale with TMS as an internal reference in $CDCl_3$. Electron-impact mass spectra (EIMS) were recorded in the form of *m/z* (intensity relative to base = 100) on a Hewlett Packard GC-MSD (5890II-5972) system. High-resolution mass spectral analyses were carried out at Korea Basic Science Institute, Seoul, Korea.

General Experimental Procedure. 100 M% of the corresponding aldehyde or ketone **6** was added to 100 mg of L-pentahomoserine **5** in 10 mL of 2,2,2-trifluoroethanol and the reaction mixture was stirred for several hours. The solution was cooled to 0 °C and 110 M% of an isocyanide **7** was added. When the reaction was complete at room temperature controlled by the tlc, the solvent was removed in vacuo. The crude mixture was dissolved in 30 mL of methylene chloride and the organic layer was washed with 10 mL of brine solution, and dried over magnesium sulfate. The residue after solvent evaporation was purified by flash column chromatography on silica gel using 1 : 1 or 1 : 2 mixture of hexane and ethyl acetate as an eluent.

***N*-*tert*-Butyl-3-methyl-2-(2-oxo-tetrahydro-pyran-3-yl-amino)-butyramide (8-1)**. Diastereomeric ratio was determined by GC/Mass analysis (Retention time; major: 3.59 min, minor: 3.66 min); R_f 0.25 (*n*-hexane : ethyl acetate, 2 : 1); FT-IR (neat) 3340 (NHCH), 2990 (aliphatic), 1620 (C(O)), 1545 (C(O)NH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.83-1.05 (m, 6H, $CH(\underline{CH_3})_2$), 1.32 (s, 9H, $C(\underline{CH_3})_3$), 1.87-2.10 (m, 1H, $CH_3\underline{CH}CH_3$), 2.40 (s, 1H(br), CH<u>NH</u>CH) 2.81 (d, 1H, C(O)<u>CH</u>NH), 3.32 (m, 2H, $CH_2\underline{CH}$NH), 6.98 (s, 1H, C(O)<u>NH</u>); HRMS *m/z* Calcd for $C_{14}H_{26}N_2O_3$ (M+): 270.1943; Found: 270.1940.

***N*-*tert*-Butyl-3,3-dimethyl-2-(2-oxo-tetrahydro-pyran-3-ylamino)-butyramide (8-2)**. Diastereomeric ratio was determined by GC/Mass analysis (Retention time; major: 3.66 min, minor: 3.71 min); R_f 0.41 (*n*-hexane : ethyl acetate, 1 : 1); FT-IR (neat) 3347 (NHCH), 2975 (aliphatic), 1765 (C(O)), 1580 (C(O)NH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.96 (m, 9H, $C(CH_3)_3$), 1.30 (s, 9H, $C(CH_3)_3$), 1.54-1.62 (m, 1H, $OCH_2\underline{CH_2}$), 1.84-1.99 (m, 1H, $OCH_2CH_2\underline{CH_2}$), 2.14-2.32 (m, 1H, $OCH_2\underline{CH_2}$, 2.70 (s, 1H, <u>CH</u>$C(CH_3)_3$), 3.25 (m, 1H, $CH_2\underline{CH}$NH), 4.37 (m, 2H, $O\underline{CH_2}CH_2$); ^{13}C NMR (125 MHz, $CDCl_3$, Diastereomer mixtures) δ 21.26, 21.81, 25.80, 26.67, 26.81, 27.11, 27.16, 28.65, 28.77, 33.65, 33.91, 50.60, 50.76, 55.49, 56.94, 67.58, 68.09, 70.32, 72.59, 171.63, 172.12, 173.57; HRMS *m/z* Calcd for $C_{15}H_{28}N_2O_3$ (M+): 284.2100; Found: 284.2100.

1-(2-Oxo-tetrahydro-pyran-3-ylamino)-cyclohexane-carboxylic acid *tert*-butyl amide (8-3). R_f 0.35 (*n*-hexane : ethyl acetate, 1 : 1); mp 140 °C; FT-IR (KBr) 3365 (NHCH), 2942 (aliphatic), 1663 (C(O)), 1519 (C(O)NH), 1170 (C(O)) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.46-1.68 (m, $OCH_2\underline{CH_2}$, $CCH_2CH_2\underline{CH_2}$), 1.80-2.02 (m, $OCH_2CH_2\underline{CH_2}$, $CCH_2\underline{CH_2}CH_2$), 2.15-2.24 (m, $O\underline{CH_2}CH_2$, $C\underline{CH_2}CH_2CH_2$), 2.49 (br. s, 1H, CH<u>NH</u>CH), 3.35-3.42 (dd, 1H, *J* = 7.4 Hz, *J* = 11.6 Hz, $CH_2\underline{CH}$NH), 4.27-4.31 (t, 2H, $O\underline{CH_2}CH_2$), 6.87 (s, 1H, C(O)<u>NH</u>); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.55, 21.66, 25.27, 27.74, 28.56, 30.10, 34.98, 50.32, 51.79, 60.65, 67.89, 174.63, 176.51; HRMS *m/z* Calcd for $C_{16}H_{28}N_2O_3$ (M+): 296.2100; Found: 297.2170.

***N*-*tert*-Butyl-2-(2-oxo-tetrahydro-pyran-3-ylamino)-2-phenyl-acetamide (8-4)**. Diastereomeric ratio was determined by ^1H NMR analysis (major: 3.28 ppm, minor: 3.40 ppm); R_f 0.39 (*n*-hexane : ethyl acetate, 1 : 2); mp 119 °C; FT-IR (KBr) 3309 (NHCH), 3060 (aromatic), 2969 (aliphatic), 1722 (C(O)), 1671 (C(O)NH) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.33 (s, 9H, $C(CH_3)_3$), 1.58-1.68 (m, 1H, $OCH_2\underline{CH_2}$), 1.80-1.97 (m, 1H, $OCH_2CH_2\underline{CH_2}$), 2.16-2.31 (m, 1H, $OCH_2\underline{CH_2}$), 3.05 (br. s, 1H, CH<u>NH</u>CH), 3.25-3.50 (dd, 1H, *J* = 7.5 Hz, *J* = 11.5 Hz, $CH_2\underline{CH}$NH), 4.10-4.28 (m, 2H, $O\underline{CH_2}CH_2$), 4.34 (s, 1H, <u>CH</u>Ph), 6.77 (s, 1H, C(O)<u>NH</u>), 7.23-7.36 (m, 5H, aromatic); ^{13}C NMR (125 MHz, $CDCl_3$, Diastereomer mixtures) δ 21.29, 21.74, 26.18, 26.34, 28.34, 28.48, 28.61, 28.76, 50.73, 50.84, 54.48, 55.54, 65.67, 66.59, 67.52, 76.83, 127.11, 127.51, 127.93, 128.02, 128,67, 128.70, 139.12, 170.95, 171.52, 173.43, 173.65; HRMS *m/z* Calcd for $C_{17}H_{24}N_2O_3$ (M+): 304.1787; Found: 304.1791.

