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Application of the Cleavable Isocyanide in Efficient Approach to Pyroglutamic Acid Analogues with Potential Biological Activity

A. M. Jassem[a,*], H. M. Al-Ajely[b], F. A. K. Almashal[a], and B. Chen[c]

[a] *College of Education for Pure Sciences, Department of Chemistry, Basrah University, Basrah, 61004 Iraq*
[b] *College of Science, Department of Chemistry, Mosul University, Mosul, 41002 Iraq*
[c] *Department of Chemistry, University of Sheffield, Sheffield, S3 7HF United Kingdom*
**e-mail: ahmed.majedd@uobasrah.edu.iq*

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Abstract—Two efficient procedures have been developed for the synthesis of pyroglutamic acid analogues **28**, **29**, and **34**. According to the first method the Ugi (4C3C) reaction is followed by a post-transformation reaction, and the second method involves the Michael addition reaction. The present methodologies demonstrate the applicability of 1-(2,2-dimethoxyethyl)-2-isocyanobenzene (**15**) as a cleavable isocyanide in the Ugi/ post-transformation reaction and a strong nucleophile in the Michael addition reaction. The framework of pyroglutamic acid analogues has been constructed by the selective cleavage of the *C*-terminal amide bond and nucleophilic addition to the activated α,β-unsaturated carbonyl group.

Keywords: cleavable isocyanide, Ugi (4C3C) reaction, Michael addition, pyroglutamic acid analogues

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Pyroglutamic acid is a core-structure of many bioactive compounds [1]. Examples of biological activities of pyroglutamic acid analogues include antibiotics such as omuralide **1** which shows an inhibitory effect toward 20*S* proteasome in bacterial cells [2, 3]. Lactacystin **2**, salinosporamide A **3** [4, 5], and dysibetaine **4** are currently used in treatment of human cancer. In addition, (–)-Pramanicin **5** and (+)-epolactaene **6** can induce apoptosis in a human leukemia B-cell line [6] (see the figure).

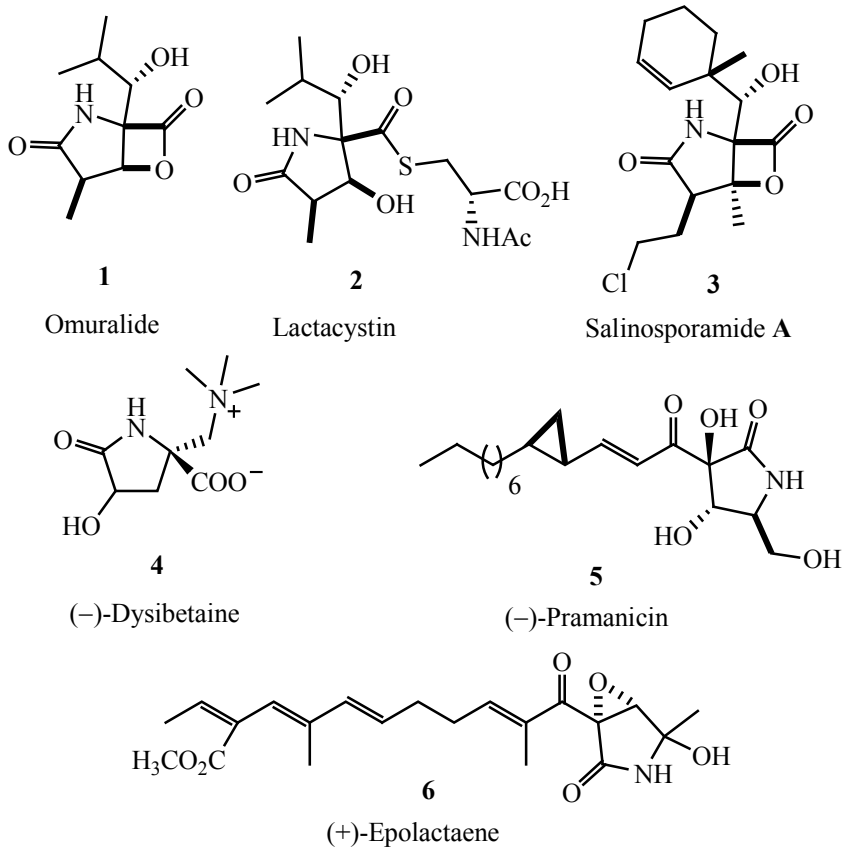
Multicomponent reactions (MCRs) are characterized by the unique ability to generate highly complex molecular structures from various starting materials in one-pot processes [7]. A combination of reactions with other strategies (such as Ugi–post-transformations) has been extensively used in synthesis of biologically active products [8, 9] and structures of multitude functionality [10, 11].

Isocyanide-based multicomponent reactions (IMCRs) have attracted close attention due to their applicability to generate biologically active molecules in a single step. Although isocyanides have demonstrated the utility in multicomponent reactions, they have not been demonstrated as "cleavable" in cleavage of α-acyloxyamide derivatives [12]. Therefore, the design and synthesis of cleavable isocyanides are required to provide an efficient access to biologically active molecules. Among the cleavable isocyanides are (β-isocyanoethyl) ethyl carbonate **7** [13], 1-cyclohexenylisonitrile **8** [14–16], *tert*-butylisonitrile **9** [17], *p*-methoxy phenyl isocyanide **10** [18, 19], diphenyl methyl isocyanide **11** [20], 1-isocyanomethyl benzotriazoles **12** [21], 4-isocyanopermethyl-butane-1,1,3-triol **13** [22], 2-nitrophenyl isocyanide **14** [23], and 1-(2,2-dimethoxyethyl)-2-isocyanobenzene **15** [24].

Although it has not been possible to cleave the hindered *C*-terminal amides of some α -acyloxyamide derivatives generated from multicomponent products, 1-(2,2-dimethoxyethyl)-2-isocyanobenzene (**15**) has been synthesized for a selective cleavage of the resultant *C*-terminal amide bond as well as it's applicability in the stereocontrolled synthesis [25–27]. In our ongoing approach to efficient methods of synthesis of biologically active pyroglutamic acid analogues, we have synthesized isocyanide **15** and studied its application in Ugi–post-transformation and Michael addition reaction in the synthesis of new pyroglutamic acid analogues **28**, **29**, **34** (Scheme 1).

