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Preparation of New Derivatives of Enaminolactones

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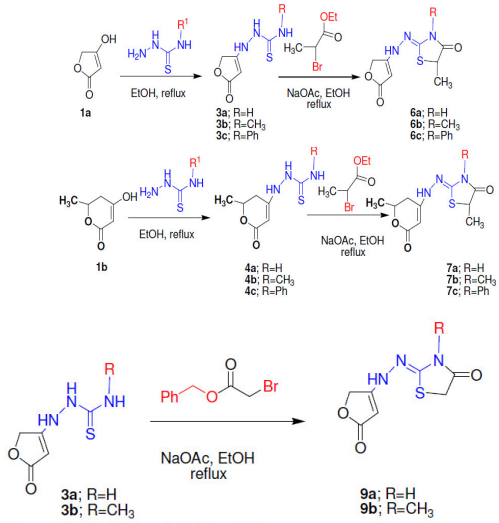
Abstract
The 1,3-dipolar cycloaddition reaction of Substituted benzyl azides and quomarinee was studied . Where interacted Substituted benzyl azides with quomarine produced seven vehicles of the type Inaminolactone (a, b, c, d, e, f, g).The 1,3-dipolar cycloaddition reaction of 3- methoxy benzyl azide and quomarinee carried out in p-xylene at reflux. and product was formed in high yield .The isolated and purified products were characterized by spectral methods , IR , ^{1}HNMR , Cosy , ^{13}CNMR , Dept-135 and GC/MS. Moreover, the compounds belong to Enaminolactones class and compounds of great importance,are used as inhibitor to corrosion and rust and these compounds have therapeutic value, and they are intermediate compounds in organic synthesis for the preparation of some medical products. The reactions 1,3- dipolar cycloaddition of substituted benzyl azides with quomarine using to one time for preparing the enaminolactones, and this way is new.
Keywords: Enaminolactones; benzyl azides ; quomarinee .

1. Introduction

Azides are considered very important compounds due to their industrial and biological applications [1]. Azide derivatives have been used in rubber vulcanization, polymer cross linking, dyes, tire cord adhesives, foaming of plastics, pharmaceuticals, pesticides and herbicides [1]. One of the most useful synthetic applications of azides is the preparation of 1,2,3-triazoles via 1,3-dipolar cycloaddition. 1,2,3-Triazoles are an important class of heterocycles due to their importance as synthetic intermediates and pharmaceuticals[2]. Several therapeutically interesting 1,2,3-triazoles, including anti-HIV agents [3–6], antimicrobial compounds [7], β3-selective adrenergic receptor agonists [8], kinase inhibitors [9,10] and other enzyme inhibitors [11,12] have been reported. The 1,2,3-triazole moiety is also present in a number of drugs, for example, the β-lactam antibiotic tazobactam [13] and cephalosporin cefatrizine [14]. However, few reports were issued on calculational studies of 1,2,3-triazoles, although the B3LYP/6-31G method has been used to compute the structure of 4-phenyl- and 5-phenyl-1,2,3-triazoles acting as dienes toward DMAD in microwave-assisted solvent-free Diels–Alder cycloadditions [15].

A convenient two step conversion of heterocyclic enaminolactones to heterocyclic fused 2-pyran-1-ones is reported. The use of this method can be applied to a wide variety of aromatic and heteroaromatic amines to give potentially biologically active compounds in good yields [16].

Enaminones 3 and 4 scheme (1), precursors of 4-thiazolidinones, were prepared by condensing tetronic acid (1a) and 4-hydroxy 6-methyl pyrone (1b) respectively with thiosemicarbazide derivatives 2 in refluxing ethanol. The 4-thiazolidinones 6, 7 derivatives were obtained by reacting compounds 3 or 4 with ethyl 2- bromo propionate 5 in the presence of anhydrous sodium acetate in ethalonic medium. Similarly, 9 products were synthesized by action of benzyl 2-bromo acetate 8 on 3 [17].

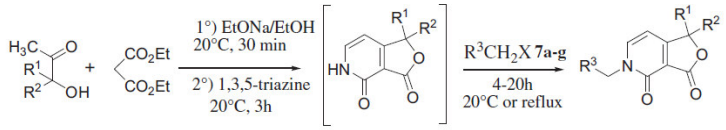


Scheme 1. Synthesis of 4-thiazolidinone structures.

