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Synthesis of biheterocyclic α-amino acids

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Summary. We report here the synthesis of biheterocyclic α-amino acids by 1,3 dipolar cycloaddition of acetylenic compounds on α-azido α-amino esters.

Keywords: α-Amino acids – Triazole – Tetrazole – Azide – Alcyne – Cycloaddition

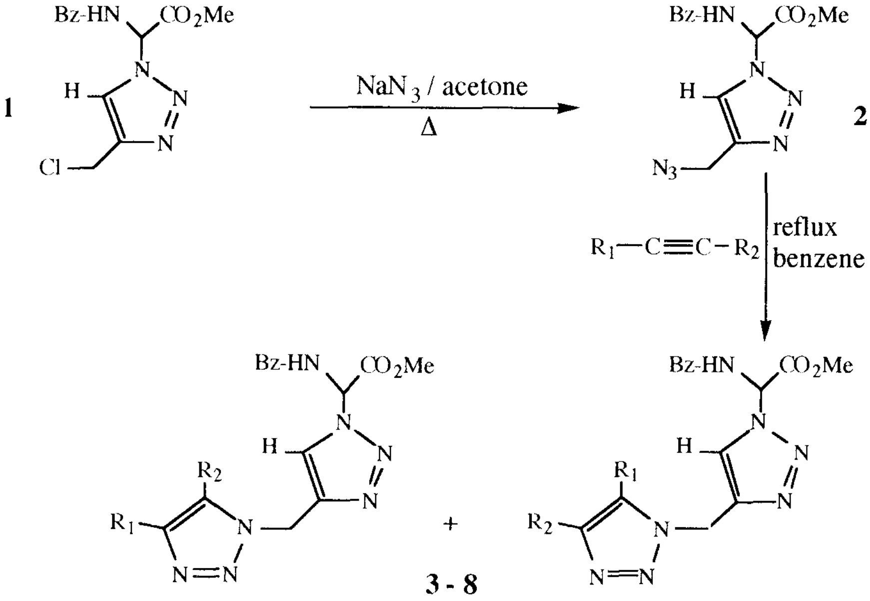
Introduction

Continuing our research (Achamlale et al., 1997; Alami et al., 1996; Elachqar et al., 1994; Elhajji, 1992; Zaïd, 1996) concerning heterocyclic α-amino acids which present interesting biological activity due to the presence of the heterocyclic cores as in the case of tetrazolic glycine (Lunn et al., 1992; Schoepp et al., 1992) and proline (Monn et al., 1993) derivatives, we describe three approaches to the synthesis of α-amino acids carrying in the α position a variety of heterocycles "triazole-triazole" and "triazole-tetrazole" (Scheme 1, 2 and 5).

These three approaches are based on 1,3 dipolar cycloaddition reactions of commercial dipolarophile or acetylenic compounds synthesised in the laboratory using different azides.

Results

The first strategy involves the preparation of 2-benzoylamino-2-(4-azidomethyltriazolyl) glycine methyl ester **2** by action of sodium azide on 2-benzoylamino-2-(4-chloromethyltriazolyl) glycine methyl ester (Achamlale et al., 1997) in acetone at reflux. Azide **2**, prepared in this way was submitted to acetylenic compounds to lead to a mixture of regioisomers separated by chromatography over silica gel and by preparative high pressure liquid chromatography (HPLC) (Scheme 1).



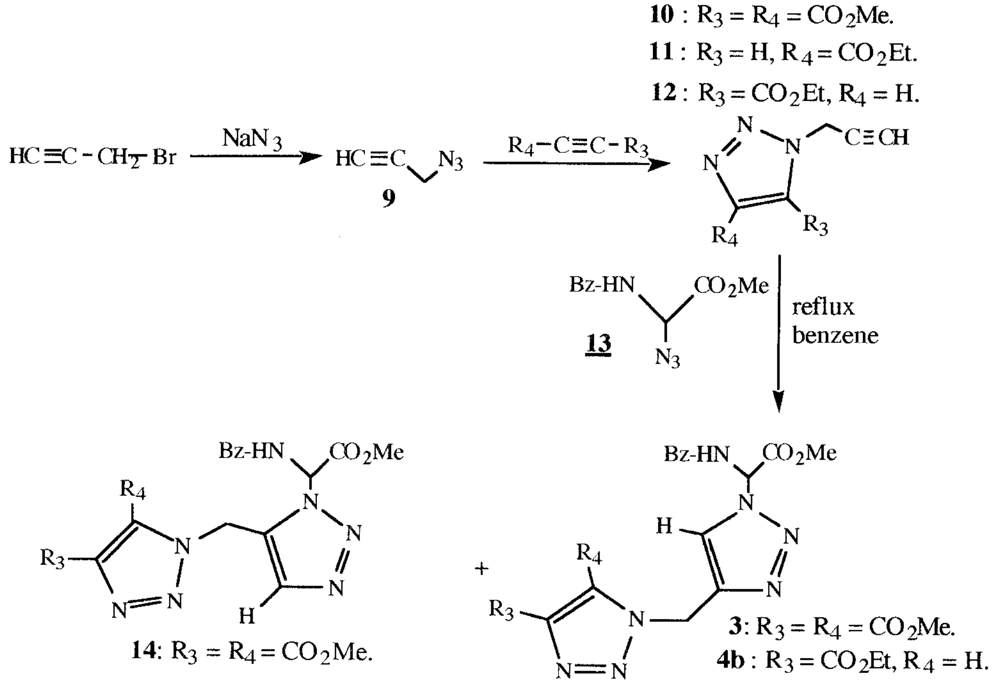
Scheme 1

Table 1. Synthesis of α-bitriazolyl α-amino acid derivatives **3** to **8**

Product	R_1	R_2	Time (h)	Yield (%)	Ratio of isomers
3	CO_2Me	CO_2Me	16[a]	86	–
4	H	CO_2Et	56[a]	87	88/12
5	H	Ph	48[b]	83	56/44
6	Ph	Ph	288[b]	38	–
7	H	CH_2Cl	48[b]	75	66/34
8	H	$CH(OH)C_2H_5$	48[b]	79	60/40

[a] Room temperature, without solvent; [b] benzene, reflux.

The chemical yields of the cycloaddition reactions depend on the nature of the substituents R_1 and R_2 of the acetylenic compounds. According to literature data (Tsypin et al., 1977) the yields of the cycloaddition reactions are better with electron withdrawing substituents (R_1 or R_2 = CO_2CH_3, $CO_2C_2H_5$...) than with electron donating substituents (R_1 = R_2 = Ph). Moreover the nature of the substituents R_1 and R_2 has a great effect on the orientation of the cycloaddition reactions, the best regioselectivity being obtained with electron withdrawing substituents (L'Abbe, 1969). The structures of the two regioisomers were assigned on the basis of literature data (Birkofer et al., 1963) concerning the chemical shifts of triazolic protons. Earlier studies (Tsypin et al., 1977) have shown that the proton signal for the 1,5 isomer lies downfield from the corresponding signal for the 1,4 isomer.



