Synthesis of Some N^1-Benzyl -6-(thio and alkyl or aryl thio) Uracil derivatives

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Abstract

New series of N^1-Benzyl -6-(thio derivatives) Uracils have been prepared by reaction of 6-chloro uracil [F_3] with benzyl chloride in dimethyl sulphoxide in presence of sodium carbonate to yield N^1-Benzyl-6-chloro uracil [F_4].Heating of [F_4] in ethanol with thiourea and treated with sodium carbonate to yield N^1-benzyl-6-marcapto uracil [F_5].Alkylation's of compound [F_5] with different reagents a new series of uracils were prepared (F7 –F17) .The structures of synthesized compounds were elucidated by using some spectroscopic methods (IR, ^{1}HNMR).

Keywords: Uracil, 2-thiouracil, pyrimidine and 6-chloro uracil

تحضير بعض مشتقات N^1- بنزايل-6- (ثايو والكايل أو ثايو ارايل)يوراسيل الجديدة

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الخلاصة

يتضمن البحث تحضير سلسلة جديدة من مشتقات اليوراسيل من خلال مفاعلة 6-كلورو يوراسيل [F_3] مع كلوريد البنزايل في DMSO بوجود كاربونات الصوديوم لينتج N^1-بنزايل-6- كلورو يوراسيل[F_4] ،بتسخين المركب [F_4] مع الثايويوريا في درجة غليان الايثانول يؤدي الى تكوين المركب N^1-بنزايل-6- ثايو يوراسيل[F_5].الكلة المشتق [F_5] مع كواشف مختلفة ليعطي مشتقات اليوراسيل (F_7 –F_{17}).
شخصت المركبات المحضرة باستخدام بعض الطرق الطيفية (^{1}H NMR و IR).