RESULTS AND DISCUSSION

In Ugi–post-transformations, the Ugi products were used efficiently in the approach to structurally complex molecules [28, 29]. The key objective for synthesis of



Some pharmacologically active pyroglutamic acid analogues.

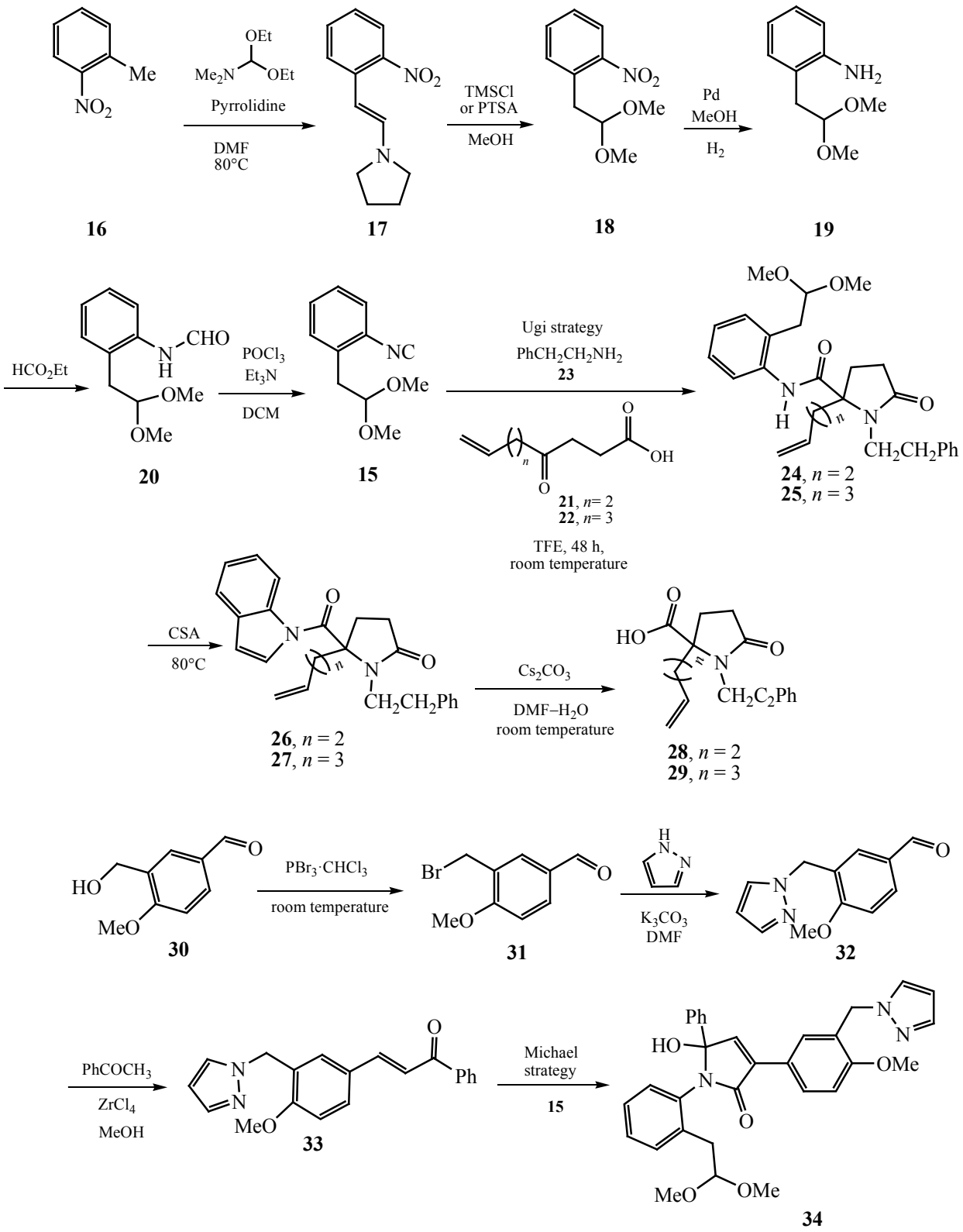
cleavable isocyanide **15** was its application in modification of the products derived from the Ugi reaction. The Ugi products **24**, **25** derived from keto acids **21, 22**, 2-phenylethanamine **23**, and a cleavable isocyanide **15** were converted to the pyroglutamic acid analogues **28**, **29** via *N*-acylindoles **26**, **27** under mild conditions. Such ability of *N*-acylindoles **26**, **27** was proven to be an efficient access to new pyroglutamic acid analogues. The achieved results demonstrated that addition of 4Å molecular sieves (20–25 mg/mmol) influenced upon yield of Ugi products **24, 25**. Although the Ugi products could be smoothly proceeded in the media of MeOH, our results indicated that using 2,2,2-trifluoroethanol (TFE) as a solvent led to higher yields. Heating the Ugi products **24**, **25** with *dl* camphorsulphonic acid (CSA) in toluene for less than 2 h resulted in the respective *N*-acylindoles derivatives **26** and **27**. Subsequently, *N*-acylindole derivatives **26**, **27** were treated with a catalytic amount of Cs_2CO_3 in DMF–H_2O (1 : 1) to afford the corresponding pyroglutamic acid analogues (**28** and **29**) in high yields.

The Michael reaction (1,4-addition) refers to formation of carbon-carbon bonds that include base-catalyzed addition of a nucleophile to an activated α,β-unsaturated carbonyl compound [30]. The new chalcone **33** acted as the core in synthesis of pyroglutamic acid analogue **34** in four steps. The first step involved bromination of alcohol **30** with formation of compound **31** which was reacted with 1*H*-pyrazole to form intermediate **32**. Its following treatment with acetophenone using $ZrCl_4$ (10 mol %) gave chalcone **33**. Finally, the pyroglutamic acid analogue **34** was successfully obtained via 1,4-addition reaction of isocyanide **15** to chalcone **33**. The reaction was first tested both in the presence MeOH and without a solvent. The reaction yielded 55% of pyroglutamic acid analogue **34** was achieved in MeOH medium at room temperature. The same reaction was also carried out under solvent-free conditions at 150°C for 6 h leading to 78% yield of product **34**.