Scheme 2

In the second approach we prepared the original triazolic dipolarophiles (**10–12**) and submitted them to 1,3 dipolar cycloaddition reactions with azide **13** (Achamlale et al., 1997) (Scheme 2).

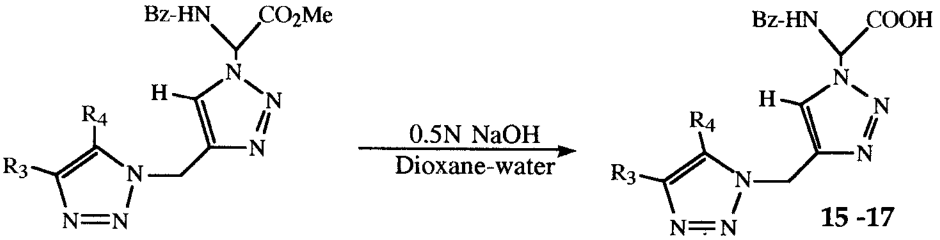
The reaction of propargylic azide **9**, prepared by the action of sodium azide on propargyl bromide at room temperature, with ethyl propiolate led to the formation of two regioisomers **11** and **12**. Assignment of these two isomers has been done using the chemical shifts of triazolic protons in positions 4 and 5 (Birkofer et al., 1963; Tsypin et al., 1977).

The reaction of acetylenic compounds **10** and **11** on azide **13** in refluxing benzene led to bi-triazolic α-amino esters respectively in 75 and 80% yield. The structures of the two isomers **3** and **14** and the product **4b** have been assigned by comparison of the spectral data of the same products **3** and **4b** obtained by the first strategy.

Hydrolysis of the ester function of the bi-triazolic α-amino esters has been carried out in a dioxane-water mixture, in the presence of 0.5 N NaOH (Scheme 3). Table 2 summarizes the results.

The last approach concerning biheterocyclic α-amino acids of the type "triazole-tetrazole" consists of preparing, firstly, tetrazolic dipolarophiles by nucleophilic substitution of propargyl bromide by 5-substituted tetrazole derivatives.

Tetrazole derivatives were obtained as described in the literature (Antonowa et al., 1976) but the yields were improved by our team (Alami et al., 1996). Reaction with propargyl bromide in the presence of triethylamine in acetone at room temperature gave the desired compounds in 70–85% yield.



15 -17

Scheme 3

Table 2. Synthesis of α-bitriazolyl α-amino acids **15** to **17**

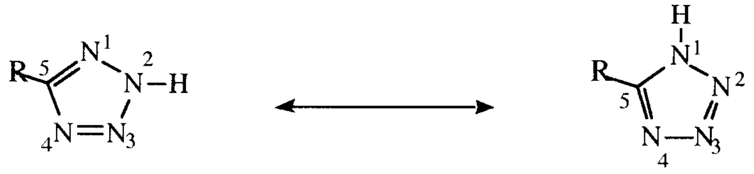
Product	R_3	R_4	m.p. (°C)	yield (%)	eq of 0.5N NaOH
15	CO_2Me	CO_2Me	103	62	1
16	H	CO_2Et	198	52	1
17	H	$CH(OH)C_2H_5$	188	80	1.5

According to the literature, the existence of the two tautomeric forms (Scheme 4) led to two regioisomers (80/20), the major isomer being separated by column chromatography over silica gel.

Previous studies (Barlin et al., 1967; Butler et al., 1967; Henry, 1951; Henry et al., 1954; Huff et al., 1970; Juby et al., 1969; Kishore et al., 1978; Padwa et al., 1978; Raap et al., 1969; Scott et al., 1967) have shown that the two isomers can be differentiated with the aid of ^{1}H NMR spectroscopy. The chemical shift of the protons of the CH_2 group on the nitrogen differs according to the isomer and depends on the nature of the substituent (Barlin et al., 1967; Huff et al., 1970; Juby et al., 1969; Raap et al., 1969). Steric factors also play an important role in reaction orientation and determination of the ratio of the two isomers. Thus the 2,5-disubstituted isomer is predominant (80–90%) for the reactions from 5-aryl tetrazoles (Henry, 1951); from 5-alkyltetrazoles (Henry et al., 1954) the two isomers were obtained in a 1/1 ratio.

The study by ^{1}H NMR of 2-(1-acetoxy-3-substituted carbamido)-5-phenyltetrazole has shown that the phenyl on position 5 can cause a greater shielding effect on the α proton of the N^1-substituent than the N^2-substituent (Kishore et al., 1978).

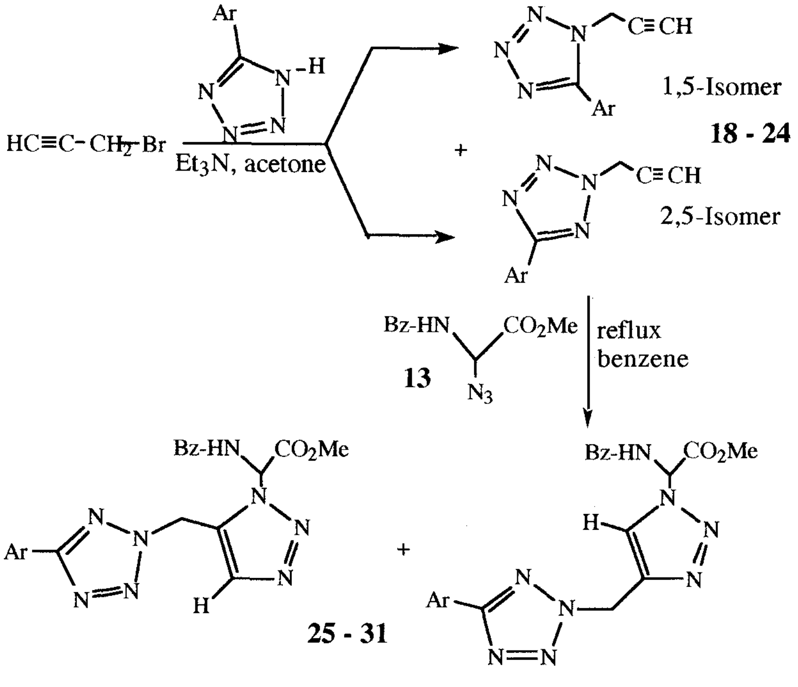
On this basis, we propose that the major isomers we 2,5 disubstituted and the minor products are 1,5-disubstituted. These assignments were



Scheme 4

Table 3. Synthesis of acetylenic tetrazole derivatives **18** to **24**

Product	Ar	Substitued position		δ CH_2N^1 (ppm)	δ CH_2N^2 (ppm)	Ratio of isomers 1.5/2.5	m.p. (°C)	Yield (%)
18	C_6H_5	1.5	–	5.26	–	19	oil	85
		–	2.5	–	5.46	81	oil	
19	p-$MeOC_6H_4$	1.5	–	5.2	–	20	62	82
		–	2.5	–	5.45	80	71	
20	p-MeC_6H_4	1.5	–	5.18	–	20	77	85
		–	2.5	–	5.41	80	53	
21	o-HOC_6H_4	–	2.5	–	5.51	>98	77	81
22	2-furyl	1.5	–	5.41	–	25	<50	70
		–	2.5	–	5.46	75	96	
23	2-thienyl	1.5	–	5.29	–	22	113	75
		–	2.5	–	5.40	78	84	
24	2-pyrryl	1.5	–	5,29	–	20	140	70
		–	2.5	–	5.38	80	114	



Scheme 5

confirmed by X-ray diffraction experiments. The results are summarized in Table 3.

