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Synthesis and radical polymerizations of acrylamides having Gabapentin moieties

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***Abstract**:* The synthesis and radical polymerizations of several acrylamides having Gabapentin(GBP) moieties were examined. The monomers were prepared by the reactions of 1-aminomethyl-1-cyclohexane acetic acid salts with acryloyl chloride in the presence of triethylamine in moderate yields. Radical polymerizations of the monomers were carried out in the presence of AIBN (3 mol%) in Dimethyl formamide (DMF) with moderate yield. The thermal behavior of the polymers was investigated by thermo gravimetric analysis (TGA) and differential scanning calorimeter (DSC) to determine the thermal degradation pattern and glass transition temperature (T_g). The resulting polymers showed a thermal stability up to 400 ^{0}C. The glass transition temperatures of the polymers were found not to depend on the substituents of the GBP moieties. Nearly the same TG's were observed for polymers. We found the molecular weights of the polymers to be between 20700 and 2300 g/mol. We obtained poly(HFCHA) as a water-soluble polymer. Poly(MFCHA), poly(EFCHA) and poly(PFCHA) were soluble in common solvents.

*Keywords:*Gabapentin, acrylamide, radical polymerization, water soluble polymer

Introduction

Polymeric materials have gained increasing interest throughout the 20th century and served in a vast number of medical and/or pharmaceutical applications such as orthopedic, dental or breast implants, artificial organs, pacemakers, sutures, vascular grafts, heart valves, intraocular and contact lenses, renal dialysers and other medical devices or controlled drug delivery systems [1, 2]. A polymeric drug is a polymer which contains a drug unit either as part of the polymer backbone, as a terminal unit, or a pendant unit. In some cases the polymer itself functions as the therapeutic agent where low molecular weight analogs are inactive. It has been well established that natural polymers play an important role in every aspect of biological existence. More recently it has been found that certain synthetic polymers can also elicit a number of interesting biological effects. For example, synthetic polyanionic polymers demonstrate a broad range of physicological properties [3-4] such as interferon induction as well as antiviral and antitumor activity. These synthetic polymers are water soluble which is essential for systemic administration and transport within the host. The synthetic polymers that exhibit the best biological response behave similarly to proteins, glycoproteins, and polynucleotides which are known to modulate immune responses.

Gabapentin [1-(aminomethyl) cyclohexaneacetic acid] (GBP) is a antiepileptic drug currently being introduced in therapy worldwide [5–7]. GBP is a widely used drug with anticonvulsant, antinociceptive and anxiolytic properties [8]. We have developed

polymers having GBP moieties as synthetic functional polymers, which are prepared by the radical polymerization method. Radical polymerization of acrylamides having drug moieties has been the focus of much attention, and many articles have also been reported by other groups [9].

Acrylic polymers are not biodegradable. Depending on their structure and on the pH, some of them are water-soluble. The water-insoluble ones are stable in an aqueous/physiological environment, thus can be used for the encapsulation of cells. Soluble ones can be used for the design of hydrogels. Hydrogels are hydrophilic three-dimensional networks, which are insoluble due to the presence of chemical and/or physical crosslinks. They can nevertheless degrade, since the crosslinks are susceptible to hydrolysis in vivo, allowing the hydrogel to degrade into soluble polymers. A drug can be released from the matrix by diffusion and/or by gel degradation. Polymeric drug delivery systems are used not only to improve aqueous solubility of drug molecules but also to achieve desirable pharmacokinetics and an enhanced therapeutic index. New polymers are needed to improve the biodistribution and targeting-ability of polymeric carriers.

In earlier work we have incorporated gababentin moiety in order to achieve both water solubility and controlled biodistribution. The biodistribution of pristine gababentin group has been evaluated by us previously [10]. In this study, the synthesis and characterization of poly(HFCHA), poly(MFCHA), poly(EFCHA) and poly(PFCHA) containing GBP units is described. The polymers were obtained by radical polymerization of HFCHA, MFCHA, EFCHA and PFCHA.