A convenient method for obtaining pyridine alkaloid cerpegin and its various new C-1 and N-5 derivatives in high yields has been developed. Starting enaminolactones, synthesized by means of various tertiary keto-alcohols, have been condensed with primary aliphatic, aromatic or heterocyclic amines for a

pyridine cycle formation. Bromine derivatives of furo[3,4-c]pyridinenones are obtained as well[18].

Simple and efficient routes to the natural alkaloid Cerpegin and new analogues are described herein. In a first approach, we extend the scope of a one pot three steps reaction, which permits the synthesis of new analogues of Cerpegin, substituted in different ways. In a second line of approach, we present an unprecedented synthesis of Cerpegin and analogues where methylfuranones are condensed with dimethylformamide diethylacetal (DMFDEA) to yield enaminolactone esters, which react easily with various primary amines affording Cerpegin and new analogues. We applied this second approach to the synthesis of new bis-Cerpegins and N-amino-Cerpegins. Most of the syntheses are performed under environmental friendly conditions [19].



A large number of substituted piperidines and pyrrolidines have been reported as constituents from the venoms of ants in the related genera Monomorium and Solenopsis, many of which display significant biological activity.

Although the relative configurations of these compounds have been determined by racemic syntheses, their absolute configuration have not been yet established, probably owing to the scarcity of natural material, we report here the enantiospecific synthesis of (3S, 5R, 8S) -3- heptyl-3- methyl pyrrolizidine (1) , which is the only known bicyclic alkaloid from a Solenopsis species , as well as being the only known natural 3,5- dialky pyrrolizidine .

The first asymmetric synthesis was described by Takano et al, from a chiral epoxide, the second by Husson et al, by utilizing a chiral 2- cyano-6-oxazolopiperidine sunthon, and the third by Momose et al. From alanine .The relative stereochemistry at C-3, C-5, and C-8 of pyrrolizidine 1 have been well established in both syntheses, yet the reported optical rotations are contradictory: the synthetic alkaloid 1 was stated to be levorotatory in the work of Takano and dextrorotatory in the syntheses of Husson and Momose for the same reported absolute configurations. Here we present a new strategy for the synthesis of such compound[20].

A study on cerpegin analogues synthesis, a serendipitous reactivity of enaminolactone nitrile has been observed . Instead expecting iminocerpegins, we have gained new class of substituted 2- aminobyridines. The methodology has been applied on a wide range of primary amines, as aliphatic, aromatic, heteroaromatic and also , diamines, hydrazines and chiral amines[21].

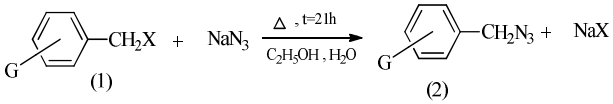
The objective of this work is to study the regioselectivity of the reaction of substituted benzyl azides with quomarine .

2. Experimental section

2.1. Synthesis of Substituted Benzyl Azides:

100 ml ethanol is added to the benzyl chloride (0,1mole, 12.65g) and mixed with sodium azide solution (0,2mole, 13g) dissolved in 1oo ml of water and heated the mixture in the flask provider condenser on a water bath for 21 hours. Separated by more benzyl output extraction by di ethyl ether layer and dried anhydrous magnesium sulfate, the aide separated evaporating the solvent is used as without purification.

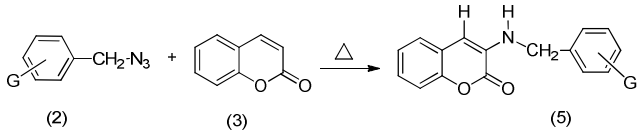
Where was prepared substituted benzyl azides same way.This can be illustrated prepare azides interaction following :



G=H, 2-Cl, 3-Cl, 2,6-Cl, 3-OCH_3, 4-OCH_3, 4-NO_2

2.2. Synthesis of Enaminolactones by Reaction of Substituted Benzyl Azides with Quomarine:

In addition to the round-bottom flask provider condenser for boiling the apostate (12mmole) of azido benzyl or its derivatives, quomarine (8mmole) and solvent P- xylene or THF (depending on the solubility of the reactants). And leave the mix for a period of time (the time required to form enaminolactones) at the boiling point of the solvent (the track the progress of the reaction using thin layer chromatography), separated the products and separated by filtration.