***N*-*tert*-Butyl-2-(4-methoxy-phenyl)-2-(2-oxo-tetrahydro-pyran-3-ylamino)-acetamide (8-5)**. Diastereomeric ratio was determined by ^1H NMR analysis (major: 3.25 ppm, minor: 3.37 ppm); R_f 0.44 (ethyl acetate); mp 42 °C; FT-IR (KBr) 3324 (NHCH), 3040 (aromatic), 2966 (aliphatic), 1735 (C(O)), 1662 (C(O)NH), 1178 (C(O)) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.31 (s, 9H, $C(CH_3)_3$), 1.62-1.70 (m, 1H, $OCH_2\underline{CH_2}$), 1.87-2.03 (m, 1H, $OCH_2CH_2\underline{CH_2}$), 2.17-2.33 (m, 1H, $OCH_2\underline{CH_2}$), 3.23-3.42 (dd, 1H, *J* = 7.5 Hz, *J* = 11.5 Hz, $CH_2\underline{CH}$NH), 3.79 (s, 3H, $O\underline{CH_3}$), 4.15 (s, 1H, <u>CH</u>Ph), 4.23-4.33 (m, 2H, $O\underline{CH_2}CH_2$), 6.59 (s, 1H, C(O)<u>NH</u>), 6.84-7.31 (m, 4H, aromatic); ^{13}C NMR (125 MHz, $CDCl_3$, Diastereomer mixtures) δ 21.32, 21.79, 26.20, 26.41, 28.36, 28.43, 28.52, 28.65, 28.75, 50.73, 50.84, 54.33, 55.14, 55.52, 65.04, 66.02, 67.52, 67.84, 114.13, 114.15, 128.30, 128.75, 131.13, 131.29, 159.29, 159.37, 171.27, 171.46, 173.52, 173.75; HRMS *m/z* Calcd for $C_{18}H_{26}N_2O_4$ (M+): 334.1893; Found: 335.1977

***N*-*tert*-Butyl-2-(3-methoxy-phenyl)-2-(2-oxo-tetrahydro-pyran-3-ylamino)-acetamide (8-6)**. Diastereomeric ratio

was determined by ^{1}H NMR analysis (major: 3.28 ppm, minor: 3.39 ppm); R_f 0.14 (n-hexane:ethyl acetate, 1 : 1); FT-IR (neat) 3324 (NHCH), 3040 (aromatic), 2966 (aliphatic), 1735 (C(O)), 1662 (C(O)NH), 1145 (C(O)) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (s, 9H, $C(CH_3)_3$), 1.58-1.74 (m, 1H, $OCH_2\underline{CH_2}$), 1.83-2.04 (m, 1H, $OCH_2CH_2\underline{CH_2}$), 2.16-2.36 (m, 1H, $OCH_2\underline{CH_2}$), 2.47 (br. s, 1H, CH<u>NH</u>CH), 3.26-3.43 (dd, 1H, *J* = 7.5 Hz, *J* = 11.4 Hz, $CH_2\underline{CH}NH$), 3.80 (s, 3H, $O\underline{CH_3}$), 4.22-4.33 (m, 2H, $O\underline{CH_2}CH_2$), 4.37 (s, 1H, <u>CH</u>Ph), 6.62 (s, 1H, C(O)<u>NH</u>), 6.84-7.29 (m, 5H, aromatic); ^{13}C NMR (125 MHz, $CDCl_3$, Diastereomer mixtures) δ 21.35, 21.80, 26.23, 26.49, 28.40, 28.54, 28.68, 28.81, 50.81, 50.92, 50.93, 54.40, 55.13, 55.16, 55.58, 65.71, 66.59, 67.60, 67.84, 112.82, 113.02, 113.65, 113.80, 119.45, 119.96, 129.77, 129.79, 140.61, 140.71, 159.80, 159.88, 170.77, 171.04, 173.40, 173.72, 173.73; HRMS *m/z* Calcd for $C_{18}H_{26}N_2O_4$ (M+): 334.1893; Found: 335.1897.

***N*-*tert*-Butyl-2-(2-methoxy-phenyl)-2-(2-oxo-tetrahydro-pyran-3-ylamino)-acetamide (8-7)**. Diastereomeric ratio was determined by ^{1}H NMR analysis (major: 3.31 ppm, minor: 3.45 ppm); R_f 0.15 (*n*-hexane : ethyl acetate, 1 : 1); FT-IR (neat) 3336 (NHCH), 3068 (aromatic), 2966 (aliphatic), 1737 (C(O)), 1673 (C(O)NH), 1143 (C(O)) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33 (s, 9H, $C(CH_3)_3$), 1.56-1.75 (m, 1H, $OCH_2\underline{CH_2}$), 1.82-2.06 (m, 1H, $OCH_2CH_2\underline{CH_2}$), 2.18-2.41 (m, 1H, $OCH_2\underline{CH_2}$), 3.29-3.47 (m, 1H, $CH_2\underline{CH}NH$), 3.86 (s, 3H, $O\underline{CH_3}$), 4.27-4.32 (m, 2H, $O\underline{CH_2}CH_2$), 4.69 (s, 1H, <u>CH</u>Ph), 6.89-7.35 (5H, aromatic); ^{13}C NMR (125 MHz, $CDCl_3$, Diastereomer mixtures) δ 21.16, 21.50, 25.62, 26.38, 28.43, 28.47, 28.56, 28.63, 28.74, 50.59, 50.63, 54.48, 54.86, 55.31, 59.96, 60.70, 67.59, 68.08, 110.87, 111.07, 120.58, 120.97, 127.34, 127.94, 128.68, 128.79, 128.99, 129.29, 156.75, 156.98, 171.06, 171.36, 172.82, 173.50; HRMS *m/z* Calcd for $C_{18}H_{26}N_2O_4$ (M+): 334.1893; Found: 335.1973.

***N*-*tert*-Butyl-2-(2-oxo-tetrahydro-pyran-3-ylamino)-2-*p*-tolyl-acetamide (8-8)**. Diastereomeric ratio was determined by GC/Mass analysis (Retention time; major: 6.17 min, minor: 6.22 min); R_f 0.19 (*n*-hexane : ethyl acetate, 1 : 1); FT-IR (neat) 3324 (NHCH), 3060 (aromatic), 2967 (aliphatic), 1737 (C(O)), 1664 (C(O)NH), 1143 (C(O)) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27 (s, 9H, $C(CH_3)_3$), 1.48-1.69 (m, 1H, $OCH_2\underline{CH_2}$), 1.77-1.98 (m, 1H, $OCH_2CH_2\underline{CH_2}$), 2.10-2.24 (m, 1H, $OCH_2\underline{CH_2}$), 2.29 (s, 3H, $PhCH_3$), 2.54 (br. s, 1H, CH<u>NH</u>CH), 3.21-3.28 (dd, 1H, *J* = 7.5 Hz, *J* = 11.4 Hz, $CH_2\underline{CH}NH$), 4.13-4.28 (m, 2H, $O\underline{CH_2}CH_2$), 4.30 (s, 1H, <u>CH</u>Ph), 6.71 (s, 1H, C(O)<u>NH</u>), 7.09-7.23 (4H, <u>Ph</u>); ^{13}C NMR (125 MHz, $CDCl_3$, Diastereomer mixtures) δ 20.95, 21.29, 21.73, 26.16, 26.38, 28.36, 28.49, 28.62, 50.69, 50.79, 54.39, 55.50, 65.40, 66.29, 67.52, 67.80, 126.98, 127.42, 129.38, 136.09, 136.12, 137.70, 137.73, 171.13, 171.33, 173.43, 173.69; HRMS *m/z* Calcd for $C_{18}H_{26}N_2O_3$ (M+): 318.1943; Found: 318.1943.