EXPERIMENTAL

All starting compounds and solvents were purchased from Sigma Aldrich. All reactions were carried out under the atmosphere of nitrogen. TLC was performed on

Scheme 1. Use of isocyanide **15** in Ugi/post transformation and Michael addition reactions



plates precoated with silica gel 60 UV 254 (Merck). An alkaline aqueous solution of $KMnO_4$ was used to visualize the chromatograms. All synthesized compounds were purified by flash chromatography with SiO_2 (60 Å, 230–400 mesh, Merck). Majority of the synthesized compounds was isolated in >95% purity. ^1H and ^{13}C NMR spectra were measured on a Bruker AV-400 spectrometer at 400 MHz (^1H) and 100.5 MHz (^{13}C) at room temperature (Sheffield, UK). $CDCl_3$ and DMSO-d_6 were used as the internal references (^1H NMR, $CDCl_3$, δ 7.26 ppm; DMSO-d_6, δ 2.50 ppm; ^{13}C NMR, $CDCl_3$, δ 77.16 ppm; DMSO-d_6, δ 39.52 ppm). Melting points were determined on a Gallenkamp melting point apparatus in capillary tubes. HRMS were performed on a Micro Mass LCT operating in Electrospray mode (ES) (Sheffield, UK). IR spectra were recorded on a Perkin Elmer Paragon 100 FTIR spectrophotometer (Sheffield, UK).

Synthesis of convertible isocyanide **15** was carried out according to the developed earlier method [31, 32].

1-[(*E*)-2-(2-Nitrophenyl)vinyl]pyrrolidine (17). A solution of 2-nitrotoluene (**16**) (5.0 g, 36.2 mmol), dimethylformamide diethyl acetal (5.1 g, 42 mmol) and pyrrolidine (3.0 g, 42.2 mmol) in DMF (25 mL) was refluxed under the atmosphere of nitrogen for 5 h, during that time the mixture turned dark. ^1H NMR spectra of a reaction aliquot exhibited a 3 : 1 ratio of 2-nitrotoluene (**16**) to the desired product **17**. Therefore, the temperature of reaction was increased to 180°C for 19 h. After that time, ^1H NMR spectra demonstrated no 2-nitrotoluene **(16)** present. The resulting dark mixture was evaporated to dryness on a rotary evaporator and the residue was poured in H_2O (50 mL). After the extraction with ethyl acetate (5×200 mL), the combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification was performed by flash chromatography (petroleum ether–ethyl acetate, 4 : 1, R_f 0.28) to give enamine **17** as a red oil. Yield 70%, FTIR spectrum, ν, cm^{-1}: 3010 (C–H, C_6H_5), 1615 (C=C, C_6H_5), 1510 (C=C), 982 (N–C). ^1H NMR spectrum, δ, ppm: 8.01–7.79 m (1H, CH, C_6H_5), 7.87–7. 84 m (1H, CH, C_6H_5), 6.93 d (1H, J = 12.9 Hz, CH), 5.85 d (1H, J = 13.5 Hz, CH), 3.41–3.35 m (4H, $2CH_2$), 2.00–1.95 m (4H, $2CH_2$). ^{13}C NMR spectrum, δ_C, ppm: 25.3 (CH_2), 49.2 (CH_2), 91.0 (CH), 122.0 (CH), 125.5 (CH, C_6H_5), 126.8 (CH, C_6H_5), 128.9 (C, C_6H_5), 132.7 (CH, C_6H_5), 133.0 (CH, C_6H_5), 140.0 (C, C_6H_5). HRMS (ESI): 219.1110 $[M + H]^+$, calculated for $C_{12}H_{14}N_2O_2H^+$: 219.

(2,2-Dimethoxyethyl)-2-nitrobenzene (18). A solution of enamine **17** (4.5 g, 4.4 mmol) in MeOH (40 mL) was added to a solution of *para*-toluenesulfonic acid (4.70 g, 24.5 mmol) in MeOH (25 mL). The reaction mixture was refluxed for 12 h to full conversation according to TLC. The reaction mixture was cooled down, Na_2CO_3 (0.7 g, 6.3 mmol) was carefully added to it, and the mixture was stirred for 15 min. An excess solvent was removed and the resulting mixture was separated between toluene (20 mL) and H_2O (20 mL). The aqueous layer was then extracted with toluene (3×50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification was performed by flash chromatography (petroleum ether–ethyl acetate, 4 : 1, R_f 0.24) to give compound **18** as an orange oil. Yield 60%. FTIR spectrum, ν, cm^{-1}: 1510 (C=C, C_6H_5), 1355 (C–H), 1120 (C–O), 980 (N–C). ^1H NMR spectrum, δ, ppm: 7.91–7. 87 m (1H, CH, C_6H_5), 7.57–7. 52 m (1H, CH, C_6H_5), 7.45–7. 38 m (2H, CH, C_6H_5), 4.59 t (1H, J = 5.4 Hz, CH), 3.38 s (6H, $2OCH_3$), 3.24 d (2H, J = 5.5 Hz, CH_2). ^{13}C NMR spectrum, δ_C, ppm: 37.0 (CH_2), 54.4 (OCH_3), 104.6 (CH), 124.5 (CH, C_6H_5), 127.6 (CH, C_6H_5), 131.6 (CH, C_6H_5); 132.6 (CH, C_6H_5), 133.7 (CH, C_6H_5), 150.0 (C, C_6H_5). HRMS (EI^+): 234.0742 $[M + Na]^+$, calculated for $C_{10}H_{13}NO_4Na$: 234.0732.