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Results and discussion

The monomers were prepared by the reactions of the corresponding amino acid ester hydrochlorides with acryloyl chloride in the presence of triethylamine in satisfactory yields. The structures of the monomers were determined by ^{1}H NMR, ^{13}C-NMR, and FTIR. FTIR spectrum of poly(MFCHA) is given in Figure1.

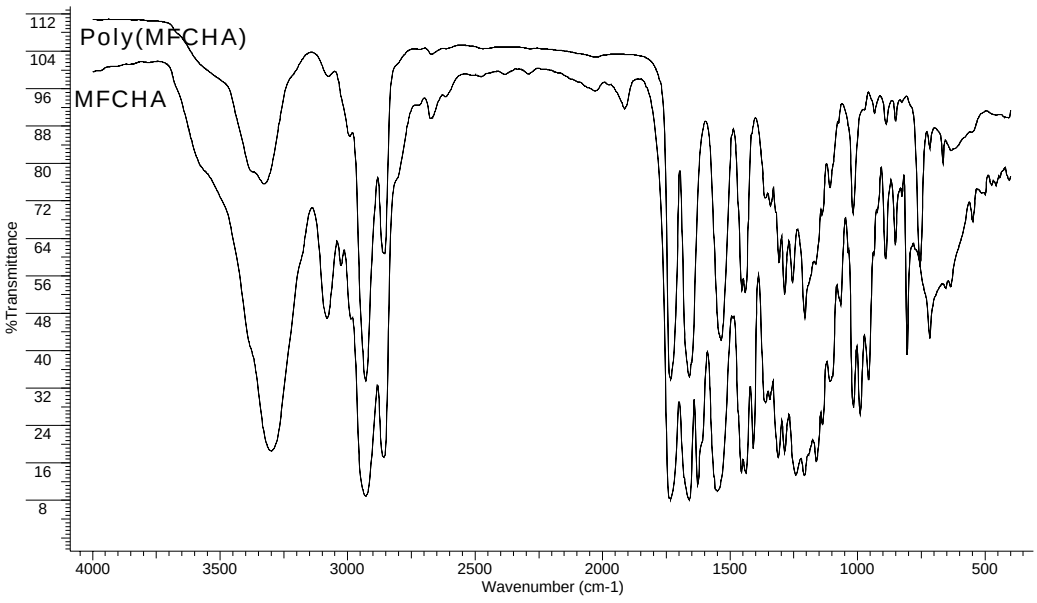


Fig. 1. FTIR spectrum of MFCHA and poly(MFCA).

Radical polymerizations of N-[(1-1-hydroxyformoyl-1'-methyl)cyclohexylmethyl] acrylamides were carried out in the presence of AIBN (1 mol %) at 60 ^{0}C for 20 h in DMF, polymers were isolated by reprecipitation with methanol. The structures of the polymer were determined by ^{1}H NMR, ^{13}C-NMR, and FTIR. The thermal behavior of the polymers was investigated by thermo gravimetric analysis (TGA) and differential scanning calorimeter (DSC) to determine the thermal degradation pattern and glass transition temperature (T_g). The resulting polymers showed a thermal stability up to 400 ^{0}C. We acquired polymers, which are between 20711 g/mol and 23352 g/mol. The results obtained are given in Table 1.

Tab. 1. Thermal properties and molecular weights of polyacrylamides having gabapentin moieties.

Monomer	Yield (%)	M_n	M_w/M_n	T_g (^{0}C)	T_d 10 (^{0}C)
HFCHA	60	23300	2,36	65.8	190
MFCHA	55	20700	2,21	63.4	320
EFCHA	58	22700	2,44	62.2	320
PFCHA	59	21200	2,74	62.8	320

The reaction was carried out in DMF at 60 °C under dry nitrogen in a glass tube .5 mmol monomer and (3% mol) radical initiator were introduced to polymerization tube.