***N*-*tert*-Butyl-2-(4-tert-butyl-phenyl)-2-(2-oxo-tetrahydro-pyran-3-ylamino)-acetamide (8-9)**. Diastereomeric ratio was determined by GC/Mass analysis (Retention time; major: 7.06 min, minor: 7.03 min); R_f 0.15 (*n*-hexane : ethyl acetate, 1 : 1); FT-IR (neat) 3324 (NHCH), 3060 (aromatic), 2964 (aliphatic), 1739 (C(O)), 1660 (C(O)NH), 1160 (C(O)) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28 (s, 9H, $C(CH_3)_3$), 1.38 (s, 9H, $PhC(CH_3)_3$), 1.44-1.80 (m, 1H. $OCH_2\underline{CH_2}$), 1.83-2.04 (m, 1H, $OCH_2CH_2\underline{CH_2}$), 2.20-2.40 (m, 1H, $OCH_2\underline{CH_2}$), 2.51 (br. s, 1H, CH<u>NH</u>CH), 3.23-3.37 (dd, 1H, *J* = 7.5 Hz, *J* = 11.7 Hz, $CH_2\underline{CH}NH$), 4.07-4.30 (m, 2H, $O\underline{CH_2}CH_2$), 4.31 (s, 1H, <u>CH</u>Ph), 6.86 (s, 1H, C(O)<u>NH</u>), 7.26-7.36 (4H, aromatic); ^{13}C NMR (125 MHz, $CDCl_3$, Diastereomer mixtures) δ 21.36, 21.90, 26.25, 26.38, 28.42, 28.59, 28.73, 28.81, 31.21, 34.45, 50.7850.82, 54.77, 55.76, 65.46, 66.42, 67.60, 67.96, 125.71, 126.83, 127.16, 136.02, 136.07, 150.85, 150.98, 171.31, 171.48, 173.44, 173.68; HRMS *m/z* Calcd for $C_{21}H_{32}N_2O_3$ (M+): 360.2413; Found: 361.2463.

***N*-*tert*-Butyl-2-(4-fluoro-phenyl)-2-(2-oxo-tetrahydro-pyran-3-ylamino)-acetamide (8-10)**. Diastereomeric ratio was determined by ^{1}H NMR analysis (major: 3.24 ppm, minor: 3.33 ppm); R_f 0.52 (ethyl acetate); mp 142 ^{o}C; FT-IR (KBr) 3322 (NHCH), 3066 (aromatic), 2967 (aliphatic), 1735 (C(O)), 1662 (C(O)NH), 1145 (C(O)) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (s, 9H, $C(CH_3)_3$), 1.52-1.76 (m, 1H, $OCH_2\underline{CH_2}$), 1.80-2.01 (m, 1H, $OCH_2CH_2\underline{CH_2}$), 2.14-2.35 (m, 1H, $OCH_2\underline{CH_2}$), 2.45 (br. s, 1H, CH<u>NH</u>CH), 3.22-3.37 (dd, 1H, *J* = 7.65 Hz, *J* = 11.6 Hz, $CH_2\underline{CH}NH$), 4.15-4.29 (m, 2H, $O\underline{CH_2}CH_2$), 4.32 (s, 1H, <u>CH</u>Ph), 6.76 (s, 1H, C(O)<u>NH</u>), 6.95-7.36 (5H, aromatic); ^{13}C NMR (125 MHz, $CDCl_3$, Diastereomer mixtures) δ 21.43, 21.90, 26.36, 26.49, 28.59, 28.64, 28.73, 28.89, 50.92, 51.05, 54.53, 55.65, 65.07, 66.08, 67.61, 68.00, 115.61, 115.66, 115.78, 115.83, 128.92, 128.98, 129.29, 129.35, 135.01, 135.03, 161.57, 163.52, 170.79, 173.67; HRMS *m/z* Calcd for $C_{17}H_{23}FN_2O_3$ (M^+): 322.1693; Found: 322.1701.

***N*-*tert*-Butyl-2-(3-fluoro-phenyl)-2-(2-oxo-tetrahydro-pyran-3-ylamino)-acetamide (8-11)**. Diastereomeric ratio was determined by GC/Mass analysis (Retention time; major: 5.62 min, minor: 5.65 min); R_f 0.40 (*n*-hexane : ethyl acetate, 1 : 1); mp 101 ^{o}C; FT-IR (KBr) 3301 (NHCH), 3079 (aromatic), 2971 (aliphatic), 1741 (C(O)), 1643 (C(O)NH), 1149 (C(O)) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (s, 9H, $C(CH_3)_3$), 1.54-1.71 (m, 1H. $OCH_2\underline{CH_2}$), 1.82-2.01 (m, 1H, $OCH_2CH_2\underline{CH_2}$), 2.12-2.38 (m, 1H, $OCH_2\underline{CH_2}$), 2.46 (s, 1H(br), CH<u>NH</u>CH), 3.24-3.30 (dd, 1H, *J* = 7.5 Hz, *J* = 11.4 Hz, $CH_2\underline{CH}NH$), 4.17-4.31 (m, 2H, $O\underline{CH_2}CH_2$), 4.36 (s, 1H, <u>CH</u>Ph), 6.72 (s, 1H, C(O)<u>NH</u>), 6.92-7.38 (4H, aromatic); ^{13}C NMR (125 MHz, $CDCl_3$, Diastereomer mixtures) δ 21.33, 21.77, 26.24, 26.36, 28.48, 28.62, 28.78, 50.88, 51.00, 54.46, 55.47, 65.24, 66.11, 67.57, 67.91, 114.10, 114.18, 114.45, 114.84, 114.95, 114.97, 115.12, 115.14, 122.95, 123.38, 130.23, 130.30, 141.74, 161.89, 163.85, 170.32, 170.51, 173.42, 173.62; HRMS *m/z* Calcd for $C_{17}H_{23}FN_2O_3$ (M+): 322.1693; Found: 322.1691.

***N*-*tert*-Butyl-2-(4-chloro-phenyl)-2-(2-oxo-tetrahydro-pyran-3-ylamino)-acetamide (8-12)**. Diastereomeric ratio was determined by GC/Mass analysis (Retention time; major: 11.77 min, minor: 11.92 min); R_f 0.42 (*n*-hexane : ethyl acetate, 1 : 1); FT-IR (neat) 3324 (NHCH), 3068 (aromatic),

2967 (aliphatic), 1735 (C(O)), 1664 (C(O)NH), 1145 (C(O)) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.32 (s, 9H, $C(CH_3)_3$), 1.54-1.69 (m, 1H, OCH_2CH_2), 1.81-2.02 (m, 1H, OCH_2-CH_2CH_2), 2.10-2.15 (m, 1H, OCH_2CH_2), 3.24-3.30 (dd, 1H, J = 7.4 Hz, J = 11.3 Hz, CH_2CHNH), 4.09-4.33 (m, 2H, OCH_2CH_2), 4.36 (s, 1H, CHPh), 6.67 (s, 1H, C(O)NH), 7.27-7.40 (5H, aromatic); ^{13}C NMR (125 MHz, $CDCl_3$, Diastereomer mixtures) δ 20.90, 21.35, 21.80, 26.26, 26.38, 28.36, 28.51, 28.64, 28.78, 28.83, 50.90, 51.03, 54.47, 55.46, 65.02, 65.90, 67.56, 67.95, 128.59, 128.87, 128.92, 128.95, 129.08, 129.48, 133.85, 133.92, 137.62, 137.69, 170.59, 170.74, 173.48, 173.63; HRMS *m/z* Calcd for $C_{17}H_{23}ClN_2O$=(M+): 338.1397; Found: 339.1488.