2-(2,2-Dimethoxyethyl)aniline (19). The H-cube reactor of ThalesNano system was fitted with a 10% Pd/C cartridge and hydrogen mode was primed at 1 mL/min using MeOH for 5 min. A 0.1 M solution of compound **18** (0.42 g, 2.0 mmol) in MeOH (40 mL) was passed through the H-cube reactor at a rate of 0.5 mL/min under hydrogen pressure of 80 bar and temperature 80°C. The output stream was collected and the solvent was removed under reduced pressure to yield a 5 : 1 mixture of **19** and **18** respectively. Purification was performed by flash chromatography (petroleum ether–ethyl acetate, 4 : 1, R_f 0.35) to give the product **19** as yellow oil. Yield 80%. FTIR spectrum, ν, cm^{-1}: 3430 (N–H), 1121 (C–O), 980 (N–C). ^1H NMR spectrum, δ, ppm: 7.10–7. 06 m (2H, CH, C_6H_5), 6.78–6.69 m (2H, CH, C_6H_5), 4.52 t (1H, J = 5.34 Hz, CH), 4.08 br.s (2H, NH_2), 3.42 s (6H, $2OCH_3$), 2.89 d (2H, J = 5.5 Hz, CH_2). ^{13}C NMR spectrum, δ_C, ppm: 36.5 (CH_2), 54.0 (OCH_3), 106.6 (CH), 116.3 (CH, C_6H_5), 118.7 (CH, C_6H_5), 122.4 (C, C_6H_5), 127.8 (CH, C_6H_5), 131.3 (CH, Ar C_6H_5), 146.0 (CH, C_6H_5). HRMS (ESI): 182.1776 $[M + H]^+$, calculated for $C_{10}H_{15}NO_2H^+$: 182.1176.

***N*-[2-(2,2-Dimethoxyethyl)phenyl]formamide (20).** To a solution of hexamethyldisilazane (4.6 mL, 22.0 mmol) in THF (40 mL), *n*-butyl lithium (25 mL, 1.0 M in hexane) was added at 0°C over a period 30 min. Addition of solution of **19** (2.0 g, 11.0 mmol) in THF (40 mL) was followed by ethyl formate (1.4 mL, 16.6 mmol). The mixture was further refluxed for 18 h until TLC (diethyl ether–petroleum ether, 1 : 1) detected full conversion. A saturated aqueous solution of NH_4Cl (100 mL) was added and the resulting mixture was extracted with ethyl acetate (3×50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification was performed by flash chromatography (petroleum ether–ethyl acetate, 7 : 3, R_f 0.5) to give compound **20** as brown oil. Yield 50%. FTIR spectrum, ν, cm^{-1}: 1650 (C=O), 1116 (C–O), 995 (N–C). ^1H NMR spectrum, δ, ppm: 8.79 s (1H, CHO), 8.52–8.44 m (1H, CH, C_6H_5), 7.94 d (1H, J = 8.04 Hz, CH), 7.74–7. 71 m (1H, CH, C_6H_5), 7.56–7. 54 m (1H, CH, C_6H_5), 4.48–4.40 m (1H, CH), 3.44 s (3H, OCH_3), 3.41 s (3H, OCH_3), 2.96 d (2H, J = 6.0 Hz, CH_2). ^{13}C NMR spectrum, δ_C, ppm: 36.2 (CH_2), 55.0 (OCH_3), 100.5 (CH), 102.9 (C, C_6H_5), 123.2 (CH, C_6H_5), 126.4 (CH, C_6H_5), 127.9 (CH, C_6H_5), 129.5 (CH, C_6H_5), 130.2 (C, C_6H_5). HRMS (ESI^+): 232.0950 [M + $Na]^+$, calculated for $C_{11}H_{15}NO_3Na$: 232.0943.

1-(2,2-Dimethoxyethyl)-2-isocyano benzene (15). To a solution of compound **20** (1.2 g, 5.8 mmol) in dry THF (20 mL), TEA (2.0 mL, 14.6 mmol) was added, and the mixture was cooled down to –60°C in an EtOH–dry ice bath. $POCl_3$ (0.8 mL, 8.6 mmol) was added dropwise. Subsequently, the mixture was allowed to warm up to room temperature and stirred until TLC (diethyl ether–petroleum ether, 1 : 1) indicated full conversion (ca 1 h). The resulting mixture was poured into an ice water (150 mL) then extracted with diethyl ether (3×100 mL). The combined organic layers were washed with NaCl sat. solution (100 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification was performed by flash chromatography (petroleum ether–ethyl acetate, 7 : 3, R_f 0.6) to give compound **15** as brown oil. Yield 77%. FTIR spectrum, ν, cm^{-1}: 2987 (C–H, C_6H_5), 2853 (C–H), 2834 (C–H), 1590 (C=C, C_6H_5). ^1H NMR spectrum, δ, ppm: 7.37–7. 34 m (2H, CH, C_6H_5), 7.28–7. 23 m (2H, CH, C_6H_5), 4.62 t (1H, J = 4.9 Hz, CH), 3.4 s (6H, $2OCH_3$), 3.2 d (2H, J = 5.3 Hz, CH_2). ^{13}C NMR spectrum, δ_C, ppm: 36.0 (CH_2), 54.0 (OCH_3), 100.4 (CH), 103.8 (C, C_6H_5), 124.0 (CH, C_6H_5), 126.9 (CH, C_6H_5), 127.5 (CH, C_6H_5), 129.4 (CH, C_6H_5), 131.4 (C, C_6H_5). HRMS (ESI): 192.0927 [M + H]$^+$, calculated for $C_{11}H_{13}NO_2H^+$: 192.1025.

Synthesis of ketoacids was carried out according to the method [33].

4-Oxooct-7-enoic acid (21). 4-Bromo-1-butene (2.0 mL, 16.8 mmol) in dry THF (20 mL) was added dropwise to a vigorously stirred suspension of magnesium (0.534 g, 22.0 mmol) in dry THF (20 mL) over a period 1 h under the atmosphere of N_2. The resulting Grignard reagent was immediately transferred dropwise to a solution of succinic anhydride (1.69 g, 16.8 mmol) and copper iodide (0.09 g, 0.49 mmol) in dry THF (40 mL) at –20°C. Thus formed mixture was warmed up to 0°C and stirred for 3 h then quenched with 2M HCl (40 mL) and concentrated under reduced pressure. The organic layer was extracted with DCM (2×100 mL). The combined organic layers were washed with 2 M NaOH (2×100 mL). The combined aqueous layers were re-extracted with DCM (3×100 mL) after acidification with conc. HCl to pH 2. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash chromatography (petroleum ether–ethyl acetate–acetic acid, 6.95 : 3 : 0.05, R_f 0.4) gave ketoacid **21** as yellow viscous oil. Yield 50%. FTIR spectrum, ν, cm^{-1}: 3078 (O–H); 2983 (C–H, C_6H_5), 2918 (C–H), 2668 (C=C), 1711 (C=O). ^1H NMR spectrum, δ, ppm: 5.87–5.74 m (1H, CH), 5.16–4.98 m (2H, CH_2), 2.76–2.72 m (2H, CH_2), 2.70–2.62 m (2H, CH_2), 2.58 t (2H, J = 7.4 Hz, CH_2), 2.43–2.34 m (2H, CH_2). ^{13}C NMR spectrum, δ_C, ppm: 27.7 (CH_2), 29.0 (CH_2), 36.9 (CH_2), 41.8 (CH_2), 115.4 (CH_2), 136.9 (CH), 178.3 (C=O), 208 (C=O). HRMS (ESI^-): 155.0716, calculated for $C_8H_{12}O_3$: 155.0714.