Poly(HFCHA): ^{1}H NMR δ (DMSO) 12.1 (br, 1H),2,36 (br, 2H), 2,23(br, 2H),1,97 (br, 1H), 1,86-1,1 (br, 12 H) ppm.
Poly(MFCHA): ^{1}H NMR δ ($CDCl_3$) 3,64 (br,s, 3 H), 2,34 (br, 2H), 2,23(br, 2H),1,95 (br, 1H), 1,8-1,12 (br, 12 H) ppm.
Poly(EFCHA): ^{1}H NMR δ ($CDCl_3$) 7,2-6,6 (br, 1 H), 4,1(s, 2 H), 2,308 (br, 2 H), 2,167(br, 2H) 1,95 (br, 1H), 1,7-0,9(br, 15 H) ppm.
Poly(PFCHA): ^{1}H NMR δ ($CDCl_3$) 3,98 (s, 2 H), 2,323 (br, 2 H), 2,164 (br, 2 H), 1,182(br, 1H)1,6-1,1 (br, 14 H), 0,9 (s, 3 H) ppm.

DSC and TG(DTG) measurements (Figure 2 and Figure 3) were made to study the thermal behaviour and thermal stability of the prepared polyacrylamides containing GBP units. The results are collected in Table 1. Investigation of the DSC curves showed that T_g's of polyacrylamides as a second order transition were in the range of 62,2–65,8 ^{0}C. The polyacrylamides made from N-[(1-1-hydroxyformoyl-1'-methyl)cyclohexylmethyl] acrylamide showed almost the same T_g values. As shown in the Table 1, the poly(HFCHA) containing acid group has the highest T_g and poly(EFCHA) which contains ethoxy group has the lowest T_g in this category. TG and Differential TG (DTG) thermograms revealed that poly(MFCHA), poly(EFCHA) and poly(PFCHA) degradation take place in two stages but poly(HFCHA) degradation takes place in three stages. The first being at a temperature around 260 ^{0}C that corresponds to a very small mass loss of about 3%; the second occurs at about 350 ^{0}C and is the main degradation stage. The first broad peak which appears on DTG thermogram of poly(HFCHA) only, may be due to the release of water between either two carbonyl groups which are, thus, bonded each other via an -o- bridge or amide and carboxyl groups forming a zwitter ion.The 10% weight loss of the polymers as a criterion of thermal stability occurred in the range of 190–320 ^{0}C which indicated good thermal stability of the prepared polyacrylamides.