الكلمات الدالة: يوراسيل ، 2- ثايو يوراسيل، بيريميدين، 6- كلورو يوراسيل

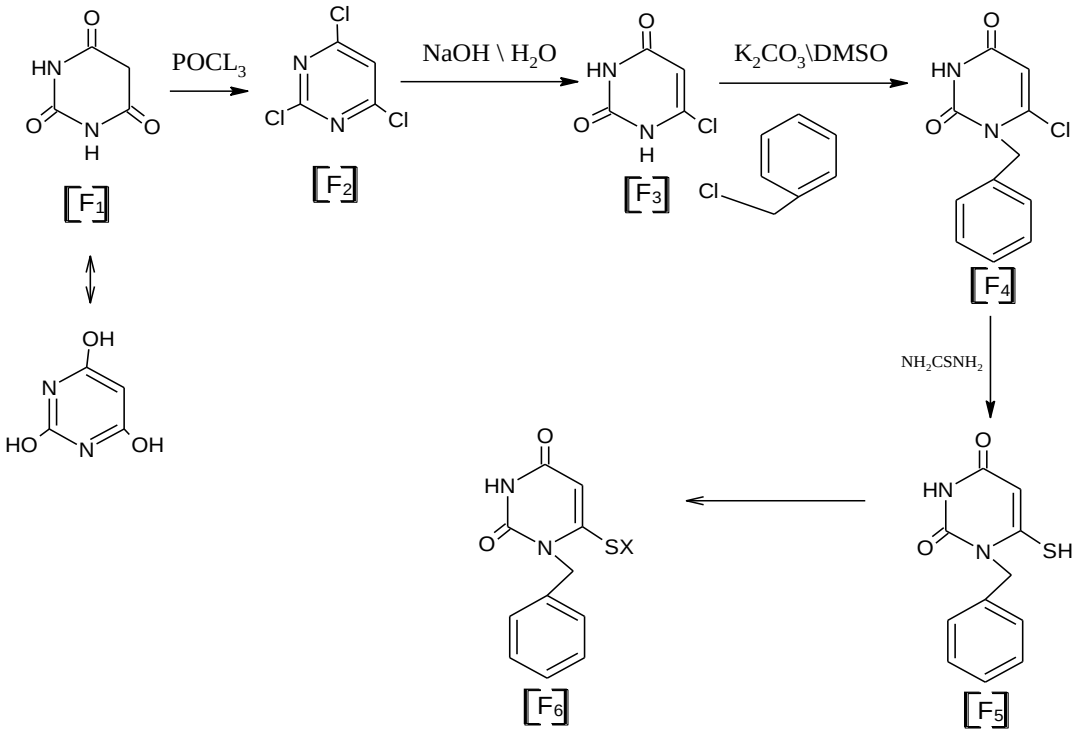
Introduction

Heterocyclic compounds those containing in their structures at lest tow different types of atoms, nitrogen, oxygen and sulfur are the most comment types compounds.Hetrocyclic compounds are widely distribute in the nature and they are very necessary for life in different types [1]. Uracil play a vital role in metabolic functions serving as a moiety of biomolecules e.g. nucleic acid as well as key building blocks for pharmaceutics such as antivirals, anticancers antibacterials and antifungals Their thio analogs; thiouracils are also used as therapeutic agents for antivirals and anticancer Analogs compounds like 5-and 5,6-substituted 2-thiouracil were reported as inhibitors of human immunodeficiency virus type-1 [2]. A large

number of pyrimidine nucleosides are clinically useful in the control of retroviral infections [3]. A broad spectrum of antiviral activity has been described for 5-substituted pyrimidine nucleosides [4], although many approaches for the synthesis of 5-substituted pyrimidine bases have been reported [5] .A new synthetic method of 5-substituted uracil derivatives are still of particular in tersest in terms of new drug development [6].Antitumor active compounds are widely utilized in cancer therapy, and 5-fluoro uracil was found to have antitumor activity for cancer of the digestive organs [7]. Potent antiviral activity was also reported among several tricycles derivatives [8]. Because of the essential role that nucleic acid plays in metabolic processes, much emphasis has been placed on the design of anti metabolites with a similar structure. For instance, analogs of nucleosides have been successfully used as antineoplasic and antiviral agents [9]. The structures can be modified to effect the base ring, thus, most research in this area has focused on the preparation of nucleosides or their derivatives with pyrimidinic bases, and particularly uracils especially the substituent in position 5 or 6 of the ring [10].

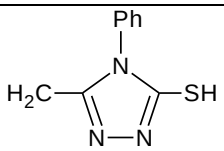
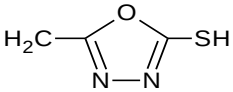
Results and Discussion

6-chloro uracil [F_3], the key starting material necessary for this study, was synthesized from barbituric acid [F_1] via reaction with phosphorus oxychloride and dimethyl aniline to yield 2,4,6-tri chloro pyrimidine[F_2], [11] which was subsequently hydrolysed with aqueous sodium hydroxide [12] to yield [F_3]. Interaction of 6-chloro uracil [F_3] with benzyl chloride in dimethyl sulphoxide, in the presence of potassium carbonate yielded the corresponding N^1-benzyl-6-chloro uracil [F4] [13], interaction of compound [F_4] with thiourea in ethanol and further treatment with sodium carbonate yielded N^1-benzyl-6-marcapto uracil [F5] [14]. The alkylations of the compound [F_5] with different reagents resulted into formation of a new series of N^1-Benzyl-6-alkylthio derivatives Uracil (F7 –F17) scheme (1). Table (1) shows the synthesized compounds according to the following scheme and table (2) shows the characterization data of these compounds.



Scheme (1)