4-Oxonon-8-enoic acid (22) was synthesized by the method similar to that for 4-oxooct-7-enoic acid **21** and obtained as pale oil. Yield 58%. FTIR spectrum, ν, cm^{-1}: 3084 (O–H), 2979 (C–H, Ar), 2940 (C–H), 1699 (C=O). ^1H NMR spectrum, δ, ppm: 1.72–1.70 m (2H, CH_2), 2.11–2.05 m (2H, CH_2), 2.48 t (2H, J = 7.5 Hz, CH_2), 2.66–2.63 m (2H, CH_2), 2.73 t (2H, J = 6.2 Hz, CH_2), 5.06–4.98 m (2H, CH_2), 5.83–5.73 m (1H, CH). ^{13}C NMR spectrum, δ_C, ppm: 27.8 (CH_2), 22.8 (CH_2), 33.0 (CH_2), 36.9 (CH_2), 41.8 (CH_2), 115 (CH_2), 137.9 (CH), 178.5 (C=O), 208.7 (C=O). HRMS (ESI^-): 169.0876, calculated for $C_9H_{14}O_3$: 169.0870.

Synthesis of the Ugi products. *a.* A solution of keto acid (1.0 mmol) in TFE (5 mL) was added to a solution of 2-phenylethanamine **23** (1.25 mmol) in TFE (5 mL) and stirred for 45 min. 1-(2,2-Dimethoxyethyl)-2-isocyano benzene **15** (1.0 mmol) was then added and the mixture was stirred at room temperature for 48 h. The excess solvent was removed under reduced pressure and the residue re-dissolved in ethyl acetate (20 mL). The organic phase was washed with 2 M HCl (10 mL), $NaHCO_3$ sat. solution (10 mL) and brine (10 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The corresponding crude Ugi products were purified by flash chromatography.

2-(But-3-en-1-yl)-*N*-[2-(2,2-dimethoxyethyl)-phenyl]-5-oxo-1-phenethylpyrrolidine-2-carboxamide (24). Brown oil, yield 75%. FTIR spectrum, ν, cm^{-1}: 3331 (N–H), 3065 (C–H, C_6H_5), 2937 (C–H), 2836 (C–H), 1686 (C=O), 1585 (C=C), 1515 (C–H). ^1H NMR spectrum, δ, ppm: 9.04 s (1H, NH), 7.75 d (1H, J = 7.4 Hz, CH, C_6H_5), 7.32–7.11 m (8H, CH, C_6H_5), 5.92–5.82 m (1H, CH), 5.15–5.04 m (2H, CH_2), 4.47 t (1H, J = 5.2 Hz, CH), 3.61 d.d (1H, J = 16.1 Hz, 6.7 Hz, CH), 3.40 s (3H, OCH_3), 3.35 s (3H, OCH_3), 3.08 d.d (1H, J = 16.9 Hz, 6.1 Hz, CH), 2.92–2.81 m (2H, CH_2), 2.71–2.51 m (4H, $2CH_2$), 2.46–2.37 m (4H, $2CH_2$), 2.1–1.99 m (2H, CH_2). ^{13}C NMR spectrum, δ_C, ppm: 27.5 (CH_2), 29.2 (CH_2), 29.8 (CH_2), 33.8 (CH_2), 34.5 (CH_2), 36.8 (CH_2), 44.2 (CH_2), 53.9 (OCH_3), 54.4 (OCH_3), 60.3 (CH), 70.3 (C), 106.4 (CH), 115.5 (CH_2), 124.2 (CH, C_6H_5), 124.4 (CH, C_6H_5), 125.5 (CH, C_6H_5), 126.5 (CH, C_6H_5), 127.7 (CH, C_6H_5), 128.5 (CH, C_6H_5), 128.6 (C, C_6H_5), 131.2 (CH, C_6H_5), 136.1 (C, C_6H_5), 137.1 (CH, C_6H_5), 138.8 (C, C_6H_5), 172.1 (C=O), 175.6 (C=O). HRMS (ESI^+): 473.2414 [M + Na]$^+$, calculated for $C_{27}H_{34}N_2O_4Na$: 473.2411**.**

***N*-[2-(2,2-Dimethoxyethyl)phenyl]-5-oxo-2-(pent-4-en-1-yl)-1-phenethylpyrrolidine-2-carboxamide (25).** Dark brown oil, yield 60%. FTIR spectrum, ν, cm^{-1}: 3333 (N–H), 3027 (C–H, C_6H_5), 2937 (C–H), 2845 (C–H), 1684 (C=O), 1587 (C=C), 1520 (C–H). ^1H NMR spectrum, δ, ppm: 8.99 m (1H, NH), 7.75 d (1H, J = 8 Hz, CH, C_6H_5), 7.33–7. 12 m (8H, CH, C_6H_5), 5.87–5.77 m (1H, CH), 5.1–5.0 m (2H, CH_2), 4.46 t (1H, J = 5.4 Hz, CH), 3.56 d.d (1H, CH, J = 17.9 Hz, 6.8 Hz, CH), 3.40 s (3H, OCH_3), 3.36 s (3H, OCH_3), 3.06 d.d (1H, J = 17.1 Hz, 6.2 Hz, CH), 2.92–2.85 m (2H, CH_2), 2.65–2.54 m (4H, $2CH_2$), 2.45–2.38 m (4H, $2CH_2$), 2.25–2.12 m (2H, CH_2), 1.94–1.54 m (2H, CH_2). ^{13}C NMR spectrum, δ_C, ppm: 27.5 (CH_2), 28.3 (CH_2), 29.2 (CH_2), 29.7 (CH_2), 33.8 (CH_2), 34.5 (CH_2), 36.9 (CH_2), 44.2 (CH_2), 53.9 (OCH_3), 54.5 (OCH_3), 70.4 (C), 106.5 (CH), 115.5 (CH_2), 124.5 (CH, C_6H_5), 125.5 (CH, C_6H_5), 126.6 (CH, C_6H_5), 127.6 (CH, C_6H_5), 128.6 (CH, C_6H_5), 128.7 (C, C_6H_5), 131.2 (CH, C_6H_5), 136.2 (C, C_6H_5), 137 (CH, C_6H_5), 138.8 (C, C_6H_5), 172.0 (C=O), 175.5 (C=O). HRMS (ESI^+): 487.2567 [M + Na]$^+$, calculated for $C_{28}H_{36}N_2O_4Na$: 487.2570.