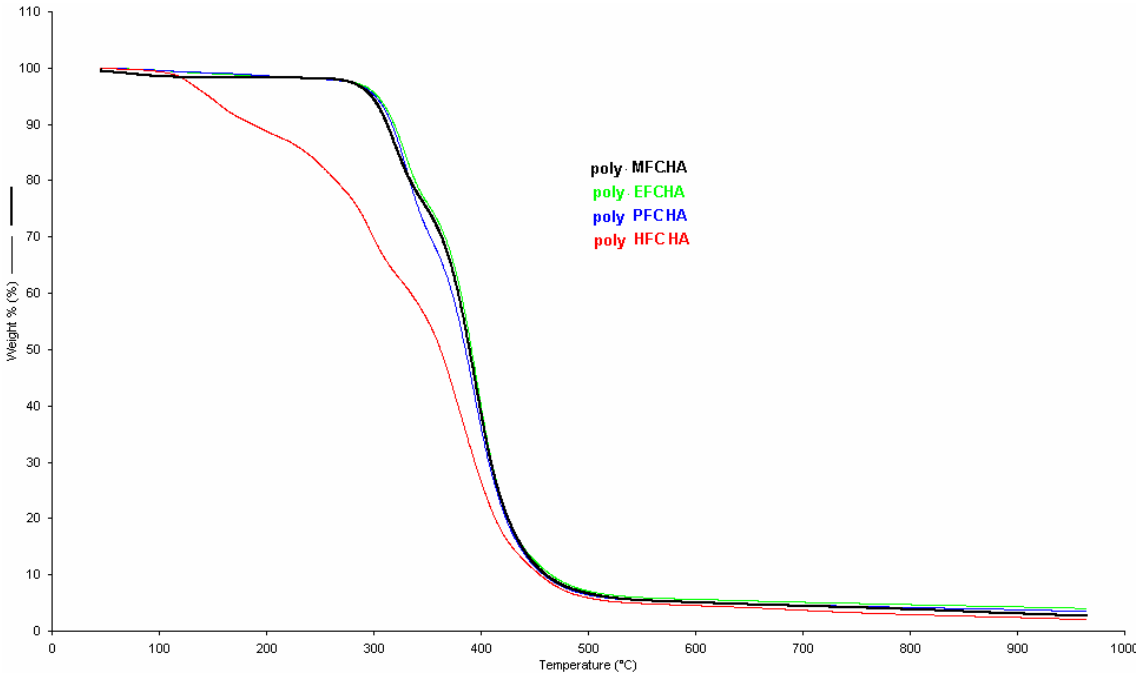


Fig. 2. TG thermograms of polymers.

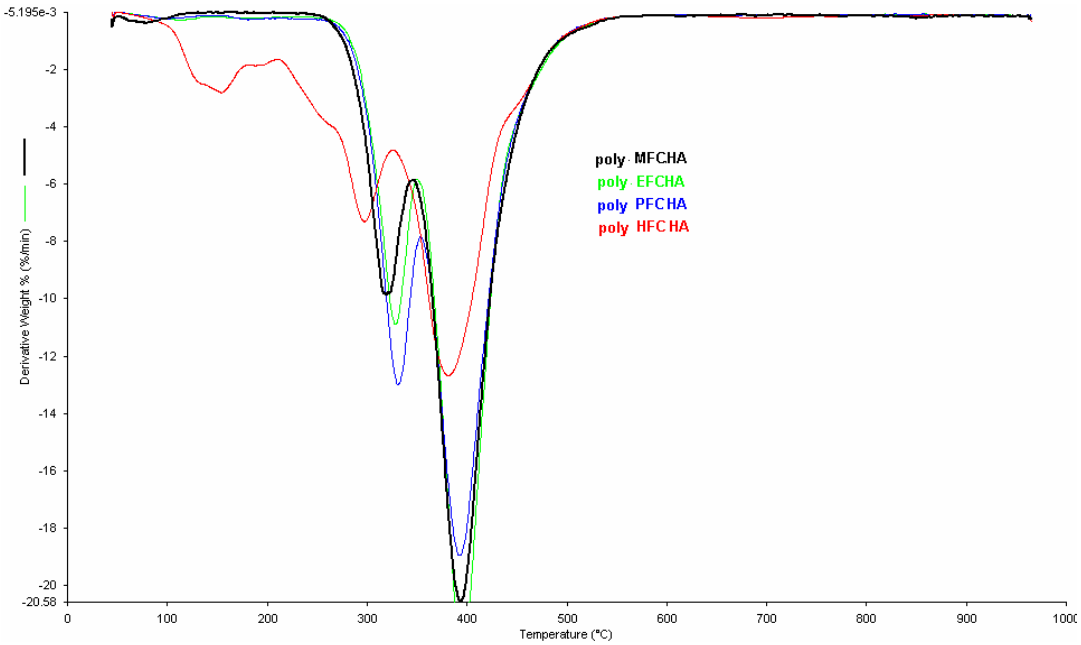


Fig. 3. DTG thermograms of polymers

Solubility

For rigid thermally stable polymers, solubility in common organic solvents is a very important factor, determining their processability. Therefore the solubility behavior of the polyacrylamides was examined in different solvents. As shown in Table 2 these polymers were readily soluble in polar aprotic solvents and they were also soluble in

chloroform, dichloromethane and tetrahydrofuran. Only Poly(HFCHA) was water soluble due to the acid group at pH ≥9

Tab. 2. Solubilty of polyacrylamides in common organic solvents.