Table (1) the structures and names of the synthesized compounds

Comp No.	X	Comp. Name
[F_7]	H_2C—≡—H	N^1-Benzyl-6-(thio propynyl) Uracil.
[F_8]	H_2C—≡—$CH_2N(CH_3)_2$	N^1-Benzyl-6-(thio 4′ N, N-dimethyl amino-2′-butnyl) Uracil.
[F_9]	CH_2COOH	N^1-Benzyl-6-(thio carboxyl methyl) Uracil.
[F_{10}]	$CH_2COOCH_2CH_3$	N^1-Benzyl-6-(thio ethyl carboxyl methyl) Uracil.
[F_{11}]	$CH_2COONHNH_2$	N^1-Benzyl-6-(thio acetic hydrazide) Uracil.
[F_{12}]	$CH_2COONHNHCSNHPh$	N^1-Benzyl-6--(thio acetyl 4′-phenyl thio semicarbazido) Uracil.
[F_{13}]	$CH_2\ CO_2CH_2$—≡—H	N^1-Benzyl-6-(thio propynyl acetate) Uracil.
[F_{14}]	$CH_2\ CO_2CH_2$—≡—$CH_2N(CH_3)_2$	N^1-Benzyl-6-(thio 4′ N, N-dimethyl amino-2′-butnyl carboxyl methyl) Uracil.
[F_{15}]	$CH_2\ CO_2CH_2$—≡—$CH_2N(C_6H_{11})_2$	N^1-Benzyl-6-(thio 4′ N, N-bicycle hexyl amino-2′-butnyl carboxyl methyl) Uracil.
[F_{16}]		N^1-Benzyl-6-(thio methyl N′ -phenyl-2′-thio 1′-3′-4′-triazolyl) Uracil.
[F_{17}]		N^1-Benzyl-6-(thio methyl -2′-thio -1′-3′-4′-Oxadiazolyl) Uracil.

Comp. No.	Cryst. Solvent	M.P. (C^0)	Yield (%)	Mol. Formula (Mol. Wt.)
[F_7]	Acetone\H2O (1:1)	Oil	45	$C_{14}H_{12}O_2N_2S$ (272)
[F_8]	Benzene	Oil	50	$C_{17}H_{19}O_2N_3S$ (329)
[F_9]	Etanol\H2O (1:1)	200-202	70	$C_{13}H_{13}O_4N_2S$ (293)
[F_{10}]	Etanol\H2O (1:1)	250-252	85	$C_{15}H_{16}O_4N_2S$ (320)
[F_{11}]	Chloroform	Oil	65	$C_{13}H_{14}O_3N_4S$ (306)
[F_{12}]	Benzene	130-132 (decomp.)	95	$C_{20}H_{19}O_3N_5S_2$ (441)
[F_{13}]	Chloroform	Oil	35	$C_{16}H_{14}O_4N_2S$ (330)
[F_{14}]	Benzene	Oil	40	$C_{19}H_{21}O_4N_3S$ (387)
[F_{15}]	Chloroform	Oil	42	$C_{29}H_{37}O_4N_3S$ (523)
[F_{16}]	Etanol\H2O (1:1)	190-192	75	$C_{20}H_{17}O_2N_5S_2$ (423)
[F_{17}]	Benzene	Oil	45	$C_{15}H_{10}O_3N_4S_2$ (358)

Experimental section

All melting points (˚C) were determined on galnghame melting point apparatus and are uncorrected.Infra red spectra were recorded as KBr disc using a Unicom SP 1000 Infra red spectrometer and expressed in wave number (cm^{-1}) .^{1}H NMR spectra were obtained using a Bruker AC 250 FT NMR spectrometer operating at 250 MHz, the chemical shifts are expressed in δ units using tetra methyl silan (TMS) as internal reference and DMSO-D_6 or $CDCl_3$ as solvent.

Chemical synthesis

1) N^1-Benzyl -6-chloro uracil [F4]. [13]

A mixture of 6-chloro uracil [F_3] (2.93g,0.02mol),benzyl chloride (4.83g,0.03mol)and potassium carbonate (1.38g,0.01mol)in dimethyl sulphoxide (20ml)were stirred at 60-70˚C for 1hour and 0.1N sodium hydroxide (20ml)was then added to the hot reaction mixture with stirring. The mixture was extracted with benzene (2×10ml) and the aqueous phase was adjusted to pH (2-3) with conc. HCl. the resulting aqueous mixture was refrigerated overnight and the precipitated product was filtered and washed with water, dried , and recrystllized from acetone \H_2O(1:1), yield 3.8g(70%),M.P.179-180 ˚C .δ_H (500 MHz, Chloroform) 7.76 (1 H,

s), 7.26 (5 H, m), 5.88 (1 H, t, *J* 2.9), 5.05 (1 H, s), 4.23 (1 H, s), 3.07 (1 H, dd, *J* 12.5, 2.9), 2.76 (1 H, dd, *J* 12.4, 2.8).