Synthesis of *N*-acylindole derivatives. *b*. To a solution of an Ugi product (1.0 mmol) in toluene (5 mL), *dl* camphorsulphonic acid (0.5 mmol) was added. The reaction mixture was stirred at 80°C for 2 h, then cooled down, quenched with a saturated solution of $NaHCO_3$ (10 mL) and extracted with ethyl acetate (3×20 mL). The organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification was performed by a flash chromatography to obtain the corresponding *N*-acylindole derivatives.

5-(But-3-en-1-yl)-5-(1*H*-indole-1-carbonyl)-1-phenethylpyrrolidin-2-one (26). Yellow viscous oil, yield 82%. FTIR spectrum, ν, cm^{-1}: 3065 (C–H, C_6H_5), 3029 (C–H, C_6H_5), 2932 (C–H), 1691 (C=O), 1537 (C=C), 1450 (C–H). ^1H NMR spectrum, δ, ppm: 8.53 d (1H, J = 8.3 Hz, CH, C_6H_5), 7.58 d (1H, J = 7.5 Hz, CH, C_6H_5), 7.41 t (1H, J = 7.4 Hz, CH, C_6H_5), 7.34–7. 14 m (6H, CH, C_6H_5), 6.67 d (1H, J = 3.6 Hz, CH, C_6H_5), 5.92–5.84 m (1H, CH), 3.49–3.30 m (2H, CH_2), 2.86–2.79 m (2H, CH_2), 2.73–2.61 m (4H, $2CH_2$), 2.43–2.18 m (4H, 2 CH_2), 2.02–1.99 m (2H, CH_2). ^{13}C NMR spectrum, δ_C, ppm: 27.0 (CH_2), 27.6 (CH_2), 29.6 (CH_2), 33.7 (CH_2), 35.7 (CH_2), 44.5 (CH_2), 71.5 (CH_2), 110.5 (CH, C_6H_5), 115.8 (CH_2), 117.1 (CH, C_6H_5), 120.9 (CH, C_6H_5), 123.7 (CH, C_6H_5), 124.4 (CH, C_6H_5), 125.8 (CH, C_6H_5), 126.5 (CH, C_6H_5), 128.5 (C, C_6H_5), 128.7 (CH, C_6H_5), 129.4 (C, C_6H_5), 136.5 (CH), 136.7 (C, C_6H_5), 138.5 (C, C_6H_5), 171.6 (C=O), 175.1 (C=O). HRMS (ESI^+): 387.2067 [M + H]$^+$, calculated for $C_{25}H_{26}N_2O_2$: 387.2067.

5-(1*H*-Indole-1-carbonyl)-5-(pent-4-en-1-yl)-1-phenethyl pyrrolidin-2-one (27). Yellow viscous oil, yield 70%. FTIR spectrum, ν, cm^{-1}: 3060 (C–H, C_6H_5), 3029 (C–H, C_6H_5), 2932 (C–H), 1696 (C=O), 1542 (C=C), 1450 (C–H). ^1H NMR spectrum, δ, ppm: 8.53 d (1H, J = 8.4 Hz, CH, C_6H_5), 7.52 d (1H, J = 7.6 Hz, CH, C_6H_5), 7.4 t (1H, J = 7.2 Hz, CH, C_6H_5), 7.35–7. 14 m (5H, CH, C_6H_5), 6.66 d (1H, J = 3.8 Hz, CH, C_6H_5), 5.88–5.77 m (1H, CH), 5.12–5.04 m (2H, CH_2), 3.42–

3.30 m (2H, CH_2), 2.86–2.76 m (2H, CH_2), 2.72–2.60 m (2H, CH_2), 2.40–2.32 m (4H, $2CH_2$), 1.60–1.27 m (4H, $2CH_2$). ^{13}C NMR spectrum, δ_C, ppm: 22.2 (CH_2), 24.3 (CH_2), 27.8 (CH_2), 29.7 (CH_2), 33.7 (CH_2), 36.1 (CH_2), 44.6 (CH_2), 71.7 (C), 110.4 (CH, C_6H_5), 115.9 (CH_2), 117.2 (CH, C_6H_5), 120.9 (CH, C_6H_5), 123.8 (CH, C_6H_5), 124.3 (CH, C_6H_5), 125.7 (CH, C_6H_5), 126.5 (CH, C_6H_5), 128.5 (CH, C_6H_5), 128.8 (CH, C_6H_5), 129.5 (C, C_6H_5), 136.7 (CH), 137.5 (C, C_6H_5), 138.6 (C, C_6H_5), 171.8 (C=O), 175.2 (C=O). HRMS (ESI^+): 401.2219 [M + H]$^+$, calculated for $C_{26}H_{28}N_2O_2$: 401.2224.

Synthesis of pyroglutamic acid analogues. *c.* To a solution of *N*-acylindole products (1.0 mmol) in DMF–H_2O (1 : 1, 4 mL), Cs_2CO_3 (1.0 mmol) was added. The mixture was stirred at 22°C for 6 h, then diluted with H_2O (10 mL), made basic with 1M solution of NaOH and extracted with ethyl acetate (2×20 mL). The aqueous layer was then acidified with 1M HCl and extracted with ethyl acetate (2×20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification was performed by flash chromatography to obtain the titled pyroglutamic acid analogues.