***N*-*tert*-Butyl-2-(3-chloro-phenyl)-2-(2-oxo-tetrahydro-pyran-3-ylamino)-acetamide (8-13)**. Diastereomeric ratio was determined by GC/Mass analysis (Retention time; major: 6.54 min, minor: 6.58 min); R_f 0.18 (*n*-hexane : ethyl acetate, 1 : 1); mp 126 °C; FT-IR (KBr) 3324 (NHCH), 3066 (aromatic), 2967 (aliphatic), 1735 (C(O)), 1662 (C(O)NH), 1145 (C(O)) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.30 (s, 9H, $C(CH_3)_3$), 1.56-1.74 (m, 1H, $OCH_2\underline{CH_2}$), 1.82-2.03 (m, 1H, OCH_2CH_2-$\underline{CH_2}$), 2.13-2.35 (m, 1H, $OCH_2\underline{CH_2}$), 2.44 (br. s, 1H, CH<u>NH</u>CH), 3.20-3.43 (m, 1H, $CH_2\underline{CH}NH$), 4.15-4.31 (m, 2H, $O\underline{CH_2}CH_2$), 4.33 (s, 1H, <u>CH</u>Ph), 6.74 (s, 1H, C(O)<u>NH</u>), 7.20-7.41 (5H, aromatic); ^{13}C NMR (125 MHz, $CDCl_3$, Diastereomer mixtures) δ 21.36, 21.81, 26.26, 26.41, 26.43, 28.53, 28.67, 51.08, 54.54, 55.47, 65.26, 66.07, 67.61, 67.96, 125.42, 125.84, 127.44, 127.66, 128.22, 128.31, 130.38, 141.25, 170.31, 170.49, 173.41, 173.60; HRMS *m/z* Calcd for $C_{17}H_{23}ClN_2O_3$ (M+): 338.1397; Found: 338.1399.

***N*-*tert*-Butyl-2-(2-chloro-phenyl)-2-(2-oxo-tetrahydro-pyran-3-ylamino)-acetamide (8-14)**. Diastereomeric ratio was determined by ^1H NMR analysis (major: 3.29 ppm, minor: 3.40 ppm); R_f 0.27 (*n*-hexane : ethyl acetate, 1 : 1); FT-IR (neat) 3324 (NHCH), 3066 (aromatic), 2967 (aliphatic), 1735 (C(O)), 1670 (C(O)NH), 1162 (C(O)) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.33 (s, 9H, $C(CH_3)_3$), 1.52-1.74 (m, 1H, $OCH_2\underline{CH_2}$), 1.82-2.02 (m, 1H, $OCH_2CH_2\underline{CH_2}$), 2.18-2.39 (m, 1H, $OCH_2\underline{CH_2}$), 3.26-3.43 (dd, 1H, J = 7.5 Hz, J = 11.0 Hz, $CH_2\underline{CH}NH$), 4.18-4.30 (m, 2H, $O\underline{CH_2}CH_2$), 4.79 (s, 1H, <u>CH</u>Ph), 6.95 (s, 1H, C(O)<u>NH</u>), 7.18-7.41 (5H, aromatic); ^{13}C NMR (125 MHz, $CDCl_3$, Diastereomer mixtures) δ 21.19, 21.58, 25.80, 26.60, 28.44, 28.52, 28.60, 28.78, 51.15, 54.82, 55.16, 62.07, 62.43, 67.79, 68.16, 127.28, 127.33, 129.04, 129.15, 129.18, 129.29, 129.80, 129.96, 133.64, 137.16, 169.99, 170.27, 172.59, 173.46; HRMS *m/z* Calcd for $C_{17}H_{23}ClN_2O_3$ (M+): 338.1397; Found: 339.1477.

2-(3-Bromo-phenyl)-*N*-*tert*-butyl-2-(2-oxo-tetrahydro-pyran-3-ylamino)-acetamide (8-15). Diastereomeric ratio was determined by GC/Mass analysis (Retention time; major: 6.95 min, minor: 6.99 min); R_f 0.22 (*n*-hexane : ethyl acetate, 1 : 1); mp 116 °C; FT-IR (KBr) 3372 (NHCH), 3064 (aromatic), 2969 (aliphatic), 1714 (C(O)), 1671 (C(O)NH), 1072 (C(O)) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.32 (s, 9H, $C(CH_3)_3$), 1.58-1.75 (m, 1H. $OCH_2\underline{CH_2}$), 1.82-2.04 (m, 1H, OCH_2-$CH_2\underline{CH_2}$), 2.16-2.34 (m, 1H, $OCH_2\underline{CH_2}$), 3.24-3.30 (dd, 1H, J = 7.7 Hz, J = 11.6 Hz, $CH_2\underline{CH}NH$), 4.18-4.30 (m, 2H, $O\underline{CH_2}CH_2$), 4.33 (s, 1H, <u>CH</u>Ph), 6.70 (s, 1H, C(O)<u>NH</u>), 7.14-7.54 (4H, aromatic); ^{13}C NMR (125 MHz, $CDCl_3$, Diastereomer mixtures) δ 21.38, 21.83, 26.28, 26.45, 28.56, 28.69, 28.86, 30.85, 50.99, 51.11, 54.55, 55.50, 65.27, 66.067, 67.622, 67.98, 122.83, 125.90, 126.32, 130.35, 130.59, 131.19, 131.28, 141.33, 141.51, 170.27, 170.46, 173.40, 173.60; HRMS *m/z* Calcd for $C_{17}H_{23}BrN_2O_3$ (M+): 382.1092; Found: 385.0938.

2-(2-Bromo-phenyl)-*N*-*tert*-butyl-2-(2-oxo-tetrahydro-pyran-3-ylamino)-acetamide (8-16). Diastereomeric ratio was determined by GC/Mass analysis (Retention time; major: 6.75 min, minor: 6.71 min); R_f 0.23 (*n*-hexane : ethyl acetate, 1 : 1); FT-IR (neat) 3307 (NHCH), 3064 (aromatic), 2967 (aliphatic), 1739 (C(O)), 1668 (C(O)NH), 1145 (C(O)) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.32 (s, 9H, $C(CH_3)_3$), 1.48-1.78 (m, 1H. $OCH_2\underline{CH_2}$), 1.80-2.02 (m, 1H, OCH_2CH_2-$\underline{CH_2}$), 2.04-2.41 (m, 1H, $OCH_2\underline{CH_2}$), 3.24-3.35 (dd, 1H, J = 7.5 Hz, J = 11.4 Hz, $CH_2\underline{CH}NH$), 4.02-4.38 (m, 2H, O<u>CH</u>CH_2), 4.81 (s, 1H, <u>CH</u>Ph), 6.87 (s, 1H, C(O)<u>NH</u>), 7.06-7.61 (4H, aromatic); ^{13}C NMR (125 MHz, $CDCl_3$, Diastereomer mixtures) δ 21.23, 21.60, 25.85, 26.73, 28.55, 28.63, 28.83, 51.21, 54.75, 55.16, 64.01, 64.61, 67.78, 68.18, 124.18, 127.99, 129.46, 133.10, 133.23, 138.88, 138.89, 169.87, 170.18, 173.52, 173.53; HRMS: *m/z* Calcd for $C_{17}H_{23}BrN_2O_3$ (M+): 382.1092; Found: 385.0929.