(2) (3) (5)

G=H, 2-Cl, 3-Cl, 2,6-Cl, 3-OCH_3, 4-OCH_3, 4-NO_2

Some of the resulting compounds was a isolate difficult has therefore been a isolated using column chromatography was used chromatographic column (0.3*12) cm and used chloroform mobile phase. Of the total sum was obtained resulting yellow crystals orange and weighing between 130-150 mg.

The compounds 4f, 4b, 4a were separated in this way and then recrystallization using ethanol and THF. the table (1) shows : Molecular formulas - Time of reflex - the yield – the melting point and Crystallization Solvent for the produces (5).

Tab(1)

Product	G	Molecular Formula	Reaction Solvent	Reflux Time [h]	Yield [%]	m.p [°C]	Crystallization Solvent
5 a	H	$C_{16}H_{13}NO_2$	P-xylene	11	66	168-169	EtOH
5 b	4-NO_2	$C_{16}H_{12}N_2O_4$	P-xylene	20	77	275-277	THF
5 c	2-Cl	$C_{16}H_{12}ClNO_2$	THF	6	68	279-281	**EtOH:THF** 1:2
5 d	3-Cl	$C_{16}H_{12}ClNO_2$	P-xylene	18	68	223-224	Acetone
5e	2,6-Cl	$C_{16}H_{11}Cl_2NO_2$	P-xyline	3	84	290-291	EtOAc:EtOH 1:2
5 f	3-OCH_3	$C_{17}H_{15}NO_3$	**P-xylene**	5	63	204-205	EtOH:THF 1:5
5 g	4-OCH_3	$C_{17}H_{15}NO_3$	P-xylene	27	62	240-241.5	EtOH:THF 9:1

the table (2) shows: the spectral description: IR ^{1}HNMR, ^{13}CNMR , Dept-135 and GC/MS:

tab(2)

Product	IR KBr,cm^{-1}	^{1}H-NMR δ,ppm	^{13}C-NMR δ,ppm	NMR Solvent	MS Peaks Z / e
5 a	3414 1665 1543 1050 910	4.39(d,2H) 5.34(s,1H) 7.35(m,Ar) 7.75(bt,1H)	159.59 153.64 121-137(Ar) 85.03 47.46	$CDCl_3$	M^+(251) 222 206 174 146 118 91 28
5 b	3333 1664 1553 1343 1253 950 758	8.48(bt,1H) 8.22(d,2H) 7.50(d,2H) 7.33(m,Ar) 5.03(s,1H) 4.69(d,2H)	161.81 153.55 147.15 122.9-147.15(Ar) 83.34 45.26	DMSO	M^+(296) 268 221 207 161 151 136 118 86 28
5 c	3436 1726 1661 1453 1275 1106 936 756	8.43(bt,1H) 8.21(d,1H) 7.41(m,Ar) 5.03(s,1H) 4.65(d,2H)	161.80 153.61 122-134.77(Ar) 82.99 43.97	DMSO	M^+(285.5) 256 250 222 194 146 125 89 28