2) N^1-Benzyl-6-mercapto uracil [F5]. [14]

A mixture of compound [F_4](7.5g,0.02mole) in (20ml Ethanol),thio urea(3.5g,o.o4mol) in (15ml)ethanol was added to round bottom flask and refluxed with stirring for about 3 hours After cooling, ethanol was evaporated then sodium carbonate solution was added. The precipitate formed after cooling was filtrated and recrystallized from benzene. ^{1}H NMR($CDCl_3$): δ4.2(s,2H,CH_2), 5.9(s,1H,C5-H), 7.14(d,2H,Ar-H), 7.06(d,2H,Ar-H), 7.07(s,1H,Ar-H),11.7(br. s,1H,NH), 3.25(br. s,1H,SH).

3) N^1-Benzyl-6-(thio propynyl) uracil [F_7].

A mixture of(2.02g,0.002mole) of compound [F_6] , (1.09g,0.01mole)from triethyl amine were added to flask and dissolved with (50)ml Ethanol and (1.19g,0.01mole)from propagel bromide and refluxed for about 4 hours ,cooled ,and add (15)ml cooled water ,the precipitated compound was recrystllized from Ethanol . δ_H (500 MHz, Chloroform) 7.36 – 7.10 (5 H, m), 6.66 (1 H, s), 5.82 (1 H, s), 5.15 (1 H, s), 5.05 (1 H, s), 4.07 (2 H, d, *J* 3.1), 1.92 (1 H, t, *J* 2.9). I.R:3310(NH), 1640(C=O), 2200-2220 (C≡C).

4) N^1-Benzyl-6-(thio 4′ N, N-dimethyl amino-2′-butnyl) uracil. [F_8]

A mixture of (0.002mole) of compound [F_7], (0.06g, 0.002mole) of Para formaldehyde were added and dissolved with (15) ml Isopropyl alcohol. (0.05g) copperic chloride and secondary amine (0.05g) were then added .The final mixture was then refluxed for 3 hours and cooled then added to ice cooled solution .The final mixture was then extracted with chloroform and the solvent evaporated by rotary evaporator . δ_H (500 MHz, Chloroform) 7.35 – 7.17 (5 H, m), 6.68 (1 H, s), 5.88 (1 H, s), 5.20 (1 H, s), 5.09 (1 H, s), 4.06 (2 H, s), 2.36 (6 H, s). I.R:3320(NH), 1650(C=O).

5) N^1-Benzyl-6-(thio carboxyl methyl) uracil. [F_9]

Compound[F_6] (0.01mole)was dissolved in (15) ml Ethanol and (0.02mole)Marcptoacetic acid dissolved in 10% of sodium hydroxide was then added and reflexed for 4 hours ,cooled acidified by concentration HCl until it was participated , recrystllized from Ethanol\H_2O(1:1). δ_H (500 MHz, Chloroform) 9.85 (1 H, s), 7.33 – 7.27 (2 H, m), 7.27 – 7.21 (3 H, m), 6.74 (1 H, s), 6.04 (1 H, s), 5.41 (1 H, s), 5.03 (1 H, s), 3.97 – 3.93 (2 H, m). I.R:3220(NH), 1650(C=O), 3640-3500(O-H), 1730-1700(C=O) acid.

6) N^1-Benzyl-6-(thio ethyl carboxyl methyl) Uracil. [F_{10}]

A mixture of(1g,0.004mole)of [**F_9**] , thionyl chloride(8ml)were refluxed in water bath for about 3 hours **,**cooled, and (15)ml of absolute ethanol was then added and refluxed in water bath for about 3 hours **,**evaporation of the excess ethanol gave the above compound and extraction by (15)ml of benzene ,washing by sodium bi carbonate. δ_H (500 MHz, Chloroform) 7.35 – 7.15 (1 H, m), 6.73 (1 H, s), 5.84 (1 H, s), 5.39 (1 H, s), 5.30 (1 H, s), 4.17 (1 H, q, *J* 6.0), 3.93 (1 H, s), 1.38 (1 H, t, *J* 6.0).