***N*-*tert*-Butyl-2-(4-cyano-phenyl)-2-(2-oxo-tetrahydro-pyran-3-ylamino)-acetamide (8-17)**. Diastereomeric ratio was determined by ^1H NMR analysis (major: 3.26 ppm, minor: 3.37 ppm); R_f 0.51 (ethyl acetate); mp 155 °C; FT-IR (KBr) 3336 (NHCH), 3040 (aromatic), 2969 (aliphatic), 2229 (CN), 1735 (C(O)), 1664 (C(O)NH), 1145 (C(O)) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.28 (s, 9H, $C(CH_3)_3$), 1.63-1.72 (m, 1H, $OCH_2\underline{CH_2}$), 1.86-2.01 (m, 1H, $OCH_2CH_2\underline{CH_2}$), 2.18-2.32 (m, 1H, $OCH_2\underline{CH_2}$), 2.47 (br. s, 1H, CH<u>NH</u>CH), 3.24-3.40 (dd, 1H, J = 7.3 Hz, J = 11.3 Hz, $CH_2\underline{CH}NH$), 4.20-4.33 (m, 2H, $O\underline{CH_2}CH_2$), 4.42 (s, 1H, <u>CH</u>Ph), 6.87 (s, 1H, C(O)<u>NH</u>), 7.49-7.60 (5H, aromatic); ^{13}C NMR (125 MHz, $CDCl_3$, Diastereomer mixtures) δ 21.33, 21.75, 26.30, 28.46, 28.59, 51.17, 54.65, 55.41, 65.35, 67.62, 68.01, 11.88, 118.41, 128.05, 128.33, 132.46, 144.59, 169.75, 173.52; HRMS *m/z* Calcd for $C_{18}H_{23}N_3O_3$ (M+): 329.1739; Found: 329.1741.

***N*-*tert*-Butyl-2-(3-cyano-phenyl)-2-(2-oxo-tetrahydro-pyran-3-ylamino)-acetamide (8-18)**. Diastereomeric ratio was determined by ^1H NMR analysis (major: 3.27 ppm, minor: 3.37 ppm); R_f 0.48 (ethyl acetate); mp 40 °C; FT-IR (KBr) 3324 (NHCH), 3040 (aromatic), 2969 (aliphatic), 2229 (CN), 1735 (C(O)), 1664 (C(O)NH), 1149 (C(O)) cm^{-1}; ^1H NMR (300MHz, $CDCl_3$) δ 1.31 (s, 9H, $C(CH_3)_3$), 1.62-1.75 (m, 1H, $OCH_2\underline{CH_2}$), 1.86-2.01 (m, 1H, $OCH_2CH_2\underline{CH_2}$), 2.18-2.34 (m, 1H, $OCH_2\underline{CH_2}$), 3.25-3.40 (dd, 1H, J = 7.4 Hz, J = 11.3 Hz, $CH_2\underline{CH}NH$), 4.20-4.35 (m, 2H, $O\underline{CH_2}CH_2$), 4.39 (s, 1H, <u>CH</u>Ph), 6.88 (s, 1H, C(O)<u>NH</u>), 7.42-7.69 (5H, aromatic); ^{13}C NMR (125 Hz, $CDCl_3$, Diastereomer mixtures) δ 21.31, 21.73, 26.24, 28.45, 28.58, 51.16, 54.62, 55.32, 64.89, 65.64, 67.59, 68.01, 112.69, 118.44, 129.51, 130.85, 131.03, 131.60, 131.63, 131.80, 132.13, 140.86, 169.92,

169.95, 173.48, 173.56; HRMS *m/z* Calcd for $C_{18}H_{23}N_3O_3$ (M+): 329.1739; Found: 329.1730.

***N*-*tert*-Butyl-2-(2-oxo-tetrahydro-pyran-3-ylamino)-2-(4-trifluoromethyl-phenyl)-acetamide (8-19)**. Diastereomeric ratio was determined by GC/Mass analysis (Retention time; major: 5.38 min, minor: 5.43 min); R_f 0.18 (*n*-hexane : ethyl acetate, 1 : 1); FT-IR (neat) 3322 (NHCH), 2969 (aliphatic), 1774 (C(O)), 1662 (C(O)NH), 1124 (C(O)) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$); δ 1.33 (s, 9H, $C(CH_3)_3$), 1.53-1.76 (m, 1H, $OCH_2\underline{CH_2}$), 1.84-2.15 (m, 1H, $OCH_2CH_2\underline{CH_2}$), 2.17-2.38 (m, 1H, $OCH_2\underline{CH_2}$), 3.25-3.31 (dd, 1H, *J* = 7.5 Hz, *J* = 11.4 Hz, $CH_2\underline{CH}NH$), 4.04-4.34 (m, 2H, $O\underline{CH_2}CH_2$), 4.43 (s, 1H, <u>CH</u>Ph), 6.72 (s, 1H, C(O)<u>NH</u>), 7.49-7.62 (4H, aromatic); ^{13}C NMR (125 Hz, $CDCl_3$, Diastereomer mixtures) δ 21.41, 21.88, 26.36, 26.46, 28.47, 28.57, 28.70, 51.07, 51.20, 54.69, 55.59, 65.45, 66.23, 67.67, 68.05, 125.78, 125.79, 127.68, 127.99, 143.01, 143.22, 170.20, 170.35, 173.43, 173.61; HRMS *m/z* Calcd for $C_{18}H_{23}F_3N_2O_3$ (M+): 372.1661; Found: 372.1670.

***N*-*tert*-Butyl-2-(2-oxo-tetrahydro-pyran-3-ylamino)-2-(2-trifluoromethyl-phenyl)-acetamide (8-20)**. Diastereomeric ratio was determined by GC/Mass analysis (Retention time; major: 5.22 min, minor: 5.17 min); R_f 0.31 (*n*-hexane : ethyl acetate, 1 : 1); FT-IR (neat) 3307 (NHCH), 2967 (aliphatic), 1737 (C(O)), 16794 (C(O)NH), 1157 (C(O)) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.20 (s, 9H, $C(CH_3)_3$), 1.49-1.63 (m, 1H. $OCH_2\underline{CH_2}$), 1.78-2.01 (m, 1H, $OCH_2CH_2\underline{CH_2}$), 2.13-2.29 (m, 1H, $OCH_2\underline{CH_2}$), 3.23-3.29 (dd, 1H, *J* = 7.5 Hz, *J* = 11.4 Hz, $CH_2\underline{CH}NH$), 4.15-4.29 (m, 2H, $O\underline{CH_2}CH_2$), 4.72 (s, 1H, <u>CH</u>Ph), 6.56 (s, 1H, C(O)<u>NH</u>), 7.26-7.69 (4H, aromatic); ^{13}C NMR (125 Hz, $CDCl_3$, Diastereomer mixtures) δ 21.23, 21.66, 25.90, 26.52, 28.39, 28.51, 28.62, 51.14, 51.29, 54.76, 55.12, 60.33, 60.37, 60.74, 67.69, 68.28, 123.24, 125.42, 125.73, 125.78, 125.82, 125.87, 128.05, 128.8, 128.27, 129.17, 132.60, 132.79, 138.73, 169.81, 170.10, 172.67, 173.80; HRMS *m/z* Calcd for $C_{18}H_{23}F_3N_2O_3$ (M+): 372.1661; Found: 372.1733.