5d	3275 1658 1557 1438 1240 941 759	7.51(bt,1H) 7.19-7.41(m,Ar) 5.29(s,1H) 4.41(d,2H)	161.31 153.63 123-138(Ar) 85.50 46.85	$CDCl_3$	M^+(285.5) 256 222 165 146 125 63 28
5 e	3297(b) 1665 1608 1554 1482 883 761	8.15(dd,1H) 7.77(bt,1H) 7.55-7.61(m,3H) 7.43- 7.47(dd,1H) 7.26-7.34(m,2H) 5.36(s,1H) 4.61(d,2H)	161.89 153.57 123.73-136.46(Ar) 132.46 82.94 43.48	**DMSO**	M^+(320) 284 257 220 204 161 63.5 28
5 f	3267 1665 1607 1550 1257 937 751	8.36-8.38(bt,1H) 8.12-8.13(d,1H) 7.59-7.62(t,1H) 7.25-7.38(m,3H) 6.83-6.95(m,3H) 5.06(s,1H) 4.50(d,2H) 3.73(s,3H)	161.87 159.92 153.60 153.56 139.87 132.44 130.12 123.93 122.88 112.75-119.49(Ar) 83.01 55.45 45.85	DMSO	M^+(282) 253 239 210 161 146 121 77 28
5 g	3276 1657 1559 1448 1240 945 751	8.34(bt,1H) 8.11(d,2H) 7.33-7.60(m,Ar) 6.89(d,2H) 5.06(s,1H) 4.47(d,2H) 3.73(s,3H)	161.87 159.92 153.47 82.86 55.50 45.35	DMSO	M^+(282) 253 239 207 161 121 77 28

4.Result and discussion

3-methoxy benzyl azide reacted with quomarine in absolute p-xylene at reflux temperature for 5 hrs to yield product (5) (mp =204-205 ^oC , 63%). This product was isolated by filtration from reaction mixture and The product was recrystallized from (ethanol : THF)(1:5) to give compound **(7)** and gave product (5) as the only product in 63% yield.

The structure of the product was determined using the usual spectral methods : IR ^{1}HNMR ,Cosy , ^{13}CNMR , DEPT-135, and GC/ MS

The IR spectrum of compound **(5f)** (Figure 1) shows an absorption band at 1665 cm^{-1} due to C=O group and bands at 3267, 3090, 1607, 1549, 1257, 1035, 937 and 751 cm^{-1} which are characteristic of the N-H(Stretch), C-H(Stretch Aromatic), C=C(Aromatic), N-H(Bend),C-N, C-O and C-H(Bend bis substituted 1,3), respectively.

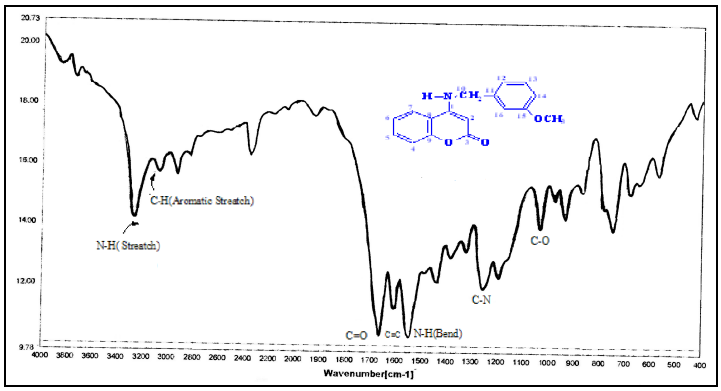


Figure 1: IR spectrum of compound (5f).

Figures 2 ,3 and 4 show the ^{1}HNMR spectrum of the product . The benzylic protons , H-10 , appear as a doublet at(δ_H = 4.50 ppm,d,2H) .The absorption of the hydrogen atom (H-2) on the double bond appears as a broad single at (δ_H = 5.06 ppm, s, 1H), and amino hydrogen atom looks as a broad triplet at (δ_H = 8.38ppm, t, 1H) (See Figure (3), which go away by adding D_2O to the sample as shown in Figs.) (2-a), (2-b)) of the compound (5g), we note that the triplet at (δ_H = 8.34 ppm) may still adding D_2O, and the single appears at (δ_H = 3.73 ppm, s, 3H) belonging to the group (OCH_3), H-7 and H-5 appear as a doublet at(δ_H = 8.14 ppm, d, 1H), and a triplet at (δ_H = 7.62ppm, t, 1H), and the other aromatic protons showed a two multiples at (δ_H = 6.83-6.95ppm, m, 3H) and at (δ_H = 7.25-7.38ppm, m, 3H) (Figure 4).