Code	DMSO	DMF	DMAC	NMP	THF	CH_2Cl_2	$CHCl_3$	H_2O	Acetone
Poly(HFCHA)	+	+	+	+	-	-	-	+*	-
Poly(MFCHA)	+	+	+	+	+	+	+	-	+
Poly(EFCHA)	+	+	+	+	-	+	+	-	+
Poly(PFCHA)	+	+	+	+	-	+	+	-	+

*pH ≥9 soluble pH=7 insoluble

Conclusions

In this article, the synthesis and radical polymerizations of several acrylamides having GBP moieties were examined. The monomers were prepared by the reactions of acryloyl chloride with GBP acid ester hydrochlorides in satisfactory yields. We obtained polymers, which have molecular weights between 20700 g/mol and 23300 g/mol. The thermal behavior of the polymers was investigated by thermogravimetric analysis (TGA) and differential scanning calorimeter (DSC). The T_gs of polymers from DSC thermograms were around 65 ^{0}C. Investigation of thermal stability of polyacrylamides by TG(DTG) showed that the polymers started to lose weight, due to thermal degradation, at about 250 ^{0}C The polymers were soluble in chloroform, THF, DMF, and DMSO, but were not soluble in diethyl ether. Polyacrylamides having GBP moieties have potential applications as polymeric drugs or as biocompatible materials.

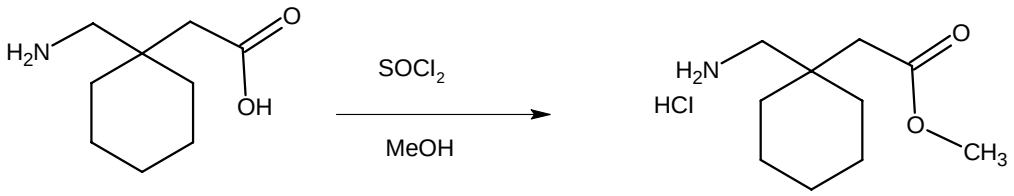
Experimental part

Measurements

^{1}H and ^{13}C-NMR spectra were recorded on Varian AS-400 spectrometers in deutero chloroform ($CDCl_3$) or deutero dimethyl sulfoxide (DMSO-d_6). FTIR spectra were obtained with a Perkin Elmer spectrophotometer. Melting points (m.p.) were measured using a Gallenkamp melting point apparatus. Molecular weights (M_n) and their distributions (M_w/M_n) were estimated by gel permeation chromatography. Molecular weights and molecular weight distributions of the polymers were measured on a gel permeation chromatography (GPC) system consisting of a Agilent 1050 pump (Agilent 79911GP-505) and an Agilent 1100 RI detector, with a DMF as solvent (flow rate 1 ml/min) according to polystyrene standards. Thermal analyses were performed using a Pyris 6 TGA Thermogravimetric Analyzer and a Pyris 6 DSC Differential Scanning Calorimeter instruments. The glass transition temperature (T_g) determined by differential scanning calorimetry (DSC) was taken as an inflection point on a trace at a heating rate of 20 ^{0}C/min.The 10% weight loss temperature (T_d10) was determined by thermogravimetric analysis (TGA) at a heating rate of 20 ^{0}C/min under a nitrogen atmosphere.

Synthesis of 1-aminomethyl-1-cyclohexane acetic acid salts

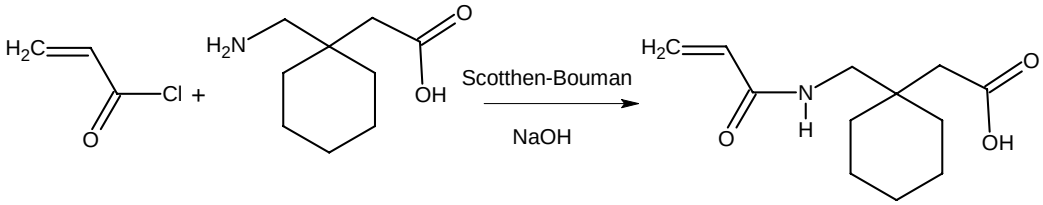
Methyl-1-aminomethyl-1-cyclohexaneacetate hydrochloride and other derivatives (ethyl,propyl) of 1-aminomethyl-1-cyclohexane acetic acid salts were synthesized and purified according to a procedure previously described [12].