I.R: 3330(NH), 1650(C=O), 1740(C=O) Ester.

7) N^1-Benzyl-6-(thio acetic hydrazide) uracil. [F_{11}]

A mixture of(1g,0.004mole)of compound [F_9] , (15ml)of Ethanol 96% were gradually added to a flask containing (hydrazine hydrate) and reflexed in water bath for about 5 hours **,**cooled, oil solution was product. δ_H (500 MHz, Chloroform) 7.26 (5 H, m), 6.55 (1 H, s), 5.76 (1 H, s), 5.12 (1 H, s), 4.95 (2 H, d, *J* 10.1), 4.56 (2 H, s), 3.91 (2 H, s), 1.99 (2 H, s).

I.R:3320(NH), 1640(C=O), 1690(C=O) ester ,3400(NH_2),3200(NH).

8) N^1-Benzyl-6--(thioacetyl 4′-phenyl thiosemicarbazide) uracil. [F_{12}]

A mixture of(1g,0.01mole) of compound [F_{11}] , (30ml)of ethanol 96% were added to a flask containing (0.01mole) of Isothiocyanate .The mixture was refluxed for 0.5 hours **,**cooled, and extracted by (15)ml of Ethyl acetate and dried by anhydrous sodium sulphate and crystallized from the appropriate solvent Table(2). δ_H (500 MHz, Chloroform) 9.14 (1 H, s), 7.42 – 7.07 (10 H, m), 6.93 (1 H, s), 5.99 (1 H, s), 5.92 (1 H, s), 5.61 (1 H, s), 5.37 (2 H, d, *J* 5.1), 5.09 (1 H, s), 4.71 (1 H, s), 3.89 (2 H, s). I.R:3320(NH), 1640(C=O), 1690(C=O) ester, 3400(NH_2), 3200-3400(NH).

9) N^1-Benzyl-6-(thiopropynyl carboxyl methyl) uracil. [F_{13}]

Using the same procedure of compound [F_{10}] compound [F_{13}] was prepared and the same way up giving oil compound which was crystallized from chloroform. δ_H (500 MHz, Chloroform) 7.34 – 7.12 (5 H, m), 6.73 (1 H, s), 5.84 (1 H, s), 5.39 (1 H, s), 5.28 (1 H, s), 5.08 (2 H, d, *J* 2.9), 3.93 (2 H, s), 2.22 (1 H, t, *J* 3.0). I.R:3320(NH), 1640(C=O), 1700(C=O) ester, 3300 (NH_2), 3300 (≡C-H).

10) N1-Benzyl-6-(thio 4′ N, N-dimethyl amino-2′-butnyl carboxyl methyl) uracil. [F_{14}]

Using the same procedure of compound [F_8] compound [F_{14}] was prepared and the same way up giving oil compound which was crystallized from benzene. δ_H (500 MHz, Chloroform) 7.27 (5 H, m), 6.87 (1 H, s), 5.84 (1 H, s), 5.20 (1 H, s), 5.11 (1 H, s), 5.06 (2 H, t, *J* 2.5), 3.98 (2 H, s), 3.03 (2 H, t, *J* 2.5), 2.37 (6 H, s). I.R:3320(NH), 1650(C=O).

11) N^1-Benzyl-6-(thio 4′ N, N-bicycle hexylamino-2′-butnyl carboxyl methyl) uracil. [F_{15}]