The 2,5-disubstituted compounds thus prepared were submitted to cycloaddition reactions with azide **13** (Scheme 5).

Table 4. Synthesis of biheterocyclic "triazolic-tetrazolic" α-amino acid derivative **25–31**

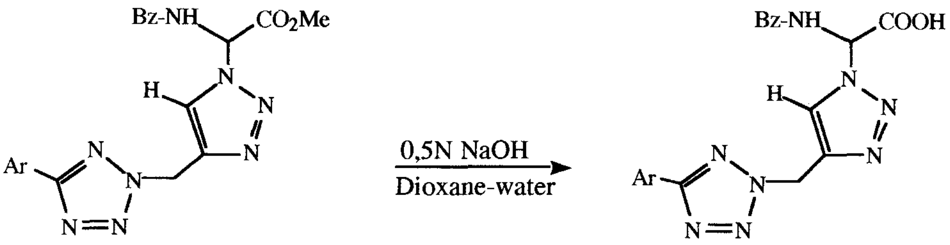
Product	Ar	δH_4 ppm	δH_5 ppm	m.p. (°C)	Time (h)	Yield (%)	Ratio of isomers 1.4/1.5
25	C_6H_5	7.6	–	150	48	79	07
		–	8.1	188			93
26	o-HOC_6H_4	7.6	–	156	36	81	12
		–	8.1	194			88
27	p-$MeOC_6H_4$	7.8	–	120	48	85	12
		–	8.1	178			88
28	p-MeC_6H_4	7.82	–	151	48	88	08
		–	8.20	170			92
29	2-furyl	7.86	–	152	48	73	12
		–	8.22	170			88
30	2-thienyl	–	8	18	48	80	05
							95
31	2-pyrryl	7.73	–	168	48	78	

The structures of the two regioisomers **25–31** were assigned on the basis of literature data (Birkofer et al., 1963; Tsypin et al., 1977) concerning the chemical shifts of triazolic protons on position 4 and 5.

In all cases, the reaction of tetrazolic acetylenic derivatives on azide **13** led to cycloaddition products with high regioselectivity and chemical yields due, essentially, to the presence of the tetrazolic core.

After the synthesis of biheterocyclic α-amino esters, we proceeded to the saponification of the ester function in basic conditions. The hydrolysis reaction was carried out in the presence of a slight excess of 0.5 N sodium hydroxide solution in a dioxane-water mixture (9/1). After 16 h at room temperature, we obtained the acids in 80 to 83% yields (Scheme 6). The results are summarized in Table 5.

By these strategies, we have prepared several biheterocyclic α-amino acids whose biological properties are under investigation.



Ar = o-HOC_6H_4, p-MeC_6H_4, p-$MeOC_6H_4$, 2-furyl, 2-thienyl.

Scheme 6

Table 5. Synthesis of α-biheterocyclic "triazolic-tetrazolic" α-amino acids **32** to **36**

Product	Ar	m.p. (°C)	eq of 0.5N NaOH	Yield (%)
32	o-HOC_6H_4	196	1.5	80
33	p-$MeOC_6H_4$	190	1.5	83
34	p-MeC_6H_4	202	1.5	83
35	2-furyl	178	1.5	80
36	2-thienyl	199	1.5	82

Experimental

Melting points were obtained on a electrothermal melting point apparatus and are uncorrected. ^1H NMR spectra were obtained on VARIAN EM-360 (60 MHz) and BRUCKER (250 MHz) instruments, TMS as internal standard ^{13}C NMR spectra were obtained on BRUCKER (200 MHz) instrument. Microanalyses were performed by the ENCT (Toulouse). Mass spectra were measured on a JEOL-JMS-DX 300 FAB instrument and Desorption in chemical ionisation with NH_3 D/CI instrument. The oxime and 5-substituted tetrazoles have been prepared using Alami's method (Alami et al., 1996).

Synthesis of the azide 2

A mixture of the compound **1** (5 mmol) and sodium azide (20 mmol) in acetone (20 ml.) was stirred at 70°C for 24 h. After reaction the solution was filtered, the solvent evaporated and the residue chromatographed on silica column (ether/hexane 30/70).

2: Yield = 83% m.p. = 50°C (ether-hexane) Rf = 0.45 (AcOEt/hexane 1/1).
^1H NMR ($CDCl_3$) δ: 3.82 (s, 3H), 4.44 (s, 2H), 7.24 (d, 1H, J = 8 Hz), 7.44–7.86 (m, 5H), 7.67 (s, 1H), 7.72 (d, 1H, J = 8 Hz).
Anal. calcd. for $C_{13}H_{13}N_7O_3$: C,49.52, H,4.12, N,31.11.
Found. C,49.13, H,4.17, N,30.91.

Cycloaddition reaction: General procedure

The azide **2** or **13** and the dipolarophile were magnetically stirred without solvent at room temperature or in a minimum volume of benzene at reflux (see Table 1 and 4 for the reaction conditions). After evaporation of the solvent, the residue was chromatographed over silica or by analytical preparative liquid chromatography (HPLC). The solid compounds were recrystallised from ether/dichloromethane and/or from acetone.

3: Yield = 86%; m.p. = 151–152°C Rf = 0.25 ether
^1H NMR ($CDCl_3$ + DMSO d_6) δ: 3.79 (s, 3H), 3.93 (s, 6H), 5.90 (s, 2H), 7.20 (d, 1H, J = 8 Hz), 7.42–7.84 (m, 5H), 7.64 (s, 1H), 7.7 (d, 1H, J = 8 Hz).
^{13}C NMR ($CDCl_3$ + DMSO d_6) δ: 45.46, 52.80, 53.60, 54.1, 67.6, 127.52, 128.8, 130.1, 132.3, 132.7, 134.84, 140.2, 142.6, 158.6, 160.3, 165.73, 166.6.
Anal. calcd. for $C_{19}H_{19}N_7O_7$: C, 49.89, H, 4.16, N, 21.44.
Found. C, 49.50, H, 4.03, N, 21.13.