Synthesis of Monomers

N-[(1-1-Hydroxyformoyl-1'-methyl)cyclohexylmethyl] acrylamide (HFCHA)

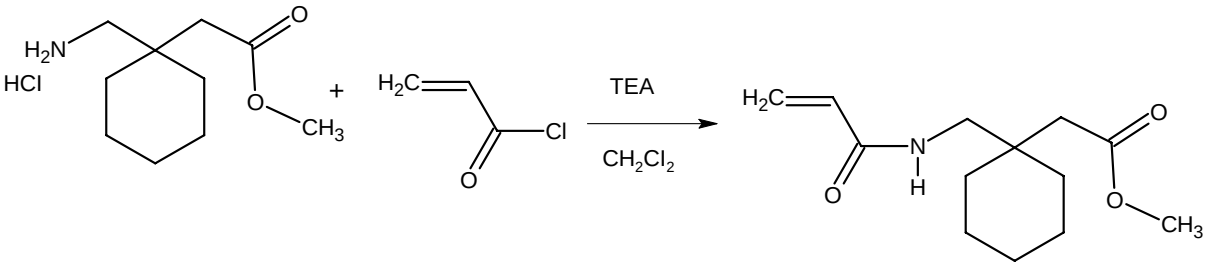
Synthesis of the acrylate derivative of 1-aminomethyl-1-cyclohexane acetic acid was prepared using the Schotten-Baumann reaction, as described by Varaprasad et al. [12]. Briefly, amino acid and NaOH aqueous solution were placed in a 3 necked flask equipped with a thermometer and a mechanical stirrer. Then, acryloyl chloride equivalent to the amino group on methyl-1-aminomethyl-1-cyclohexaneacetate hydrochloride and other derivatives was added dropwise with vigorous stirring at a temperature below 5 ^{0}C. After the addition was completed, stirrinig was continued for an additional hour to allow completion of the reaction. The solution was acidified to pH=2 with a solution of concentrated HCl (37%) and extracted four times with ethyl acetate. The extract was separated, dried with anhydrous $MgSO_4$, filtered, and concentrated using a rotary evaporator to obtain crystals. The white crystals were recrystallized from ethyl acetate. Yield 51%, ^{1}H- NMR δ (DMSO) 12.05 (broad, 1H –COOH), 6.53 (broad, 1H, - NH), 6.03–6.36 (m, 2 H, (-CH=$\underline{CH_2}$), 5.53-5.57 (dd, *J* =3.1 Hz, 1 H, (-$\underline{CH}$=CH2), 2.95–3.29 (d, 2 H, -NH-$\underline{CH_2}$), 2.18 (s, 2H, -CH_2-C=O-), 1.24-1.39 (m, 10H, (-C_6H_{10}),ppm, ^{13}C-NMR δ ($CDCl_3$) 173.57 (CO_2CH_3), 165.8 (C=O-NH-), 132.4 (-CH=$\underline{CH_2}$), 125.8 (-$\underline{CH}$=CH_2), , 45.35 (–NH-CH_2-), 40.8 (-$\underline{CH_2}$-CO_2-) 37.2-33.30-26.2-21.7 (C_6H_{10}), ppm FTIR (NaCl) 3286 (N-H), 2930 (C-H), 2636 (COOH),1712 (C=O (ester)), 1654 (C=O (amide)), 1606 (C=C), 1554, 1207, 1106 cm^{-}1.



N-[(1-1-Methoxyformoyl-1'-methyl)cyclohexylmethyl] acrylamide (MFCHA)

To a mixture of (1-aminomethyl-cyclohexyl)-acetic acid methyl ester hydrochloride (2.20 g, 10 mmol) and triethylamine (2.92mL, 21 mmol) in dichloromethane (20 mL), acryloyl chloride (0.85 mL, 10.5 mmol) was added at 0 ^{0}C. The resulting mixture was stirred at room temperature overnight under nitrogen. The reaction mixture was washed with 1*M* HCl (20 mL 1x2), saturated solution of $NaHCO_3$ (20 mL 1x1) and a saturated solution of NaCl (20 mL 1x1). The organic layer was dried over anhydrous $MgSO_4$, filtered, and the filtrate was concentrated by rotary evaporation. The residue was purified by recrystallization (cyclohexane). Yield 40%, m.p. 58–60^{0}C.^{1}H- NMR δ ($CDCl_3$) 6.44 (broad d, 1 H, - NH), 6.08–6.28 (m, 2 H, {-CH=$\underline{CH_2}$), 5.60-5.63 (dd, *J* =0.4 Hz, 1 H, (-$\underline{CH}$=CH2), 3.68 (s, 3 H, (-$CO_2\underline{CH_3}$), 3.34–3.36 (d, 2 H, -NH-$\underline{CH_2}$), 2.32 (s, 2 H{-CH_2-C=0), (m, 10H, (-C_6H_{10}) ppm, ^{13}C-NMR δ (CDCl3) 173.5 ({$\underline{CO_2}CH_3$), 165.3 (-$\underline{CO}$NH-), 130.3 ({$\underline{CH}$-CH2), 126.6 ({CH-$\underline{CH_2}$), 52.7 (-$CO_2\underline{CH_3}$-), 47.5 (–