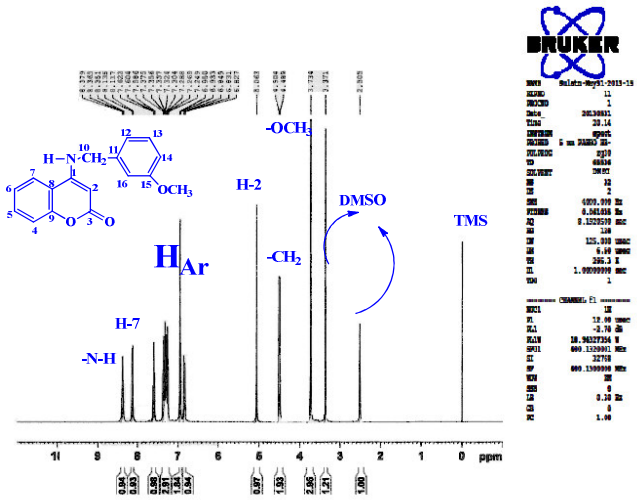


Figure 2: ^{1}H-NMR spectrum of Product(5f)

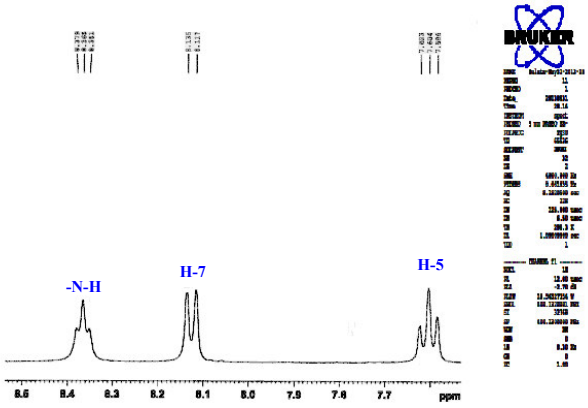


Figure 3: ^{1}H-NMR spectrum of Product(5f)

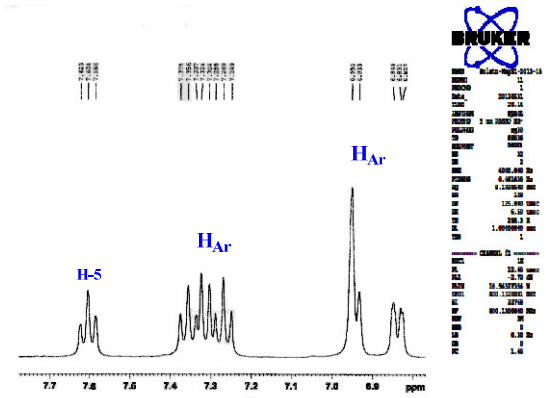


Figure 4: ^{1}H-NMR spectrum of Product(5f)

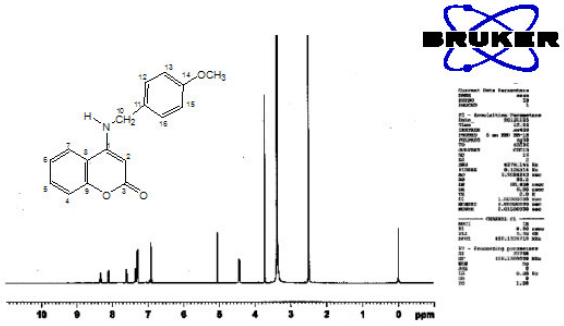


Figure 2-a: ^{1}H-NMR spectrum of Product(5g) without D_2O

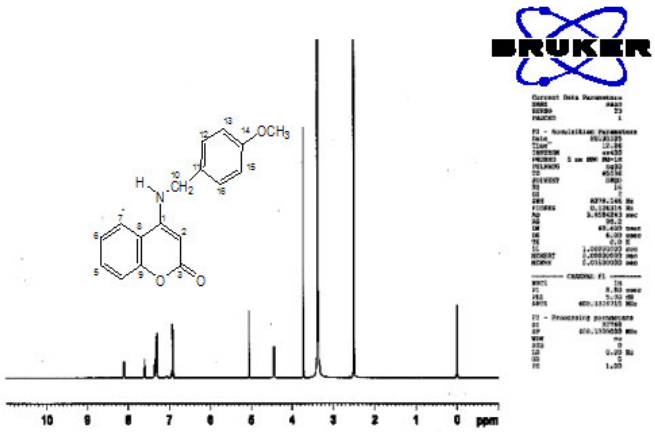


Figure 2-b: ^{1}H-NMR spectrum of Product(5g) witht D_2O

The COSY spectrum (Figure 5) showed cross-peaks between protons on C-1o with the amino proton , and the proton on C-6 with protons on C-5 and C-7.