4: Yield = 87%.
Major isomer **4b**: m.p. = 151–152°C Rf = 0.2 AcOEt/hexane 2/1
^1H NMR ($CDCl_3$ + DMSO d_6) δ: 1.36 (t, 3H, J = 7 Hz), 3.8 (s, 3H), 4.36 (q, 2H, J = 7 Hz), 5.7 (s, 2H), 7.01 (d, 1H, J = 8 Hz), 7.16–7.8 (m, 6H), 8.13 (s, 1H), 8.3 (s, 1H).
$C_{18}H_{19}N_7O_5$ (413): M.S [D.C.I/NH_3 $(M + H)^+$ = 414 and $(M + NH_4)^+$ = 431].
Minor isomer **4a**: m.p. = 100°C Rf = 0.4 AcOEt/hexane 2/1

^{1}H NMR (CDCl$_3$ + DMSO d$_6$) δ: 1.34 (t, 3H, J = 7 Hz), 3.81 (s, 3H), 4.34 (q, 2H, J = 7 Hz), 5.68 (s, 2H), 7.24 (d, 1H, J = 8 Hz), 7.42–7.86 (m, 6H), 7.66 (s, 1H), 8.14 (s, 1H).
^{13}C NMR (CDCl$_3$ + DMSO d$_6$) δ: 14.3, 45.4, 54.2, 61.40, 67.7, 127.7, 127.6, 128.8, 132.2, 132.8, 135, 140.75, 142.54, 161, 165.75, 166.70.
Anal. calcd. for $C_{18}H_{19}N_7O_5$: C,52.30, H,4.60, N,23.72.
Found. C, 51.94, H, 4.48, N, 23.63.

5: Yield = 83%.
Major isomer **5a**: m.p. = 134–136°C Rf = 0.5 AcOEt/hexane 2/1
^{1}H NMR (CDCl$_3$ + DMSO d$_6$) δ: 3.84 (s, 3H), 5.70 (s, 2H), 7.26 (d, 1H, J = 8 Hz), 7.35–7.87 (m, 11H), 7.69 (s, 1H), 7.84 (s, 1H).

^{13}C NMR (CDCl$_3$ + DMSO d$_6$) δ: 45.3, 54.2, 67.6, 119.8, 125.8, 127.5, 128.4, 128.9, 132.1, 132.8, 135.1, 137, 143.37, 155.6, 165.8, 166.6.
Anal. calcd. for $C_{21}H_{19}N_7O_3$: C,60.43, H,4.55, N,23.50.
Found. C,59.96, H,4.51, N,23.45.

Minor isomer **5b**: m.p. = 112–114°C Rf = 0.45 AcOEt/hexane 2/1
^{1}H NMR (CDCl$_3$ + DMSO d$_6$) δ: 3.80 (s, 3H), 5.60 (s, 2H), 7.16 (d, 1H, J = 8 Hz), 7.38–7.86 (m, 11H), 7.54 (s, 1H), 7.67 (s, 1H).

^{13}C NMR (CDCl$_3$ + DMSO d$_6$) δ: 45.8, 54.05, 67.55, 127.6, 128.3, 128.6, 128.80, 128.96, 129, 129.2, 129.8, 132.1, 132.5, 144, 158, 166.6, 167.3.

6: Yield = 38% m.p. = 96°C Rf = 0.74 AcOEt/hexane 2/1
^{1}H NMR (CDCl$_3$ + DMSO d$_6$) δ: 3.75 (s, 3H), 5.46 (s, 2H), 7.18–7.48 (m, 16H), 7.47 (s, 1H), 8.1 (d, 1H, J = 8 Hz).

^{13}C NMR (CDCl$_3$ + DMSO d$_6$) δ: 43.57, 53.96, 67.6, 126.8, 127.2, 127.6, 127.9, 128.5, 128.70, 129.4, 129.96, 130.14, 130.70. 132.40, 132.60, 134.86, 134.1, 143.9, 144.5, 165.9, 166.67.
$C_{27}H_{23}N_7O_3$ (493): M.S [D.C.I/NH$_3$ (M + H)$^+$ = 494 and (M + NH$_4$)$^+$ = 511].

7: Yield = 75%.
Major isomer **7a**: m.p. = 124–126°C Rf = 0.7 AcOEt
^{1}H NMR (CDCl$_3$ + DMSO d$_6$) δ: 3.82 (s, 3H), 4.66 (s, 2H), 5.26 (s, 2H), 7.24 (d, 1H, J = 8 Hz), 7.44–7.86 (m, 6H), 7.64 (s, 1H), 7.82 (s, 1H).

^{13}C NMR (CDCl$_3$ + DMSO d$_6$) δ: 36.06, 45.25, 54.14, 67.6, 132.8, 127.5, 128.8, 132.3, 132.8, 135, 143, 145.3, 165.8, 166.7.
$C_{16}H_{16}ClN_7O_3$ (389.5): M.S [FAB/Glycerol, (M + H)$^+$ = 390].

8: Yield = 79%.
Major isomer **8a**: m.p. = 145–147°C Rf = 0.28 AcOEt
^{1}H NMR (CDCl$_3$ + DMSO d$_6$) δ: 0.9 (t, 3H, J = 7 Hz), 1.81 (m, 2H), 3.70 (m, 1H), 3.8 (s, 3H), 4.75 (t, 1H, J = 7 Hz), 5.50 (s, 2H), 7.24 (d, 1H, J = 8 Hz), 7.4–7.85 (m, 5H), 7.61 (s, 1H), 7.82 (s, 1H), 8 (d, 1H, J = 8 Hz).

^{13}C NMR (CDCl$_3$ + DMSO d$_6$) δ: 9.7, 30.2, 45.2, 54.1, 67.7, 68.3, 121, 127.6, 128.8, 132.3, 132.7, 135, 143.2, 151.9, 165.8, 166.8.
Anal. calcd. for $C_{18}H_{21}N_7O_4$: C,54.13, H,5.26, N,24.56.
Found. C,53.79, H, .13, N,24.09.

Minor isomer **8b**: m.p. = 133–135°C Rf = 0.36 AcOEt
^{1}H NMR (CDCl$_3$ + DMSO d$_6$) δ: 0.9 (t, 3H, J = 7 Hz), 1.69 (m, 2H), 3.7 (s, 3H), 4.6 (m, 1H), 4.8–5.2 (s, 1H), 5.73 (s, 2H), 7.03 (d, 1H, J = 8 Hz), 7.41–7.95 (m, 5H), 7.4 (s, 1H), 7.69 (s, 1H), 9.92 (d, 1H, J = 8 Hz).

^{13}C NMR (CDCl$_3$ + DMSO d$_6$) δ: 9.7, 28.8, 42.9, 63.9, 68.07, 127.7, 128, 130.9, 131.8, 132.5, 133.7, 140.24, 143.2, 166.35, 166.6.
$C_{18}H_{21}N_7O_4$ (399): M.S [D.C.I/NH$_3$ (M + H)$^+$ = 400 and (M + NH$_4$)$^+$ = 417].

*Synthesis of the azide **9***

The mixture of the propargyl bromide and sodium azide (5 equivalent) in minimum of acetone was stirred at room temperature overnight. The residue was distilled carefully at normal pressure.

9: Yield = 66% b.p. = 59–64°C.
^{1}H NMR ($CDCl_3$) δ: 2.5 (t, 1H, J = 3 Hz), 3.3 (d, 2H, J = 3 Hz).

*Synthesis of acetylenic triazolic derivative **10–12***

The azide **9** (4 mmol) and the dipolarophile (6 mmol) were stirred without solvent between 24 and 72 h at room temperature. After reaction, the residue was chromatographed on silica gel column (ether/hexane 40/60).