NH-$\underline{CH_2}$-), 39.05 (-$\underline{CH_2}$-C=O), 42.1-34.2-31.7- 26.2 (-C_6H_{10}), ppm. FTIR (NaCl) 3298 (N-H), 2929 (C-H), 1734 (C=O (ester)), 1657 (C=O (amide)), 1626 (C=C), 1549, 1208, 1105 cm^{-}1 .



N-[(1-1-Ethoxyformoyl-1'-methyl)cyclohexylmethyl] acrylamide (EFCHA)

This compound was prepared from 1-aminomethyl-1-cyclohexane acetic acid ethyl ester and acryloyl chloride similarly to A-A-M and purified by extraction. Yield 51%, ^{1}H- NMR δ ($CDCl_3$) 6.53 (broad d, 1 H, - NH), 6.07–6.26 (m, 2 H, {-CH=$\underline{CH_2}$), 5.57-5.61 (dd, *J* =3.9 Hz, 1 H, (-$\underline{CH}$=CH2), 4.08-4.15 (m, 2H, -CO_2-$\underline{CH_2}$), 3.32–3.34 (d, 2 H, -NH-$\underline{CH_2}$), 2.29 (s, 2 H{-CH_2-C=0), 1.22-2.16 (m, 10H, (-$C_6H_{10,}$ -CO_2 –$CH_2\underline{CH_3}$),ppm, ^{13}C-NMR δ (CDCl3) 173.3 ($\underline{CO_2}$CH3), 165.9 (-C=O-NH), 131.4 (-CH=$\underline{CH_2}$), 126.1 (-$\underline{CH}$=CH2), 60.7 (-$CO_2\underline{CH_2}$-), 46.5 (–NH-$\underline{CH_2}$-), 38.05 (-$\underline{CH_2}$-C=O), 42.4-34.5-31.6- 26.2 (-C_6H_{10}), 14.6(O-CH_2-$\underline{CH_3}$) ppm FTIR (NaCl) 3302 (N-H), 2930 (C-H), 1731 (C=O (ester)), 1660 (C=O (amide)), 1626 (C=C), 1548, 1207, 1096 cm^{-}1 .

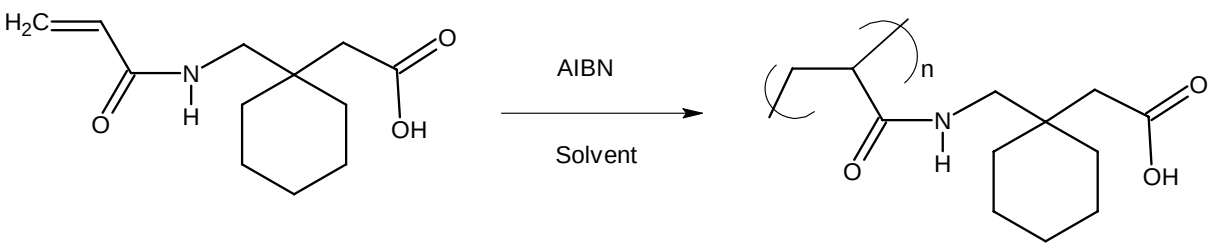
N-[(1-1-Propoxyformoyl-1'-methyl)cyclohexylmethyl] acrylamide (PFCHA)