***N*-*tert*-Butyl-2-(2-oxo-tetrahydro-pyran-3-ylamino)-2-pyridin-4-yl-acetamide (8-21)**. Diastereomeric ratio was determined by GC/Mass analysis (Retention time; major: 10.34 min, minor: 10.44 min); R_f 0.03 (*n*-hexane : ethyl acetate, 1 : 1); FT-IR (neat) 3363 (NHCH), 3062 (aromatic), 2967 (aliphatic), 1710 (C(O)), 1673 (C(O)NH), 1072 (C(O)) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.30 (s, 9H, $C(CH_3)_3$), 1.62-1.75 (m, 1H. $OCH_2\underline{CH_2}$), 1.84-2.06 (m, 1H, $OCH_2CH_2\underline{CH_2}$), 2.17-2.34 (m, 1H, $OCH_2\underline{CH_2}$), 3.24-3.30 (dd, 1H, *J* = 7.5 Hz, *J* = 11.4 Hz, $CH_2\underline{CH}NH$), 4.02-4.32 (m, 2H, $O\underline{CH_2}CH_2$), 4.35 (s, 1H, <u>CH</u>Ph), 6.76 (s, 1H, C(O)<u>NH</u>), 7.25-8.58 (4H, aromatic); ^{13}C NMR (125 Hz, $CDCl_3$, Diastereomer mixtures) δ 21.30, 21.73, 26.28, 28.45, 28.58, 51.03, 51.15, 54.62, 55.39, 64.79, 64.84, 65.47, 67.62, 67.98, 122.13, 122.46, 147.68, 148.05, 150.01, 150.04, 150.09, 169.52, 169.64, 173.48; HRMS *m/z* Calcd for $C_{16}H_{23}N_3O_3$ (M+): 305.1739; Found: 305.1738.

***N*-*tert*-Butyl-2-(2-oxo-tetrahydro-pyran-3-ylamino)-2-pyridin-3-yl-acetamide (8-22)**. Diastereomeric ratio was determined by ^1H NMR analysis (major: 3.28 ppm, minor: 3.37 ppm); R_f 0.06 (*n*-hexane : ethyl acetate, 1 : 1); FT-IR (neat) 3351 (NHCH), 3052 (aromatic), 2977 (aliphatic), 1745 (C(O)), 1679 (C(O)NH), 1155 (C(O)) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.30 (s, 9H, $C(CH_3)_3$), 1.52-1.74 (m, 1H. $OCH_2\underline{CH_2}$), 1.82-2.02 (m, 1H, $OCH_2CH_2\underline{CH_2}$), 2.15-2.32 (m, 1H, $OCH_2\underline{CH_2}$), 2.42 (r. s, 1H, CH<u>NH</u>CH), 3.25-3.40 (dd, 1H, *J* = 7.4 Hz, *J* = 11.6 Hz, $CH_2\underline{CH}NH$), 4.00-4.30 (m, 2H, $O\underline{CH_2}CH_2$), 4.37 (s, 1H, <u>CH</u>Ph), 6.89 (s, 1H, C(O)<u>NH</u>), 7.24-8.59 (4H, aromatic); ^{13}C NMR (125 Hz, $CDCl_3$, Diastereomer mixtures) δ 21.26, 21.70, 26.20, 28.43, 28.56, 50.94, 51.04, 54.58, 55.35, 63.30, 64.14, 67.53, 67.93, 123.59, 134.77, 134.95, 135.137, 148.67, 148.95, 149.18, 149.25, 170.08, 173.49; HRMS *m/z* Calcd for $C_{16}H_{23}N_3O_3$ (M+): 305.1739; Found: 305.1731

***N*-*tert*-Butyl-2-(2-oxo-tetrahydro-pyran-3-ylamino)-2-pyridin-2-yl-acetamide (8-23)**. Diastereomeric ratio was determined by ^1H NMR analysis (major: 7.36 ppm, minor: 7.42 ppm); R_f 0.05 (*n*-hexane : ethyl acetate, 1 : 1); FT-IR (neat) 3315 (NHCH), 3062 (aromatic), 2967 (aliphatic), 1743 (C(O)), 1648 (C(O)NH), 1164 (C(O)) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.30 (s, 9H, $C(CH_3)_3$), 1.67-1.82 (m, 1H, $OCH_2\underline{CH_2}$), 1.88-2.06 (m, 1H, $OCH_2CH_2\underline{CH_2}$), 2.22-2.39 (m, 1H, $OCH_2\underline{CH_2}$), 3.40-3.52 (dd, 1H, *J* = 7.5 Hz, *J* = 11.5 Hz, $CH_2\underline{CH}NH$), 4.24-4.34 (m, 2H, $O\underline{CH_2}CH_2$), 4.39 (s, 1H, <u>CH</u>Ph), 7.36-7.42 (s, 1H, C(O)<u>NH</u>), 7.17-8.54 (4H, aromatic); ^{13}C NMR (125 Hz, $CDCl_3$, Diastereomer mixtures) δ 21.37, 21.71, 26.25, 26.42, 28.52, 28.59, 50.73, 50.81, 55.47, 55.73, 65.77, 65.79, 66.36, 67.69, 67.88, 122.57, 122.61, 122.62, 122.73, 136.54, 136.62, 148.52, 148.62, 156.77, 157.64, 157.65, 170.13, 170.73, 173.14, 173.32.

***N*-*tert*-Butyl-2-naphthalen-1-yl-2-(2-oxo-tetrahydro-pyran-3-ylamino)-acetamide (8-24)**. Diastereomeric ratio was determined by GC/Mass analysis (Retention time; major: 7.91 min, minor: 7.83 min); R_f 0.18 (*n*-hexane : ethyl acetate, 1 : 1); FT-IR (neat) 3324 (NHCH), 3066 (aromatic), 2966 (aliphatic), 1735 (C(O)), 1670 (C(O)NH), 1144 (C(O)) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.26 (s, 9H, $C(CH_3)_3$), 1.50-1.04 (m, 1H, $OCH_2\underline{CH_2}$), 2.08-2.22 (m, 1H, $OCH_2CH_2\underline{CH_2}$), 2.32-2.46 (m, 1H, $OCH_2\underline{CH_2}$), 2.58 (br. s, 1H, CH<u>NH</u>CH), 3.25-3.31 (dd, 1H, *J* = 7.5 Hz, *J* = 11.1 Hz, $CH_2\underline{CH}NH$), 4.08-4.33 (m, 2H, $O\underline{CH_2}CH_2$), 4.98 (s, 1H, <u>CH</u>Ph), 6.34 (s, 1H, C(O)<u>NH</u>), 7.42-8.28 (5H, aromatic); ^{13}C NMR (125 Hz, $CDCl_3$, Diastereomer mixtures) δ 21.40, 21.62, 26.38, 26.84, 28.49, 28.70, 28.88, 30.89, 51.11, 51.14, 54.182, 55.759, 62.76, 67.70, 67.87, 123.65, 124.13, 124.99, 125.23, 125.32, 125.88, 125.93, 126.37, 126.68, 128.76, 128.82, 128.84, 129.00, 131.47, 134.19, 134.25, 134.98, 135.45, 171.05, 171.57, 173.22, 173.99; HRMS *m/z* Calcd for $C_{21}H_{26}N_2O_3$ (M+): 354.1943; Found: 354.1943.