10: (reaction of the azide **9** with acetylene metyl dicarboxylate):
Yield = 60% m.p. = 84–86°C Rf = 0.66 ether
^{1}H NMR ($CDCl_3$) δ: 2.53 (t, 1H, J = 3 Hz), 3.94 (s, 3H), 4 (s, 3H), 5.46 (d, 2H, J = 3 Hz).
Anal. calcd. for $C_9N_9N_3O_4$: C,48.43, H,4.03, N,18.83.
Found. C,48.13, H,4.02, N,18.87.

Compounds **11** and **12** (reaction of the azide **9** with ethyl propiolate) Yield = 50%

Minor isomer **12**: (10%) m.p. = 62°C Rf = 0.72 ethyl acetate/hexane 1/1
^{1}H NMR ($CDCl_3$) δ: 1.46 (t, 3H, J = 7 Hz), 2.48 (t, 1H, J = 3 Hz), 4.46 (q, 2H, J = 7 Hz), 5.5 (d, 2H, J = 3 Hz), 8.1 (s, 1H).

Major isomer **11**: (90%) m.p. = 74–76°C Rf = 0.58 ethyl acetate/hexane 1/1
^{1}H NMR ($CDCl_3$) δ: 1.43 (t, 3H, J = 7 Hz), 2.78 (t, 1H, J = 3 Hz), 4.48 (q, 2H, J = 7 Hz), 5.36 (d, 2H, J = 3 Hz), 8.56 (s, 1H).
$C_8H_9N_3O_2$ (179): M.S [D.I.C/NH_3 $(M + H)^+$ = 180 and $(M + NH_4)^+$ = 197].

Compounds **14** and **3** (reaction of the azide **13** with triazolic alcyne **10**) Yield = 75%
Minor isomer 14: (48%) m.p. = 161–162°C Rf = 0.13 ether
^{1}H NMR ($CDCl_3$ + DMSO d_6) δ: 3.77 (s, 3H), 3.89 (s, 3H), 3.93 (s, 3H), 5.93 (s, 2H), 6.94 (d, 1H, J = 8 Hz), 7.39–7.82 (m, 5H), 8.17 (s, 1H), 8.31 (d, 1H, J = 8 Hz).

^{13}C NMR ($CDCl_3$ + DMSO d_6) δ: 45.46, 52.78, 53.64, 54.16, 64.4, 125, 127.6, 128.8, 130.1, 131.7, 132.9, 140, 140.7, 158.77, 160.4, 165.4, 167.3.
Anal. calcd. for $C_{19}H_{19}N_7O_7$: C,49.89, H,4.16, N,21.44.
Found. C,49.50, H,4.03, N,21.13.
Major isomer **3** (52%).

Hydrolysis of the ester function: General procedure

To a solution of amino ester (8 mmol) in dioxane-water mixture (9/1) (40 ml.) a 0.5 N NaOH solution (8 to 12 mmol) was added in portions with vigorous stirring over a period of 30 minutes. The reaction mixture was further stirred at room temperature for 16 h. After reaction the solution was concentrated, the residue was dissolved in 10 ml of water and extracted thrice with dichloromethane. The aqueous layer was acidified with 1 N HCl (pH = 2–2.5) and extracted with ethyl acetate. The organic layer was dried with Na_2SO_4 and evaporated to dryness. The acid was recrystallized from acetone-ether mixture.

15: Yield = 62% m.p. = 103°C
^{1}H NMR ($DMSO_3$) δ: 3.83 (s, 3H), 3.86 (s, 3H), 5.88 (s, 2H), 6.01–6.5 (ma, 1H), 7.04 (d, 1H, J = 8 Hz), 7.36–7.9 (m, 5H), 7.63 (s, 1H), 9.31 (d, 1H, J = 8 Hz).

^{13}C NMR ($DMSO_3$ d_6) δ: 45.03, 52.1, 53.02, 67.9, 127.5, 127.9, 129.6, 131.7, 132.2, 133.7, 139.3, 141.5, 157.9, 159.7, 166.4, 166.5.
$C_{18}H_{17}N_7O_7$ (443): M.S [D.C.I/NH_3 $(M + H)^+$ = 444 and $(M + NH_4)^+$ = 460].

16: Yield = 52% m.p. = 198°C
^1H NMR ($DMSO_3 d_6$) δ: 1.3 (t, 3H, J = 7 Hz), 4.26 (q, 2H, J = 7 Hz), 5.73 (s, 2H), 5.97–6.2 (ma, 1H), 7.08 (d, 1H, J = 8 Hz), 7.3–7.9 (m, 5H), 7.7 (s, 1H), 8.50 (s, 1H), 9.70 (d, 1H, J = 8 Hz).

^{13}C NMR (DMSO d_6) δ: 13.9, 54, 60.40, 68.8, 127.7, 128.4, 127.5, 128.10, 131.5, 132, 138.9, 139.8, 159.9, 166.5, 166.6.
$C_{17}H_{17}N_7O_5$ (399): M.S [D.C.I/NH_3 $(M + H)^+$ = 400 and $(M + NH_4)^+$ = 417].

17: Yield = 80% m.p. = 188°C
^1H NMR (DMSO d_6) δ: 0.8 (t, 3H, J = 7 Hz), 1.7 (m, 2H), 4.64 (m, 1H), 5–5.6 (ma, 1H), 5.7 (s, 2H), 7.03 (d, 1H, J = 8 Hz), 7.4–7.95 (m, 5H), 7.50 (s, 1H), 7.67 (s, 1H), 9.92 (d, 1H, J = 8 Hz).

^{13}C NMR (DMSO d_6) δ: 9.70, 28.80, 43, 64, 68.1, 127.6, 128.1, 130.9, 131.78, 132.4, 133.7, 140.24, 143.2, 166.35, 166.6.
Anal. calcd. for $C_{17}H_{19}N_7O_4$: C, 52.99, H,4.93, N,21.82.
Found.C, 53.12, H,4.40, N,22.00.

Synthesis of acetylenic tetrazolic compounds

To a suspension of tetrazole (10 mmol) in acetone (15 ml.), triethylamine (15 mmol) and propargyl bromide (15 mmol) were added dropwise. The reaction mixture was stirred at room temperature for 4 h, after reaction the precipitated triethylamine hydrobromide was filtered off and the filtrate concentrated. The residue was purified by chromatography over silica gel (ether/petroleum ether 20/80). The compounds are recrystallized from petroleum ether/dichloromethane mixture.

18: Yield = 85%.
Major isomer **18a**: oil Rf = 0.66 ether/hexane 2/1 I.R (CCl_4) v = 2,134 cm^{-1}
^1H NMR ($CDCl_3$) δ: 2.66 (t, 1H, J = 3 Hz), 5.46 (d, 2H, J = 3 Hz), 7.33–8.46 (m, 5H).
$C_{10}H_8N_4$ (184): M.S [D.C.I/NH_3 $(M + H)^+$ = 185 and $(M + NH_4)^+$ = 202].