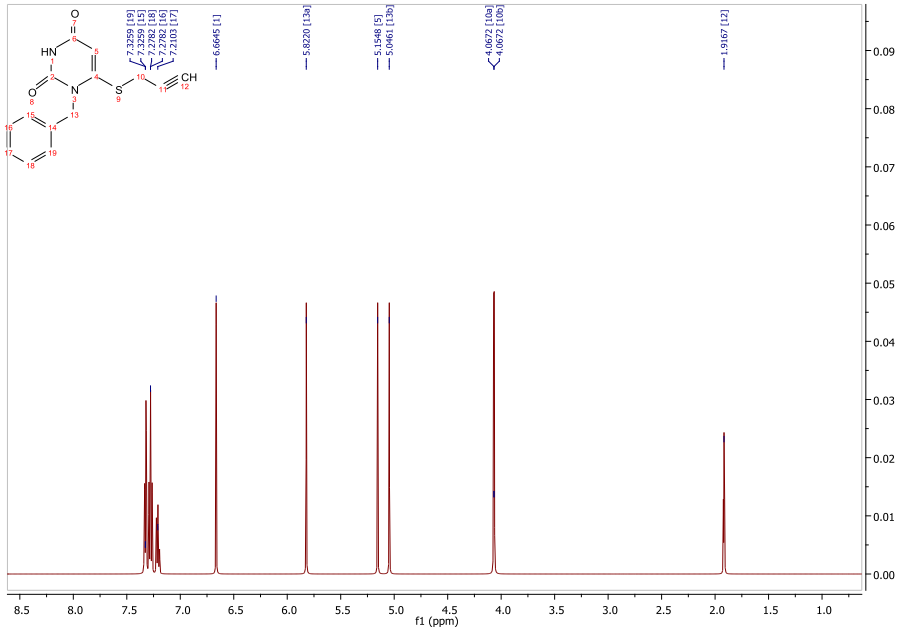
Using the same procedure of compound [F_{14}] compound [F_{15}] was prepared and the same way up giving oil compound which was crystallized from chloroform. δ_H (500 MHz, Chloroform) 7.34 – 7.25 (4H, m), 7.22 (5 H, t, *J* 7.5), 7.13 (4 H, dd, *J* 7.5, 1.5), 6.98 – 6.87 (2 H, m), 6.81 (1 H, s), 5.64 (1 H, s), 5.37 (1 H, s), 5.04 (2 H, dd, *J* 15.0, 12.5), 5.00 (1 H, s), 4.05 (2 H, t, *J* 2.5), 3.90 (2 H, s).

12) N^1-Benzyl-6-(thio methyl N′-phenyl-2′-thio 1′-3′-4′-triazolyl) uracil. [F16]

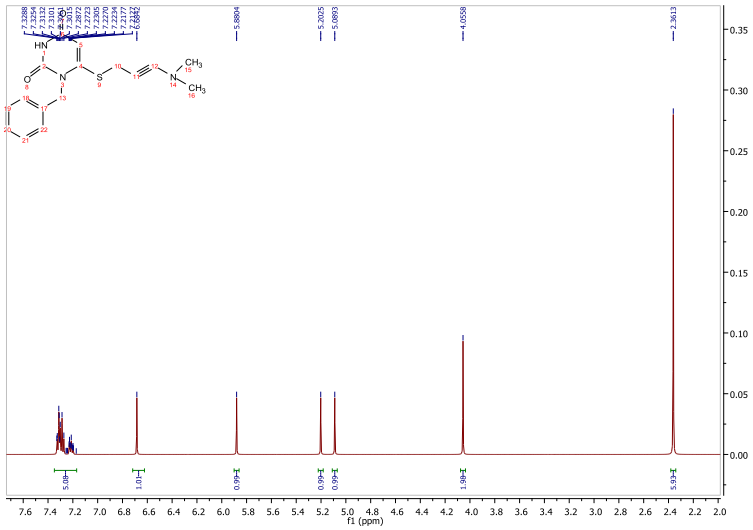
A mixture of (3.3g,0.01mole)from [F_{12}] , (20ml) of sodium hydroxide 2N was added to a flask and was refluxed for 3 hours **,**cooled, and acidified the solution by (10%)HCl, until it was participated , filtered the precipitate and recrystllized from Ethanol\H_2O(1:1). δ_H (500 MHz, Chloroform) 7.82 (2 H, dd, *J* 7.5, 1.4), 7.37 (2 H, dd, *J* 7.4, 1.3), 7.33 – 7.13 (6 H, m), 6.55 (1 H, s), 5.46 (1 H, s), 5.35 (1 H, s), 5.25 (1 H, s), 4.43 (2 H, s), 2.27 (1 H, s).