***N*-*tert*-Butyl-2-furan-2-yl-2-(2-oxo-tetrahydro-pyran-3-ylamino)-acetamide (8-25)**. Diastereomeric ratio was determined by ^1H NMR analysis (major: 3.31 ppm, minor: 3.40 ppm); R_f 0.15 (*n*-hexane : ethyl acetate, 1 : 1); FT-IR (neat) 3324 (NHCH), 2967 (aliphatic), 1737 (C(O)), 1668 (C(O)NH), 1149 (C(O)) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.32 (s, 9H, $C(CH_3)_3$), 1.52-1.74 (m, 1H, $OCH_2\underline{CH_2}$), 1.82-2.02 (m, 1H, $OCH_2CH_2\underline{CH_2}$), 2.12-2.32 (m, 1H, $OCH_2\underline{CH_2}$), 2.58 (br.

s, 1H, CHNHCH), 3.29-3.43 (dd, 1H, *J* = 7.5 Hz, *J* = 11.1 Hz, CH_2CHNH), 4.20-4.31 (m, 2H, OCH_2CH_2), 4.51 (s, 1H, CHPh), 6.73 (s, 1H, C(O)NH), 6.27-6.32, 7.34-7.36 (m, 3H); ^{13}C NMR (125 Hz, $CDCl_3$, Diastereomer mixtures) δ 21.57, 25.95, 26.10, 28.36, 28.40, 28.44, 28.50, 28.56, 28.71, 50.92, 51.00, 54.18, 55.09, 59.39, 59.78, 67.74, 67.81, 107.88, 108.50, 110.26, 110.37, 142.33, 142.39, 151.48, 168.54, 168.87, 172.99, 173.43; HRMS *m/z* Calcd for $C_{15}H_{22}N_2O_4$ (M+): 294.1580; Found: 295.1697.

***N*-Benzyl-3-methyl-2-(2-oxo-tetrahydro-pyran-3-ylamino)-butyramide (8-26)**. Diastereomeric ratio was determined by GC/Mass analysis (Retention time; major: 6.44 min, minor: 6.55 min); R_f 0.08 (*n*-hexane : ethyl acetate, 1 : 1); FT-IR (neat) 3322 (NHCH), 3060 (aromatic), 2961 (aliphatic), 1730 (C(O)), 1650 (C(O)NH), 1220 (C(O)) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83-1.05 (m, 6H, CH(CH_3)$_2$), 1.25-1.37 (m, 1H, $CH(CH_3)_2$), 1.43-2.14 (m, 3H, O$CH_2CH_2CH_2$, C$CH_2CH_2CH_2$), 3.02-3.05 (t, 1H, CHCH(CH_3)$_2$), 3.20-3.33 (dd, 1H, *J* = 7.5 Hz, *J* = 11.5 Hz, CH_2CHNH), 4.21-4.26 (q, 2H, PhCH_2NH), 4.34-4.53 (m, 2H, CCH_2CH_2), 7.19-7.36 (m, aromatic), 7.65 (s, 1H, C(O)NH); HRMS *m/z* Calcd for $C_{17}H_{24}N_2O_3$ (M+): 304.1787; Found: 304.2787.

3-Methyl-2-(2-oxo-tetrahydro-pyran-3-ylamino)-butyryl-amino]-acetic acid ethyl ester (8-27). Diastereomeric ratio was determined by GC/Mass analysis (Retention time; major: 4.54 min, minor: 4.75 min); R_f 0.06 (*n*-hexane : ethyl acetate, 1 : 1); FT-IR (neat) 3336 (NHCH), 2963 (aliphatic), 1737 (C(O)), 1679 (C(O)NH), 1203 (C(O)) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87-1.06 (m, 6H, CH(CH_3)$_2$), 1.22-1.27 (m, 3H, OCH_2CH_3), 1.52-2.36 (m, 4H, $OCH_2CH_2CH_2$, $CCH_2CH_2CH_2$, CHCH(CH_3)$_2$), 3.05-3.06 (d ,1H, C(O)CHNH), 3.31-4.47 (m, 8H, O$CH_2CH_2CH_2$, OCH_2CH_3, CHNHCH, CH_2CHNH), 7.76 (s, 1H, C(O)NH); HRMS *m/z* Calcd for $C_{14}H_{24}N_2O5$ (M+): 300.1685; Found: 300.1682.

***N*-Benzyl-3,3-dimethyl-2-(2-oxo-tetrahydro-pyran-3-yl-amino)-butyramide (8-28)**. Diastereomeric ratio was determined by GC/Mass analysis (Retention time; major: 6.46 min, minor: 6.53 min); R_f 0.32 (*n*-hexane : ethyl acetate, 1 : 1); FT-IR (KBr) 3367 (NHCH), 2973 (aliphatic), 1733 (C(O)), 1656 (C(O)NH), 1151 (C(O)) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.02 (s, 9H, C(CH_3)$_3$), 1.36-1.58 (m, 1H, OCH_2CH_2), 1.68-2.07 (m, 2H, $OCH_2CH_2CH_2$), 2.14-2.36 (m, 1H, OCH_2CH_2), 2.94 (s, 1H, CHC(CH_3)$_3$), 3.08-3.42 (dd, 1H, *J* = 7.5 Hz, *J* = 11.5 Hz, CH_2CHNH, 4.07-4.55 (m, 2H, OCH_2CH_2), 7.17-7.34 (m, aromatic); HRMS *m/z* Calcd for $C_{18}H_{26}N_2O_3$ (M+): 318.1943; Found: 318.1946.

3,3-Dimethyl-2-(2-oxo-tetrahydro-pyran-3-ylamino)-butyrylamino]-acetic acid ethyl ester (8-29). Diastereomeric ratio was determined by GC/Mass analysis (Retention time; major: 5.45 min, minor: 3.37 min); R_f 0.12 (*n*-hexane : ethyl acetate, 1 : 1); FT-IR (KBr) 3297 (NHCH), 2955 (aliphatic), 1729 (C(O)), 1643 (C(O)NH), 1192 (C(O)) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03 (s, 9H, C(CH_3)$_3$), 1.22-1.29 (t, 3H, OCH_2CH_3), 1.49-1.60 (m, 1H, $OCH_2CH_2CH_2$), 1.85-2.04 (m, 2H, OCH_2CH_2), 2.33-2.42 (m, 1H, OCH_2-CH_2CH_2), 2.97 (s, 1H, C(O)CHNH), 3.47-3.54 (dd, 1H, *J* = 7.5 Hz, *J* = 11.5 Hz, CH_2CHNH) 3.95-4.25 (m, 2H, OCH_2-CH_3), 4.27-4.32 (m, 2H, OCH_2CH_2), 7.76 (s, 1H, C(O)NH); HRMS *m/z* Calcd for $C_{15}H_{26}N_2O_5$ (M+): 314.1842; Found: 314.1845.

2-(4-Methoxy-phenyl)-2-(2-oxo-tetrahydro-pyran-3-yl-amino)-acetylamino]-acetic acid ethyl ester (8-30). Diastereomeric ratio was determined by GC/Mass analysis (Retention time; major: 6.77 min, minor: 6.88 min); R_f 0.38 (ethyl acetate); FT-IR (KBr) 3336 (NHCH), 2960 (aliphatic), 1738 (C(O)), 1679 (C(O)NH), 1249 (C(O)) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22-1.28 (m, 3H, OCH_2CH_3), 1.56-1.72 (m, 1H, $OCH_2CH_2CH_2$), 1.83-2.02 (m, 2H, OCH_2CH_2), 2.15-2.44 (m, 1H, $OCH_2CH_2CH_2$), 3.36-3.46 (dd, 1H, *J* = 7.5 Hz, *J* = 11.5 Hz, CH_2CHNH), 3.78 (s, 3H, PhOCH_3), 3.87-4.00 (m, 2H, PhCH_2NH), 4.09-4.31 (m, 2H, OCH_2CH_2), 4.52 (s, 1H, C(O)CHNH), 6.83-6.91, 7.26-7.36 (m, aromatic) 7.75 (s, 1H, C(O)NH); HRMS *m/z* Calcd for $C_{18}H_{24}N_2O_6$ (M+): 364.1634; Found: 364.1633.