Minor isomer **18b**: oil Rf = 0.33 ether/hexane 2/1 I.R (CCl_4) v = 2,132 cm^{-1}
^1H NMR ($CDCl_3$) δ: 2.63 (t, 1H, J = 3 Hz), 5.26 (d, 2H, J = 3 Hz), 7.43–8.10 (m, 5H).

19: Yield = 82%.
Major isomer **19a**: m.p. = 71°C Rf = 0.73 ether/petroleum ether 2/1 I.R (KBr) v = 2,127 cm^{-1}
^1H NMR ($CDCl_3$) δ: 2.66 (t, 1H, J = 3 Hz), 3.83 (s, 3H), 5.45 (d, 2H, J = 3 Hz), 7.63 (4H, $J_{AB} = J_{A'B'}$ = 9 Hz).
$C_{11}H_{10}N_4O$ (214): M.S [D.C.I/NH_3 $(M + H)^+$ = 215 and $(M + NH_4)^+$ = 232].

Minor isomer **19b**: m.p. = 62°C Rf = 0.3 ether/petroleum ether 2/1 I.R (KBr) v = 2,130 cm^{-1}
^1H NMR ($CDCl_3$) δ: 2.6 (t, 1H, J = 3 Hz), 3.80 (s, 3H), 5.20 (d, 2H, J = 3 Hz), 7.41 (4H, $J_{AB} = J_{A'B'}$ = 9 Hz).
$C_{11}H_{10}N_4O$ (214): M.S [D.C.I/NH_3 $(M + H)^+$ = 215 and $(M + NH_4)^+$ = 232].

20: Yield = 85%.
Major isomer **20a**: m.p. = 53°C Rf = 0.8 ether/petroleum ether 2/1 I.R (KBr) v = 2,133 cm^{-1}
^1H NMR ($CDCl_3$) δ: 2.33 (s, 3H), 2.6 (t, 1H, J = 3 Hz), 5.41 (d, 2H, J = 3 Hz), 7.46 (4H, $J_{AB} = J_{A'B'}$ = 9 Hz).
Anal. calcd. for $C_{11}H_{10}N_4$: C, 66.66, H, 5.05, N, 28.28.
Found.C, 66.60, H,5.03, N,28.39.

Minor isomer **20b**: m.p. = 77°C Rf = 0.57 ether/petroleum ether 2/1 I.R (KBr) v = 2,131 cm^{-1}

^{1}H NMR (CDCl$_3$) δ: 2.38 (s, 3H), 2.58 (t, 1H, J = 3 Hz), 5.18 (d, 2H, J = 3 Hz), 7.46 (4H, $J_{AB} = J_{A'B'} = 9$ Hz).
$C_{11}H_{10}N_4$ (198): M.S [D.C.I/NH$_3$ $(M + H)^+ = 199$ and $(M + NH_4)^+ = 216$].

21: Yield = 81% m.p. = 77°C Rf = 0.65 ether/petroleum ether I.R (KBr) 2/1 v = 2,126 cm^{-1}
^{1}H NMR (CDCl$_3$) δ: 2.63 (t, 1H, J = 3 Hz), 5.51 (d, 2H, J = 3 Hz), 6.86–8.33 (m, 4H), 10.41 (s, 1H).
$C_{10}H_8N_4O$ (200): M.S [D.C.I/NH$_3$ $(M + H)^+ = 201$ and $(M + NH_4)^+ = 218$].

22: Yield = 70%.
Major isomer **22a**: m.p. = 94–96°C Rf = 0.39 ether/hexane 2/1 I.R (KBr) v = 2,167 cm^{-1}
^{1}H NMR (CDCl$_3$) δ: 2.45 (t, 1H, J = 3 Hz), 5.41 (d, 2H, J = 3 Hz), 6.60–6.66 (m, 1H), 7.24–7.31 (m, 1H), 7.67–7.7 (m, 1H).
$C_8H_6N_4O$ (174): M.S [D.C.I/NH$_3$ $(M + H)^+ = 175$ and $(M + NH_4)^+ = 192$].

Minor isomer **22b**: Rf = 0.2 ether/petroleum ether 2/1 I.R (KBr) v = 2,166 cm^{-1}
^{1}H NMR (CDCl$_3$) δ: 2.58 (t, 1H, J = 3 Hz), 5.46 (d, 2H, J = 3 Hz), 6.50–6.60 (m, 1H), 7–7.14 (m, 1H), 7.50–7.60 (m, 1H).
$C_8H_6N_4O$ (174): M.S [D.C.I/NH$_3$ $(M + H)^+ = 175$ and $(M + NH_4)^+ = 192$].

23: Yield = 75%.
Major isomer **23a**: m.p. = 84°C Rf = 0.48 ether/petroleum ether 2/1 I.R (KBr) v = 2,125 cm^{-1}
^{1}H NMR (CDCl$_3$) δ: 2.57 (t, 1H, J = 3 Hz), 5.40 (2H, d, J = 3 Hz), 7–7.16 (m, 1H), 7.40–7.41 (m, 1H), 7.70–7.80 (m, 1H).
$C_8H_6N_4S$ (190): M.S [D.C.I/NH$_3$ $(M + H)^+ = 191$ and $(M + NH_4)^+ = 208$].

Minor isomer **23b**: m.p. = 113°C Rf = 0.16 ether/petroleum ether 2/1 I.R (KBr) v = 2,126 cm^{-1}
^{1}H NMR (CDCl$_3$) δ: 2.54 (t, 1H, J = 3 Hz), 5.29 (d, 2H, J = 3 Hz), 7.15–7.26 (m, 1H), 7.5–7.66 (m, 1H), 7.70–7.78 (m, 1H).
$C_8H_6N_4S$ (190): M.S [D.C.I/NH$_3$ $(M + H)^+ = 191$ and $(M + NH_4)^+ = 208$].

24: Yield = 70%.
Major isomer **24a**: m.p. = 114°C Rf = 0.76 ether/petroleum ether 3/1 I.R (KBr) v = 2,143 cm^{1}
^{1}H NMR (CDCl$_3$) δ: 2.58 (t, 1H, J = 3 Hz), 5.38 (d, 2H, J = 3 Hz), 6.3–6.4 (m, 1H), 6.9–7 (m, 2H), 10.5 (ma, 1H).
$C_8H_7N_5$ (173): M.S [D.C.I/NH$_3$ $(M + H)^+ = 174$ and $(M + NH_4)^+ = 191$].

Minor isomer **24b**: m.p. = 140°C Rf = 0.65 ether/petroleum ether 3/1 I.R (KBr) v = 2,142 cm^{-1}
^{1}H NMR (CDCl$_3$) δ: 2.53 (t, 1H, J = 3 Hz), 5.29 (d, 2H, J = 3 Hz), 6.36–6.47 (m, 1H), 6.9–7 (m, 1H), 7.20–7.29 (m, 1H), 11.10 (ma, 1H).
$C_8H_7N_5$ (173): M.S [D.C.I/NH$_3$ $(M + H)^+ = 174$ and $(M + NH_4)^+ = 191$].