2-(But-3-en-1-yl)-5-oxo-1-phenethylpyrrolidine-2-carboxylic acid (28). Colorless viscous oil, yield 85%. FTIR spectrum, ν, cm^{-1}: 3456 (O–H), 3024 (C–H, C_6H_5), 2920 (C–H), 2848 (C–H), 1691 (C=O), 1450 (C–H). ^1H NMR spectrum, δ, ppm: 7.60–7. 13 m (5H, CH, C_6H_5), 5.92–5.82 m (1H, CH), 5.16–5.06 m (2H, CH_2), 3.40–3.28 m (2H, CH_2), 2.85 t (2H, J = 8.6 Hz, CH_2), 2.69 t (2H J = 5.8 Hz, CH_2), 2.43–2.19 m (4H, $2CH_2$), 2.07–1.99 m (2H, CH_2). ^{13}C NMR spectrum, δ_C, ppm: 26.8 (CH_2), 30.0 (CH_2), 32.6 (CH_2), 32.9 (CH_2), 34.5 (CH_2), 45.3 (CH_2), 70.1 (C), 115.2 (CH_2), 125.8 (CH, C_6H_5), 127.5 (CH, C_6H_5), 128.6 (CH, C_6H_5), 139.1 (CH), 139.4 (C, C_6H_5), 168.6 (C=O), 180.1 (C=O). HRMS (ESI^+): 288.1594 [M + H]$^+$, calculated for $C_{17}H_{21}NO_3$: 288.1594.

5-Oxo-2-(pent-4-en-1-yl)-1-phenethylpyrrolidine-2-carboxylic acid (29). Colorless viscous oil, yield 80%. FTIR spectrum, ν, cm^{-1}: 3452 (O–H), 3026 (C–H, C_6H_5), 2933 (C–H), 2845 (C–H), 1689 (C=O), 1459 (C–H). ^1H NMR spectrum, δ, ppm: 7.25–7. 16 m (5H, CH, C_6H_5), 5.90–5.86 m (1H, CH), 5.18–5.09 m (2H, CH_2), 3.47–3.32 m (2H, CH_2), 2.88 t (2H, J = 5.9 Hz, CH_2), 2.61 t (2H, J = 5.4 Hz, CH_2), 2.47–2.20 m (4H, $2CH_2$), 2.10–1.98 m (4H, $2CH_2$). ^{13}C NMR spectrum, δ_C, ppm: 26.8 (CH_2), 28.2 (CH_2), 30.7 (CH_2), 32.8 (CH_2), 33.0 (CH_2), 34.6 (CH_2), 45.6 (CH_2), 71.0 (C), 115.5 (CH_2), 125.9 (CH, C_6H_5), 128.4 (CH, C_6H_5), 129.2 (CH, C_6H_5), 138.2 (CH), 138.8 (C, C_6H_5), 167.8 (C=O), 181.1 (C=O). HRMS (ESI^+): 302.1796 [M + H]$^+$, calculated for $C_{18}H_{23}NO_3$: 302.1774.

3-(Bromomethyl)-4-methoxybenzaldehyde (31). To a solution of 3-(hydroxymethyl)-4-methoxybenzaldehyde (**30**) (1.66 g, 10.0 mmol) in $CHCl_3$ (20 mL), PBr_3 (3.24 g, 12.0 mmol) was added. The mixture was stirred at room temperature for 3 h. After the reaction was completed (TLC), H_2O (5 mL) was added to the mixture. The organic layer was separated and the aqueous layer was extracted with DCM (3×20 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated. The pure product **31** was obtained as a colorless oil by flash chromatography (DCM–ethyl acetate, 1 : 1 R_f 0.6). Yield 69%. FTIR spectrum, ν, cm^{-1}: 1732 (C=O), 558 (C–Br). ^1H NMR spectrum, δ, ppm: 9.98 s (1H, CHO), 7.53 d (1H, J = 2.0 Hz, CH, C_6H_5), 7.41 d (1H, J = 9.0 Hz, CH, C_6H_5), 7.21 s (1H, CH, C_6H_5), 4.97 s (2H, CH_2), 3.93 s (3H, OCH_3). ^{13}C NMR spectrum, δ_C, ppm: 19.1 (CH_2), 57.1 (OCH_3), 113.8 (CH, C_6H_5), 127.4 (C, C_6H_5), 129.0 (CH, C_6H_5), 134.8 (C, C_6H_5), 140.0 (CH, C_6H_5), 157.1 (C, C_6H_5), 188.8 (C=O).

3-[(1*H*-Pyrazol-1-yl)methyl]-4-methoxybenzaldehyde(32). A mixture of 3-(bromomethyl)-4-methoxybenzaldehyde (**31**) (0.45 g, 2.0 mmol), 1*H*-pyrazole (0.13 g, 2.0 mmol) and NaH (0.14 g, 6.0 mmol) in dioxane (40 mL) was stirred for 15 min and then heated at 90°C for 72 h. Upon completion of the reaction, the resulting mixture was cooled down, poured into H_2O (100 mL) and extracted with DCM (4×30 mL). The separated organic layers were dried over $MgSO_4$, filtered and evaporated. The obtained crude product was purified by flash chromatography (petroleum ether–acetone, 2 : 1, R_f 0.8) to afford **32** as yellow crystals. Yield 56%, mp 76–77°C. FTIR spectrum, ν, cm^{-1}: 1684 (C=O), 1259 (C–H). ^1H NMR spectrum, δ, ppm: 9.83 s (1H, CHO), 7.86 d (1H, J = 8.0 Hz, CH, C_6H_5), 7.58 d (1H, J = 3.0 Hz, CH, C_6H_5), 7.48 d (1H, J = 2.0 Hz, $C_3N_2H_3$), 7.32 d (1H, J = 2.0 Hz, CH, C_6H_5), 7.26 s (1H, CH, C_6H_5), 6.31 t (1H, J = 4.5 Hz, $C_3N_2H_3$), 5.39 s (2H, CH_2), 3.97 s (3H, OCH_3). ^{13}C NMR spectrum, δ_C, ppm: 50.0 (CH_2), 56.7 (OCH_3), 105.8 (CH, $C_3N_2H_3$), 111.6 (CH, C_6H_5), 127.2 (CH, C_6H_5), 129.1 (CH, $C_3N_2H_3$), 129.7 (C, C_6H_5), 131.1 (CH, C_6H_5), 133.2 (C, C_6H_5), 161.8 (C, C_6H_5), 139.5 (CH, $C_3N_2H_3$), 191.6 (C=O).