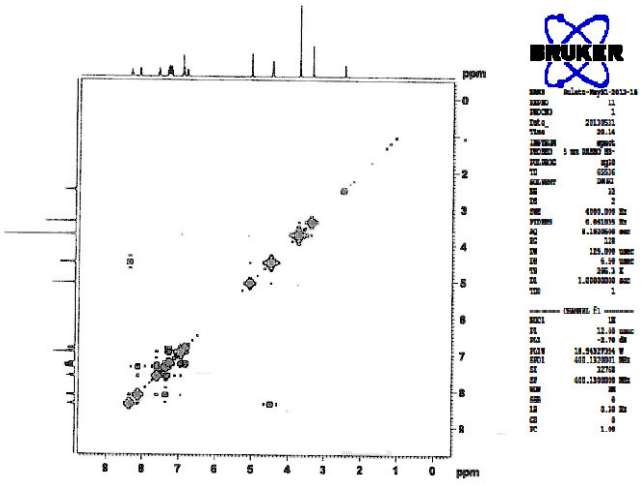


Figure 5: COSY spectrum of compound (5f)

The ^{13}C NMR spectrum of compound **(5f)** (Figure 6) showed 15 signals; that were further assigned by a DEPT-135 experiment (Figure 7) into one secondary carbon at δ 45.85 ppm corresponding to C- 10, one primary carbon at δ_c 55.45 ppm, 6 quaternary carbons at δ_c 153.56, 139.87, 130.12, 123.93, 153.60 and 161.87ppm for C-11, 9,15, 8, 1 and 3 respectively and 9 tertiary carbons at δc 159.92, 132.44, 130.12, 122.88, 114.91, 113.32, 112.75, 83.01ppm for C-14, 13, 16, 4, 12, 7, 6, 5 and 2 respectively.

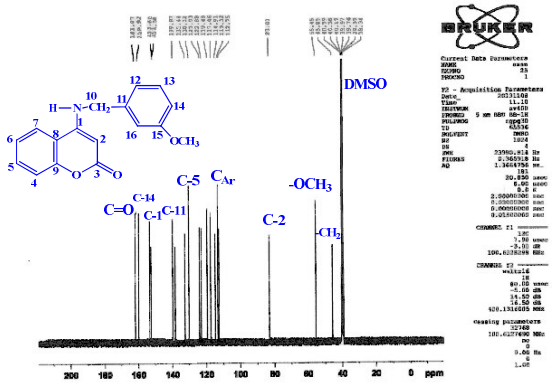


Figure 6: ^{13}C-NMR spectrum of compound(5f)

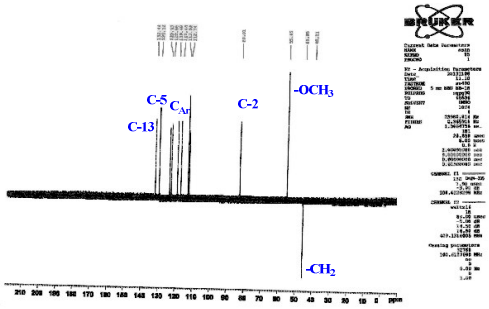


Figure 7: DEPT- 135 spectrum of compound (5f)

Finally , Figure 8 presents the d MS spectrum of the product which shows the following molecular ions:
(M^+-28), (M^+-31), Z/e= 253, ($C_6H_4–CH_2^+$ Z/e = 91)
(OCH_3-$C_6H_4–CH_2^+$ Z/e = 121) , (M^+-63) Z/e = 257
($C_9H_6O_2N^+$ Z/e = 162) , (OCH_3^+ Z/e = 31)