25: Yield = 79%.
Minor isomer **25a**: m.p. = 150°C Rf = 0.53 ether
^{1}H NMR (CDCl$_3$ + DMSO d$_6$) δ: 3.85 (s, 3H), 6 (s, 2H), 7.4 (d, 1H, J = 8 Hz), 7.50–8.46 (m, 11H), 7.60 (s, 1H).
$C_{20}H_{18}N_8O_3$ (418): M.S [D.C.I/NH$_3$ $(M + H)^+ = 419$ and $(M + NH_4)^+ = 436$].

Major isomer **25b**: m.p. = 188°C Rf = 0.4 ether
^{1}H NMR (CDCl$_3$ + DMSO d$_6$) δ: 3.6 (s, 3H), 5.8 (s, 2H), 6.8 (d, 1H, J = 8 Hz), 7.17–7.88 (m, 10H), 8.1 (s, 1H), 9.5 (d, 1H, J = 8 Hz).

^{13}C NMR (CDCl$_3$ + DMSO d$_6$) δ: 48.2, 53.60, 65.1, 124.6, 126.7, 127.1, 127.8, 128.4, 128.76, 130.3, 132, 132.4, 140.7, 165.1, 165.9, 167.3.
Anal. calcd. for $C_{20}H_{18}N_8O_3$: C, 57.42, H,4.30, N,26.79.
Found.C, 57.12, H,4.24, N,26.70.

26: Yield = 81%.
Minor isomer **26a**: m.p. = 156°C Rf = 0.48 ether
^{1}H NMR (CDCl$_3$ + DMSO d$_6$) δ: 3.70 (s, 3H), 5.7 (s, 2H), 7.6 (s, 1H), 7.8 (s, 1H), 7–8.3 (m, 11H).
$C_{20}H_{18}N_8O_4$ (434): M.S [D.C.I/NH$_3$ (M + H)$^+$ = 435 and (M + NH$_4$)$^+$ = 452].

Major isomer **26b**: m.p. = 194°C Rf = 0.42 ether
^{1}H NMR (CDCl$_3$ + DMSO d$_6$) δ: 3.6 (s, 3H), 5.76 (s, 2H), 6.67–7.73 (m, 10H), 8.1 (s, 1H), 9.3 (s, 1H), 9.6 (d, 1H, J = 8 Hz).

^{13}C NMR (CDCl$_3$ + DMSO d$_6$) δ: 48.50, 53.60, 65.15, 111.1, 117.3, 119.9, 124.8, 127.5, 127.80, 128.4, 132, 132.1, 132.4, 139.5, 156.1, 164.1, 166, 167.3.
Anal. calcd. for $C_{20}H_{18}N_8O_4$: C, 55.30, H,4.15, N,25.80.
Found.C, 54.97, H,4.12, N,25.90.

27: Yield = 85%.
Minor isomer **27a**: m.p. = 120°C Rf = 0.52 ether
^{1}H NMR (CDCl$_3$ + DMSO d$_6$) δ: 3.7 (s, 3H), 3.75 (s, 3H), 5.75 (s, 2H), 7.1 (d, 1H, J = 8 Hz), 7.2–8 (m, 10H), 7.8 (s, 1H).
$C_{21}H_{20}N_8O_4$ (448): M.S [D.C.I/NH$_3$ (M + H)$^+$ = 449 and (M + NH$_4$)$^+$ = 446].

Major isomer **27b**: m.p. = 178°C Rf = 0.28 ether
^{1}H NMR (CDCl$_3$ + DMSO d$_6$) δ: 3.60 (s, 3H), 3.65 (s, 3H), 5.75 (s, 2H), 6.76 (d, 1H, J = 8 Hz), 7.28 (4H, $J_{AB} = J_{A'B'}$ = 9 Hz), 7.16–7.7 (m, 5H), 8.1 (s, 1H), 9.5 (d, 1H, J = 8 Hz).

^{13}C NMR (CDCl$_3$ + DMSO d$_6$) δ: 48.13, 53.6, 55.21, 65.1, 114.77, 119.7, 124.6, 127.8, 128.24, 128.4, 132, 132.4, 140.5, 161.2, 165.1, 165.9, 167.3.
Anal. calcd. for $C_{21}H_{20}N_8O_4$: C, 56.23, H,4.46, N,24.99.
Found.C, 56.25, H,4.49, N,25.40.

28: Yield = 88%.
Minor isomer **28a**: m.p. = 151°C Rf = 0.44 ether
^{1}H NMR (CDCl$_3$ + DMSO d$_6$) δ: 2.3 (s, 3H), 3.8 (s, 3H), 5.92 (s, 2H), 7.24 (d, 1H, J = 8 Hz), 7.26–8 (m, 9H), 7.76 (d, 1H, J = 8 Hz), 7.82 (s, 1H).

^{13}C NMR (CDCl$_3$ + DMSO d$_6$) δ: 21.5, 48.1, 54.1, 67.6, 124.30, 126.9, 127.5, 128.8, 129.6, 132.3, 132.7, 135.2, 140.7, 142.2, 165, 165.85, 166.65.
Anal. calcd. for $C_{21}H_{20}N_8O_3$: C, 58.33, H,4.63, N,25.92.
Found.C, 57.91, H,4.39, N,25.71.

Major isomer **28b**: m.p. = 170°C Rf = 0.36 ether
^{1}H NMR (CDCl$_3$ + DMSO d$_6$) δ: 2.37 (s, 3H), 3.8 (s, 3H), 5.94 (s, 2H), 6.98 (d, 1H, J = 8 Hz), 7.6 (4H, $J_{AB} = J_{A'B'}$ = 9 Hz), 7.40–7.83 (m, 5H), 8.2 (s, 1H), 8.22 (d, 1H, J = 8 Hz).

^{13}C NMR (CDCl$_3$ + DMSO d$_6$) δ: 21.5, 48.2, 54.2, 64.4, 125.3, 124.35, 126.8, 127.6, 128.8, 129.6, 131.8, 133, 140.4, 140.65, 165, 165.4, 167.3.
Anal. calcd. for $C_{21}H_{20}N_8O_3$: C, 58.33, H,4.63, N,25.92.
Found.C, 58.37, H,4.71, N,26.23.

29: Yield = 73%.
Minor isomer **29a**: m.p. = 152°C Rf = 0.34 AcOEt/DCM 1/1
^{1}H NMR (CDCl$_3$ + DMSO d$_6$) δ: 3.67 (s, 3H), 6.44 (2H, J_{AB} = 16 Hz), 6.54–6.57 (m, 1H), 7.11–7.13 (m, 1H), 7.38 (d, 1H, J = 8 Hz), 7.41–7.85 (m, 5H), 7.56–7.59 (m, 1H), 7.86 (s, 1H), 8.10 (d, 1H, J = 8 Hz).

^{13}C NMR (CDCl$_3$ + DMSO d$_6$) δ: 44.56, 54.26, 62.18, 111.9, 112, 127.5, 128.9, 130.87, 133, 134.6, 141, 142.4, 144.67, 159, 165.20, 167.4.
$C_{18}H_{16}N_8O_4$ (408): M.S [D.C.I/NH$_3$ (M + H)$^+$ = 409 and (M + NH$_4$)$^+$ = 426].