***N*-Benzyl-2-(4-fluoro-phenyl)-2-(2-oxo-tetrahydro-pyran-3-ylamino)-acetamide (8-31)**. Diastereomeric ratio was determined by GC/Mass analysis (Retention time; major: 7.96 min, minor: 7.84 min); R_f 0.44 (ethyl acetate); FT-IR (KBr) 3353 (NHCH), 3058 (aromatic), 2959 (aliphatic), 1735 (C(O)), 1681 (C(O)NH), 1159 (C(O)) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.50-1.69 (m, 1H, $OCH_2CH_2CH_2$), 1.76-2.00 (m, 2H, OCH_2CH_2) 2.11-2.22 (m, 1H, $OCH_2CH_2CH_2$), 2.49 (s, 1H, CHNHCH), 3.22-3.28 (dd, 1H, *J* = 7.5 Hz, *J* = 11.5 Hz, CH_2CHNH) 4.13-4.28 (m, 2H, PhCH_2NH), 4.40-4.49 (m, 2H, OCH_2CH_2), 4.57 (s, 1H, C(O)CHNH), 6.84-7.39 (m, aromatic), 7.49 (s, 1H, C(O)NH); HRMS *m/z* Calcd for $C_{20}H_{21}FN_2O_3$ (M+): 356.1536; Found: 356.1534.

2-(4-Fluoro-phenyl)-2-(2-oxo-tetrahydro-pyran-3-yl-amino)-acetylamino]-acetic acid ethyl ester (8-32). Diastereomeric ratio was determined by GC/Mass analysis (Retention time; major: 6.85 min, minor: 6.74 min); R_f 0.40 (ethyl acetate); FT-IR (KBr) 3325 (NHCH), 2981 (aliphatic), 1740 (C(O)), 1678 (C(O)NH), 1219 (C(O)) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22-1.31 (m, 3H, OCH_2CH_3), 1.58-1.72 (m, 1H, $OCH_2CH_2CH_2$), 1.84-2.03 (m, 2H, OCH_2CH_2), 2.23-2.32 (m, 1H, $OCH_2CH_2CH_2$), 2.45 (s, 1H, CHNHCH) 3.38-3.44 (dd, 1H, *J* = 7.5 Hz, *J* = 11.5 Hz, CH2CHNH), 3.93-4.10 (m, 2H, PhCH_2NH), 4.17-4.33 (m, 2H, OCH_2-CH_2), 4.56 (s, 1H, C(O)CHNH), 6.99-7.10, 7.40-7.45 (m, aromatic) 7.77 (s, 1H, C(O)NH); HRMS *m/z* Calcd for $C_{17}H_{21}FN_2O_5$ (M+): 352.1435; Found: 352.1432.

Acknowledgment. This work was supported by the Ministry of Science and Technology and the Ministry of Health and Welfare.

References

1. Dömling, A.; Ugi, I. *Angew. Chem. Int. Ed.* **2000**, *39*, 3168.
2. Ugi, I. *J. Prakt. Chem*. **1997**, *339*, 499 and references therein.
3. Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. A. *Acc. Chem. Res*. **1996**, *29*, 123.
4. Ugi, I. *Proc. Estonian Acad. Sci. Chem.* **1998**, *47*, 107.
5. Bienaymé, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem. Eur. J.* **2000**, *6*, 3321.

6. Lee, D.; Sello, J. K.; Schreiber, S. L. *Org. Lett.* **2000**, *2*, 709.
7. Ugi, I. *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 810.
8. Ugi, I.; Dömling, A.; Horl, W. *Endeavor* **1994**, *18*, 155.
9. Zhang, J.; Jacobson, A.; Rusche, J. R.; Herlihy, W. *J. Org. Chem*. **1999**, *64*, 1074.
10. Pitlik, J.; Townsend, C. A. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 3129.
11. Mjalli, A. M. M.; Short, K. M. *Tetrahedron Lett*. **1997**, *38*, 359.
12. Harriman, G. C. B. *Tetrahedron Lett*. **1997**, *38*, 5591.
13. Hanusch-Kompa, C.; Ugi, I. *Tetrahedron Lett*. **1998**, *39*, 2725.
14. Short, K. M.; Ching, B. W.; Mjalli, A. M. M. *Tetrahedron* **1997**, *53*, 6653.
15. Short, K. M.; Ching, B. W.; Mjalli, A. M. M. *Tetrahedron Lett*. **1996**, *37*, 7489.
16. Bienayme, H.; Bouzid, K. *Tetrahderon Lett*. **1998**, *39*, 2735.
17. Zhang, C.; Moran, E. J.; Woiwode, T. F.; Short, K. M.; Mjalli, A. M. M. *Tetrahedron Lett*. **1996**, *37*, 751.
18. Strocker, A. M.; Keating, T. A.; Tempest, P. A.; Armstrong, R. W. *Tetrahedron Lett*. **1996**, *37*, 1149.
19. Keating, T. A.; Armstrong, R. W. *J. Am. Chem. Soc*. **1996**, *118*, 2574.
20. Mjalli, A. M. M.; Sarshar, S.; Baiga, T. J. *Tetrahedron Lett*. **1996**, *37*, 2943.
21. Hulme, C.; Morrissette, M. M.; Volz, F. A.; Burns, C. J. *Tetrahedron Lett*. **1998**, *39*, 1113.
22. Ugi, I.; Hörl, W.; Hanusch-Kompa, C.; Schmid, T.; Herdtweck, E. *Heterocycles* **1998**, *47*, 965.
23. Hulme, C.; Peng, J.; Louridas, B.; Menard, P.; Krolikowski, P.; Kumar, N. V. *Tetrahedron Lett.* **1998**, *39*, 8047.
24. Rossen, K.; Sager, J.; DiMichele, L. M. *Tetrahedron Lett.* **1997**, *38*, 3183.
25. Zychlinski, A. V.; Ugi, I. *Heterocycles* **1998**, *49*, 29.
26. Keating, T. A.; Armstrong, R. W. *J. Org. Chem*. **1996**, *61*, 8935.
27. Hulme, C.; Peng, J.; Tang, S.-Y.; Burns, C. J.; Morize, I.; Labaudiniere, R. *J. Org. Chem.* **1998**, *63*, 8021.
28. Kim, Y. B.; Choi, E. H.; Keum, G.; Kang, S. B.; Lee, D. H.; Koh, H. Y.; Kim, Y. *Org. Lett*. **2001**, *3*, 4149.
29. Park, S. J.; Keum, G.; Kang, S. B.; Koh, H. Y.; Lee, D. H.; Kim, Y. *Tetrahedron Lett*. **1998**, *39*, 7109.
30. Ko, D.; Kim, D. J.; Lyn, C. S.; Min, I. K.; Moon, H. *Tetrahedron Lett*. **1998**, *39*, 297.
31. Telford, G.; Wheeler, D.; Williams, P.; Tomkins, P. T.; Appleby, P.; Sewell, H.; Stewart, G. S. A. B.; Bycroft, B. W.; Pritchard, D. I. *Infection and Immunity* **1998**, *66*, 36.
32. Barlos, K.; Mamos, P.; Papaioannou, D.; Patrianakou, S. *J. Chem. Soc., Chem. Commun*. **1987**, 1583.
33. Goodman, M.; Felix, A. M. *Biochemistry* **1964**, *3*, 1529.
34. Barlos, K.; Papaioannou, D.; Theodoropoulos, D. *J. Org. Chem*. **1982**, *47*, 1324.