This compound was prepared from 1-aminomethyl–1-cyclohexane acetic acid ethyl ester and acryloyl chloride similarly to A-A-M and purified by extraction. Yield 70%, ^{1}H- NMR δ ($CDCl_3$) 6.53 (broad d, 1 H, - NH), 6.06–6.26 (m, 2 H, {-CH=$\underline{CH_2}$), 5.57-5.60 (dd, *J* =3.9 Hz, 1 H, (-$\underline{CH}$=CH2), 4.00-4.03 (t, 2H, CO_2-CH_2-), 3.32–3.33 (d, 2 H, -NH-$\underline{CH_2}$), 2.30 (s, 2 H{-CH_2-C=0), 1.30-1,53 (m, 15H, (-C_6H_{10}, -CO_2 -CH_2-$\underline{CH_2}$-CH_3-,-CO_2-CH2-CH_2-$\underline{CH_3}$),ppm, ^{13}C-NMR δ (CDCl3) 173.4 ($\underline{CO_2}$$CH_3$), 165.9 (C=O-NH), 131.4 (-CH=$\underline{CH_2}$), 126.1 (-$\underline{CH}$=CH2), 66.4 (-$CO_2\underline{CH_2}$-), 46.5 (–NH-$\underline{CH_2}$-), 38.05({$\underline{CH_2}$-C=O),42.3-34,5-26.0-22.1 (-C_6H_{10}),21.64 (-O-CH_2-$\underline{CH_2}$-CH_3) 10.62(-O-CH_2-CH_2-$\underline{CH_3}$) ppm FTIR (NaCl) 3302 (N-H), 2929 (C-H), 1729 (C=O (ester)), 1660 (C=O (amide)), 1626 (C=C), 1547, 1206, 1104 cm^{-}1 .

Radical Polymerization

General Procedure

To the monomer (5 mmol) in a polymerization tube was introduced a radical initiator, and subsequently a dry solvent, if required. The tube was cooled, degassed, sealed off, and heated at 60 ^{0}C for 20 h.



The resulting mixture was diluted with chloroform (3 mL) and poured into ether or methanol (100 mL) to precipitate the polymer. The solvent-insoluble polymer was filtered and dried at 50 ^{0}C overnight *in vacuo.*

References

[1] Laurencin, C.T.; Elgendy, H. in "*The biocompatibility and toxicity of degradable polymeric materials:implications for drug delivery*", Domb AJ, eds.,Wiley, New York, **1994**, pp. 27–46.
[2] Castner, D.G.; Ratner, B.D. *Surf Sci.* **2002**, *500, (1-3), 28.*
[3] Field, A.K.; Tyrell, A.A.; Lampson, G.P.; Hilleman. M.R. *Proc.Nat.Acad. Sci.* **1967,** *58(3),* 1004.
[4] Clercq, E .De.; Torreuce, P.F.; Desomer, P.; Witkop, B. *J.Biol.Chem.* **1975**, *250(7),* 2521.
[5] Walker, M .C.; Patsalos, P. N. *Pharmacology & therapeutics.* **1995**, *67(3),* 351.
[6] Gram, L. *Epilepsia.* **1996**, *37,* 12.
[7] Gareri, P.; Gravina, T.; Ferreri, G.; Sarro, G.D. *Prog. Neurobiol.***1999**, *58(5),* 389.
[8] Van Hooft, J.A.; Dougherty, J.; John, D.; Endeman, R.A.; Nichols, W.; Wadman, J. *European Journal of Pharmacology*, **2002**, *449(3),* 221.
[9] Nori, A.; Kopecˇeka, J. *Advanced Drug Delivery Reviews,* **2005**, *57,* 609.
[10] Akat, H.; Yildirim, Y.F.; Duman, Y.; Balcan, M. *Journal of Radioanalytical and Nuclear Chemistry,* **2007**, 275, in press.
[11] US pat.app.publ. **2004**, 2004014940,
[12] Varaprasad, D.; Rosthauser, J.; Winston, A. *J. Polym. Sci. Polym., Chem. Ed.* **1984**, *22(9),* 2131.