Major isomer **29b**: m.p. = 170°C Rf = 0.2 AcOEt/DCM 1/1
^{1}H NMR ($CDCl_3$ + DMSO d_6) δ: 3.82 (s, 3H), 5.96 (d, 2H, J = 2Hz), 6.5–6.53 (m, 1H), 6.97 (d, 1H, J = 8Hz), 7.01–7.09 (m, 1H), 7.4–7.8 (m, 5H), 7.52–7.55 (m, H), 8.22 (s, 1H), 8.1 (d, H, J = 8Hz).

^{13}C NMR ($CDCl_3$ + DMSO d_6) δ: 48.3, 54.24, 64.3, 111.75, 111.8, 125.3, 127.6, 128.86, 131.74, 132.95, 140.03, 142.6, 144.4, 158.7, 165.3, 167.2.
Anal. calcd. for $C_{18}H_{16}N_8O_4$: C, 52.94, H,3.92, N,27.45.
Found.C, 52.46, H,3.87, N,27.12.

30: Yield = 80%.
Major isomer **30a**: m.p. = 186°C Rf = 0.22 ether
^{1}H NMR ($CDCl_3$ + DMSO d_6) δ: 3.6 (s, 3H), 5.7 (s, 2H), 6.75 (d, 1H, J = 8Hz), 6.82–6.87 (m, 1H), 7.16–7.18 (m, 1H), 7.45–7.48 (m, 1H), 7.14–7.65 (m, 5H), 8 (s, 1H), 9.6 (d, 1H, J = 8Hz).

^{13}C NMR ($CDCl_3$ + DMSO d_6) δ: 48.14, 53.5, 65.1, 124.6, 125.4, 127.8, 128.3, 127.8, 127.9, 132, 132.3, 139.84, 140.4, 158.1, 166, 167.30.
Anal. calcd. for $C_{18}H_{16}N_8O_3S$: C, 50.94, H,3.77, N,26.41.
Found.C, 50.73, H,3.65, N,25.92.

31: Yield = 78%.
Minor isomer **31a**: m.p. = 168°C Rf = 0.2 ether
^{1}H NMR ($CDCl_3$ + DMSO d_6) δ: 3.61 (s, 3H), 6.26 (2H, J_{AB} = 16Hz), 6.15–6.17 (m, 1H), 6.72–6.73 (m, 1H), 6.83–6.84 (m, 1H), 7.43 (d, 1H, J = 8Hz), 7.37–7.9 (m, 5H), 7.73 (s, 1H), 9.7 (d, 1H, J = 8Hz), 11 (ma, 1H).

^{13}C NMR ($CDCl_3$ + DMSO d_6) δ: 44.8, 54.1, 63.7, 110, 110.5, 119.3, 121.8, 128.5, 128.9, 131.5, 133, 134.8, 132.6, 159, 166, 167.15.
$C_{18}H_{17}N_9O_3$ (407): M.S [D.C.I/NH_3 $(M + H)^+$ = 408 and $(M + NH_4)^+$ = 425].

32: Yield = 80% m.p. = 196°C
^{1}H NMR (DMSO d_6) δ: 6 (s, 2H), 7.12 (d, 1H, J = 8Hz), 6.9–7.9 (m, 9H), 7.8 (s, 1H), 8.37 (s, 1H), 9.38–9.67 (ma, 1H), 9.7 (d, 1H, J = 8Hz).

^{13}C NMR (DMSO d_6) δ: 48.8, 68.6, 125, 111.6, 117.6, 120, 129, 128.1, 128.6, 132.3, 132.9, 139.1, 141.2, 156.3, 165.1, 167.1, 167.2.
$C_{19}H_{16}N_8O_4$ (420): M.S [D.C.I/NH_3 $(M + H)^+$ = 421 and $(M + NH_4)^+$ = 438].

33: Yield = 83% m.p. = 190°C
^{1}H NMR (DMSO d_6) δ: 3.8 (s, 3H), 6 (2H, s), 6.7 (d, 1H, J = 8Hz), 7.5 (4H, J_{AB} = $J_{A'B'}$ = 8Hz), 7.4–7.9 (m, 6H), 8.34 (s, 1H), 9.4 (d, 1H, J = 8Hz).

^{13}C NMR (DMSO d_6) δ: 47.8, 55.1, 66.2, 114.3, 119.1, 123.8, 127.4, 127.80, 128.30, 131.8, 132.7, 139.3, 160.85, 164.2, 166.1, 166.5.
Anal. calcd. for $C_{21}H_{18}N_8O_4$: C, 55.30, H,4.15, N,25.80.
Found.C, 55.36, H,4.12, N,26.10.

34: Yield = 83% m.p. = 202°C
^{1}H NMR (DMSO d_6) δ: 2.33 (s, 3H), 5.93 (s, 2H), 6.95 (d, 1H, J = 8Hz), 7.42 (4H, J_{AB} = $J_{A'B'}$ = 12Hz), 7.3–7.9 (m, 6H), 8.32 (s, 1H), 9.72 (d, 1H, J = 8Hz).

^{13}C NMR (DMSO d_6) δ: 20.9, 38.2, 64.8, 123.9, 124, 126.1, 127.4, 127.9, 129.1, 131.8, 132, 139.5, 139.9, 164.6, 166.5, 166.6.
Anal. calcd. for $C_{20}H_{18}N_8O_3$: C, 57.42, H,4.30, N,26.79.
Found.C, 57.17, H,4.27, N,26.44.

35: Yield = 80% m.p. = 178°C
^{1}H NMR (DMSO d_6) δ: 6.10 (s, 2H), 6.66–6.70 (m, 1H), 7.08 (d, 1H, J = 10Hz), 7.16–7.18 (m, 1H), 7.47–7.87 (m, 6H), 7.87–7.9 (m, 1H), 7.98 (s, 1H), 10.12 (d, 1H, J = 10Hz).

^{13}C NMR (DMSO d_6) δ: 47.8, 68.3, 111.6, 111.9, 127.60, 128.30, 132, 132.4, 134.6, 139.6, 145.2, 157.6, 166.4, 166.6, 166.8.
$C_{17}H_{14}N_8O_3$ (394): M.S [D.C.I/NH_3 $(M + H)^+ = 395$ and $(M + NH_3)^+ = 412$].

36: Yield = 82% m.p. = 199°C
^1H NMR (DMSO d_6) δ: 6 (s, 2H), 6.1–6.15 (m, 1H), 6.2–6.4 (ma, 1H), 7.07 (d, 1H, J = 8 Hz), 7.18–7.23 (m, 1H), 7.42–7.6 (m, 5H), 7.94–7.98 (m, 1H), 8 (s, 1H), 10 (d, 1H, J = 8 Hz).

^{13}C NMR (DMSO d_6) δ: 47.75, 68.7, 122.5, 127.6, 127.9, 128, 128.1, 128.3, 128.98, 132, 141.14, 160.4, 166.6, 166.8, 168.
$C_{17}H_{14}N_8O_3S$ (410): M.S [D.C.I/NH_3 $(M + H)^+ = 411$ and $(M + NH_4)^+ = 428$].

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