13) N^1-Benzyl-6-(thio methyl -2′-thio -1′-3′-4′-Oxadiazolyl) uracil. [F_{17}].

A mixture of(1.8g,0.01mole)from compound [F_{11}] , (10ml)of ethanol 95% was added to a flask containing (0.01mole) of sodium carbonate (1%) and (76g,0.01mol) of CS_2 and refluxed the mixture for 3 hours ,cooled then add to ice cooled solution and acidified by (10%)HCl, recrystllized from benzene. δ_H (500 MHz, Chloroform) 7.36 (2 H, dd, *J* 7.4, 1.4), 7.26 (2 H, t, *J* 7.4), 7.22 – 7.13 (1 H, m), 6.59 (1 H, s), 5.40 (1 H, s), 5.31 (2 H, d, *J* 11.7), 4.20 (2 H, s), 2.07 (1 H, s).



^{1}HNMR chart for the compound [F_7]



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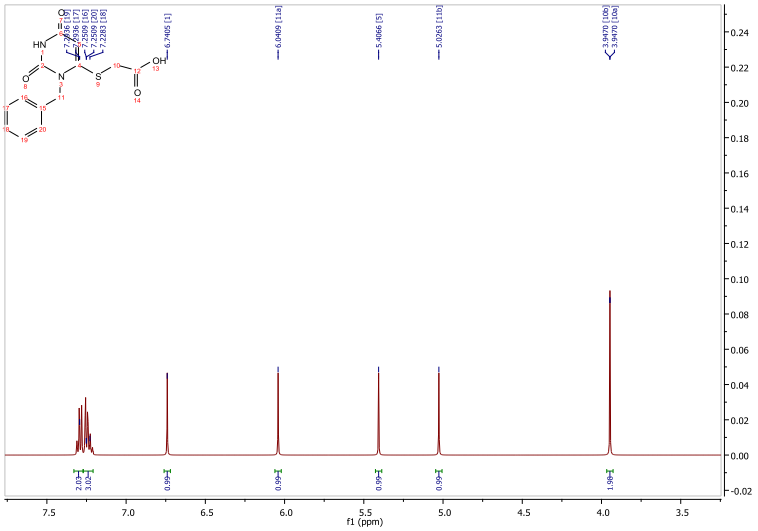
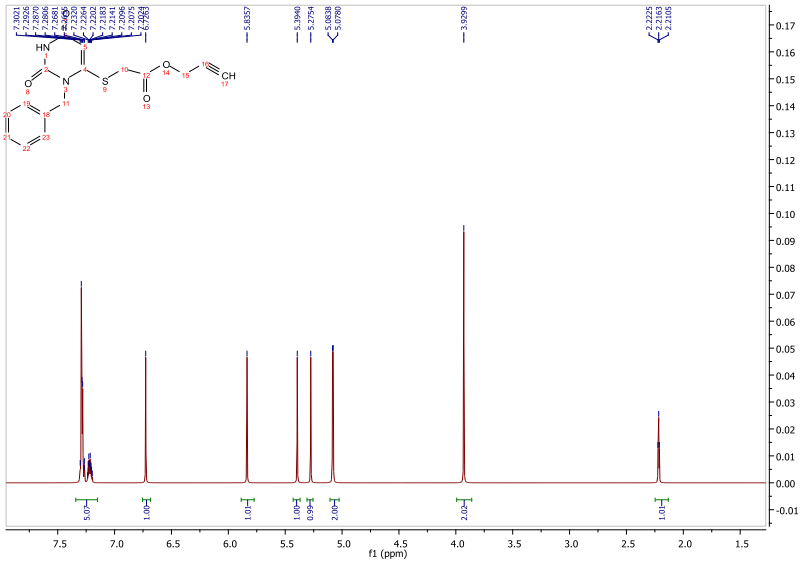
^{1}HNMR chart for the compound [F_8]



^{1}HNMR chart for the compound [F_9]



^{1}HNMR chart for the compound [F_{13}]

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