(*E*)-3-{3-[(1*H*-Pyrazol-1-yl)methyl]-4-methoxyphenyl}-1-phenylprop-2-en-1-one (33). To a solution of aldehyde **32** (0.21 g, 1.0 mmol) and acetophenone (0.13 g, 1.0 mmol) dissolved in MeOH (15 mL), $ZrCl_4$ (23.3 mg, 10 mol %) was added. The mixture was stirred at room temperature for 3 h. Upon completion of the reaction (TLC monitoring), the solvent was evaporated under reduced pressure. The residue was diluted with H_2O (20 mL) and extracted with ethyl acetate (4×20 mL). The combined organic layers were dried over Na_2SO_4, filtered and evaporated. The crude product was purified by flash chromatography (ethyl acetate– petroleum ether, 3 : 1 R_f 0.7) to give chalcone **33** as white solid. Yield 77%, mp 93-94ºC. FTIR spectrum, ν, cm^{-1}: 1611 (C=O), 1524 (C=C), 1328 (C–N). ^1H NMR spectrum, δ, ppm: 7.99 d.d (1H, J = 5.5 Hz, 2.5 Hz, CH), 7.71 d (1H, J = 13.0 Hz, CH), 7.58–7. 55 m (3H, CH, C_6H_5), 7.51 t (2H, J = 3.9 Hz, CH, C_6H_5), 7.48 t (1H, J = 3.9 Hz, CH, C_6H_5), 6.92 t (1H, J = 8.5 Hz, CH, $C_3N_2H_3$), 6.30 t (1H, J = 3.0 Hz, CH, $C_3N_2H_3$), 5.37 s (2H, CH_2), 3.91 s (3H, OCH_3). ^{13}C NMR spectrum, δ_C, ppm: 50.3 (CH_2), 56.3 (OCH_3), 105.6 (CH, $C_3N_2H_3$), 111.9 (CH, C_6H_5), 120.2 (CH), 126.2 (CH, C_6H_5), 127.4 (CH, C_6H_5), 128.7 (C, C_6H_5), 128.8 (CH, C_6H_5), 129.2 (C, C_6H_5), 130.7 (CH, C_6H_5), 131.3 (CH, $C_3N_2H_3$), 133.4 (CH, C_6H_5), 138.2 (C, C_6H_5), 139.2 (CH, $C_3N_2H_3$), 144.2 (CH), 159.4 (C, C_6H_5), 189.4 (C=O). HRMS (ESI^+): 319.1441 $[M + H]^+$, calculated for $C_{20}H_{19}N_2O_2$: 319.1439.

3-{3-[(1*H*-Pyrazol-1-yl)methyl]-4-methoxyphenyl}-1-[2-(2,2-dimethoxyethyl)phenyl]-5-hydroxy-5-phenyl-1*H*-pyrrol-2(5*H*)-one (34). A mixture of chalcone **33** (0.31 g, 1.0 mmol) with isocyanide **15** (0.19 g, 1.0 mmol) in MeOH (10 mL) was stirred at room temperature for 24 h. After consuming the starting materials (TLC monitoring), the resulting mixture was diluted with H_2O (20 mL) and extracted with ethyl acetate (3×30 mL). The combined organic layers were dried over Na_2SO_4, filtered and evaporated. The crude product was purified by flash chromatography (ethyl acetate–petroleum ether, 2 : 1 R_f 0.26) to obtain the corresponding product **34** as black amorphous compound, yield 60%. FTIR spectrum, ν, cm^{-1}: 3154 (O–H), 1663 (C=O), 1504 (C=C), 1317 (C–N). ^1H NMR spectrum, δ, ppm: 2.99 d (2H, J = 5.5 Hz, CH_2), 3.20 s (6H, $2OCH_3$), 3.88 s (3H, OCH_3), 4.60 d.d (1H, J = 12 Hz, 6.5 Hz, CH), 5.30 s (2H, CH_2), 6.26 t (1H, J = 3.1 Hz, CH, $C_3N_2H_3$), 7.11 d (1H, J = 8.1 Hz, CH, C_6H_5), 7.76–7. 13 m (14H, CH, C_6H_5+ OH), 7.88 d.d (1H, J = 8.5 Hz, 4.1 Hz, CH, $C_3N_2H_3$), 8.11 d (2H, J = 7.5 Hz, CH, C_6H_5). ^{13}C NMR spectrum, δ_C, ppm: 35.2 (CH_2), 49.8 (OCH_3), 53.3 (OCH_3), 55.8 (OCH_3), 103.3 (C), 105.2 (CH, $C_3N_2H_3$), 111.4 (CH), 119.7 (CH, C_6H_5), 125.7 (CH, C_6H_5), 126.9 (CH, C_6H_5), 127.7 (C, C_6H_5), 128.3 (CH, C_6H_5),128.7 (CH, $C_3N_2H_3$), 129.6 (CH, C_6H_5), 130.2 (C, C_6H_5), 130.8 (C, C_6H_5), 131.2 (CH, Ar), 132.9 (CH), 133.4 (C, C_6H_5), 137.7 (C), 138.7 (CH, $C_3N_2H_3$), 143.7 (C, C_6H_5), 158.9 (C, C_6H_5), 188.9 (C=O). HRMS (ESI^+): 548.2156 $[M + Na]^+$, calculated for $C_{31}H_{31}N_3O_5Na$: 548.2155.

CONCLUSIONS

Two efficient methods of synthesys of new pyroglutamic acid analogues involving the Ugi–post-condensation and the Michael addition reaction have been developed. These methodologies demonstrate the utility of 1-(2,2-dimethoxyethyl)-2-isocyanobenzene as an efficient approach to the study of it's applicability in pyroglutamic acid analogues synthesis. Subsequent tests of the potential biological activity of these compounds are ongoing. It is anticipated that the convertible isocyanide possess a potential for interesting applications in construction of bioactive molecules for drug discovery.

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CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

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