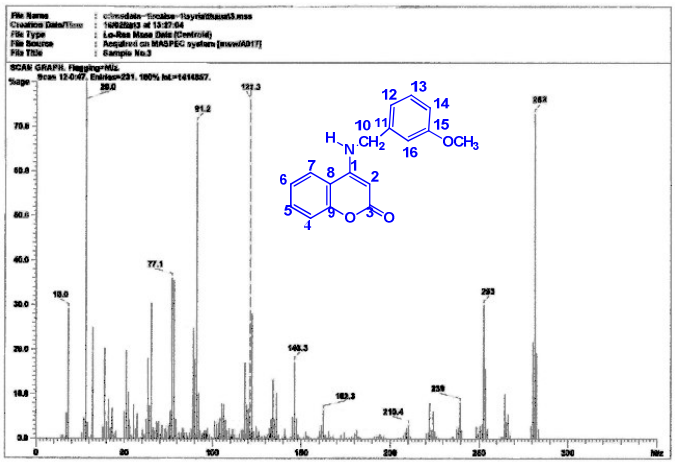
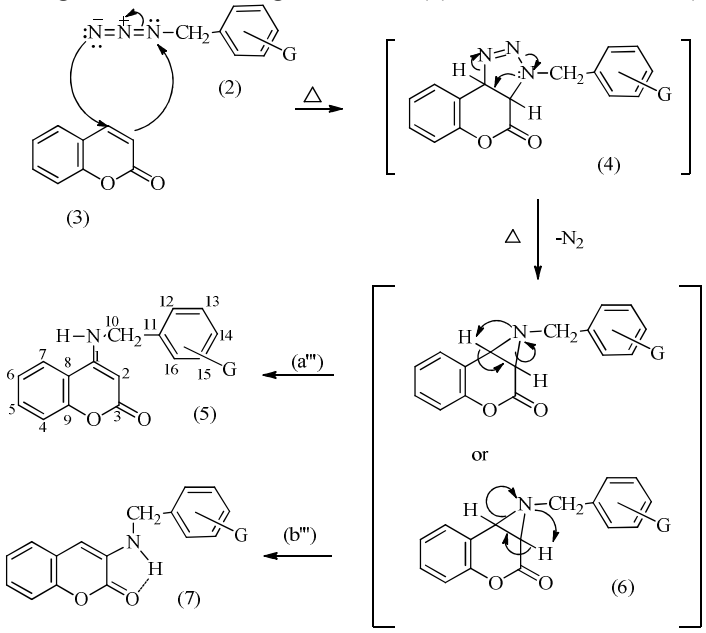


Figure 8: MS spectrum of Product(5f)

It has been verified experimentally the existence of the double bond by oxidation.

The scheme (2) indicates to the reaction mechanism as it leads azide interaction (2) and quomarine (3) to triazole (4) who loses nitrogen molecule leading to aziridine (6) then anaminolactone (5).



scheme (2)

The mechanism shows the possibility of conformation two isomers (5), (7) as a result of open aziridene cycle (6) by two transitions (a```) or (b```). I've been isolating one compound, it has been ascertained by thin layer chromatography (TLC).

The spectrum IR and NMR Data suggest the isomer (5) for the absence of hydrogen bonding in the infrared spectrum and because the amino proton shift is toward the (δ = 7.51 - 8.48 ppm). On the other hand we believe that the degree of acidity of the α- proton and β in the quomarine ring is converging and therefore the grab probability both of them are converging, but we believe that the reactionis exact a thermodynamic not a kinetic, which is also likely to be is the compound (5).The reaction offers a new way to prepare anaminolactones useful in organic synthesis.

Conclusions

Substituted benzyl azides interacted with quomarinee produced seven vehicles of the type Inaminolactones (5a, 5b, 5c, 5d, 5e, 5f, 5g). The products isolated , purified and were characterized by spectral methods , by IR, ^{1}H-NMR, ^{13}C- NMR ,Cosy ,Dept-135andGC/ MS. and suggested suitable to explain the mechanisms of their formation.The reactions were completely regioselective, so we suggest quantum calculations to find the regioselective l in these reactions because the precise form of the structure of the produces problem needs further study.

The reactions 1,3- dipolar cycloaddition of substituted benzyl azides with quomarine using to one time for preparing the enaminolactones, and this way is new.

Acknowledgment
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