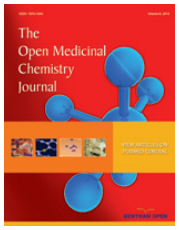

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RESEARCH ARTICLE

Antiviral Activity of Benzotriazole Based Derivatives

Paola Corona[1], Sandra Piras[1,*], Roberta Ibba[1], Federico Riu[1], Gabriele Murineddu[1], Giuseppina Sanna[2], Silvia Madeddu[2], Ilenia Delogu[2], Roberta Loddo[2,*] and Antonio Carta[a]

[1]*Department of Chemistry and Pharmacy, University of Sassari, Via Muroni, 23/A, 07100Sassari, Italy.*
[2]*Department of Biomedical Sciences, Section of Microbiology and Virology, University of Cagliari, Cittadella Universitaria, 09042, Monserrato, Italy.*

Abstract:

Background:

For the last thirty years, the benzotriazole scaffold has been the object of our group interest and we have already presented some results on the antiviral activity of our compounds.

Objective:

In this article, we conclude the exploration of *N-(4-(R-2H-benzo[d][1,2,3]triazol-2-yl)phenyl)-4-R'-benzamides* and 1-(4-*(R-2H-benzo[d][1,2,3]triazol-2-yl)phenyl)-3-R'-ureas* by synthesizing further modified derivatives, in order to have more elements for SARs evaluation.

Method:

Here, we reported the synthesis and the antiviral screening results of 38 newly synthesized benzotriazole derivatives against a panel of DNA and RNA viruses. We also analyse SARs in comparing these compounds with previously published benzotriazole analogues, taking stock of the situation.

Results and Conclusion:

Among the newly presented derivatives, compounds **17** and **18** were the most active with EC_{50} 6.9 and 5.5 µM, respectively against Coxsackievirus B5 (CV-B5) and 20.5 and 17.5 µM against Poliovirus (Sb-1).

Keywords: Benzotriazole, Enteroviruses, CV-B5, Poliovirus, SARs, Antiviral.

Article History	Received: May 28, 2020	Revised: August 12, 2020	Accepted: September 06, 2020

SUPPLEMENTARY TABLE AND FIGURE

Table. SM1. Cytotoxicity and antiviral activity of derivatives 4c-7c, 8a,b,c-15a,b,c, 16c-26c. NM 107 (20-C-methylcytidine), ribavirin, 6-azauridine, ACV (acyclovir), pleconaril, and mycophenolic acid were used as reference inhibitors.

Compounds	MDBK	BVDV	BHK-21	YFV	Reo-1	Vero76	CV-B5	Sb-1	VV	HSV-1	VSV	RSV
	[a]CC_{50}	[b]EC_{50}	[c]CC_{50}	[d]EC_{50}		[c]CC_{50}	[f]EC_{50}					
4c	>100	>100	75	75	75	>100/18	**42.8±3.2**	**19±5.7**	>100	>100	>100	>18
5c	69	69	34	34	34	>100	**41±5.6**	**50±14**	>100	>100	>100	>100
6c	>100	>100	>100	>100	>100	>100/9	**11±5**	**37±5.7**	>100	>100	>100	>9
7c	>100	>100	>100	>100	>100	>100/42	**10.2±1.8**	**3.8±1.7**	>100	>100	>100	>42
8a	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
8b	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
8c	>100	>100	>100	>100	>100	45	>45	>45	>45	>45	>45	>45
9a	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100

Compounds	MDBK	BVDV	BHK-21	YFV	Reo-1	Vero76	CV-B5	Sb-1	VV	HSV-1	VSV	RSV
	[a]CC_{50}	[b]EC_{50}	[c]CC_{50}	[d]EC_{50}		[c]CC_{50}	[f]EC_{50}					
9b	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
9c	>100	>100	>100	>100	>100	>100/27	>100	>100	>100	>100	>100	>27
10a	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
10b	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
10c	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
11a	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
11b	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
11c	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
12a	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
12b	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
12c	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
13a	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
13b	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
13c	>100	>100	>100	>100	>100	66/38	>66	>66	>66	>66	>66	>38
14a	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
14b	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
14c	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
15a	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
15b	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
15c	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
16c	>100	>100	>100	>100	>100	>100	**53±8.5**	>100	>100	>100	>100	>100
17c	>100	>100	>100	>100	>100	>100	**6.9±3.7**	**20.5±8.5**	>100	>100	>100	>100
18c	>100	>100	>100	>100	>100	>100	**5.5±0.8**	**17.5±6.4**	>100	>100	>100	>100
19c	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
20c	>100	>100	>100	>100	>100	87	>87	>87	>87	>87	>87	>87
21c	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
22c	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
23c	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
24c	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
25c	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
26c	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
Ref. compnds												
Ribavirin	>100	54±6.7										
NM 107			>100		6±2.1							
6-azauridine			>100	46±2.5		9.3±1.6						1.1±0.4
ACG						>100				2.4±0.6		
Mycophen. acid						19.3±1.6			1.5±0.3			
Pleconaril						77±6.8	0.005±0.002	2±0.6				

Data represent mean values ± SD for three independent determinations. For values where SD is not shown, variation among duplicate samples was less than 15%. The values in bold character are the most interesting results of this antiviral screening, are highlighted the EC_{50} values that are comparable with the EC_{50} of the reference drugs. [a]Compound concentration (μM) required to reduce the viability of mock-infected MDBK cells by 50%, as determined by the MTT method. [b]Compound concentration (μM) required to achieve 50% protection of MDBK cells from the BVDV-induced cytopathogenicity, as determined by the MTT method. [c]Compound concentration (μM) required to reduce the viability of mock-infected BHK-21 monolayers by 50%, as determined by the MTT method. [d]Compound concentration (μM) required to achieve 50% protection of BHK-21 cells from YFV and Reo-1 induced cytopathogenicity, as determined by the MTT method. [c]Compound concentration (μM) required to reduce the viability of mock-infected Vero76 monolayers by 50%. [f]Compound concentration (μM) required to reduce the plaque number of the indicated virus by 50% in Vero76 monolayers.

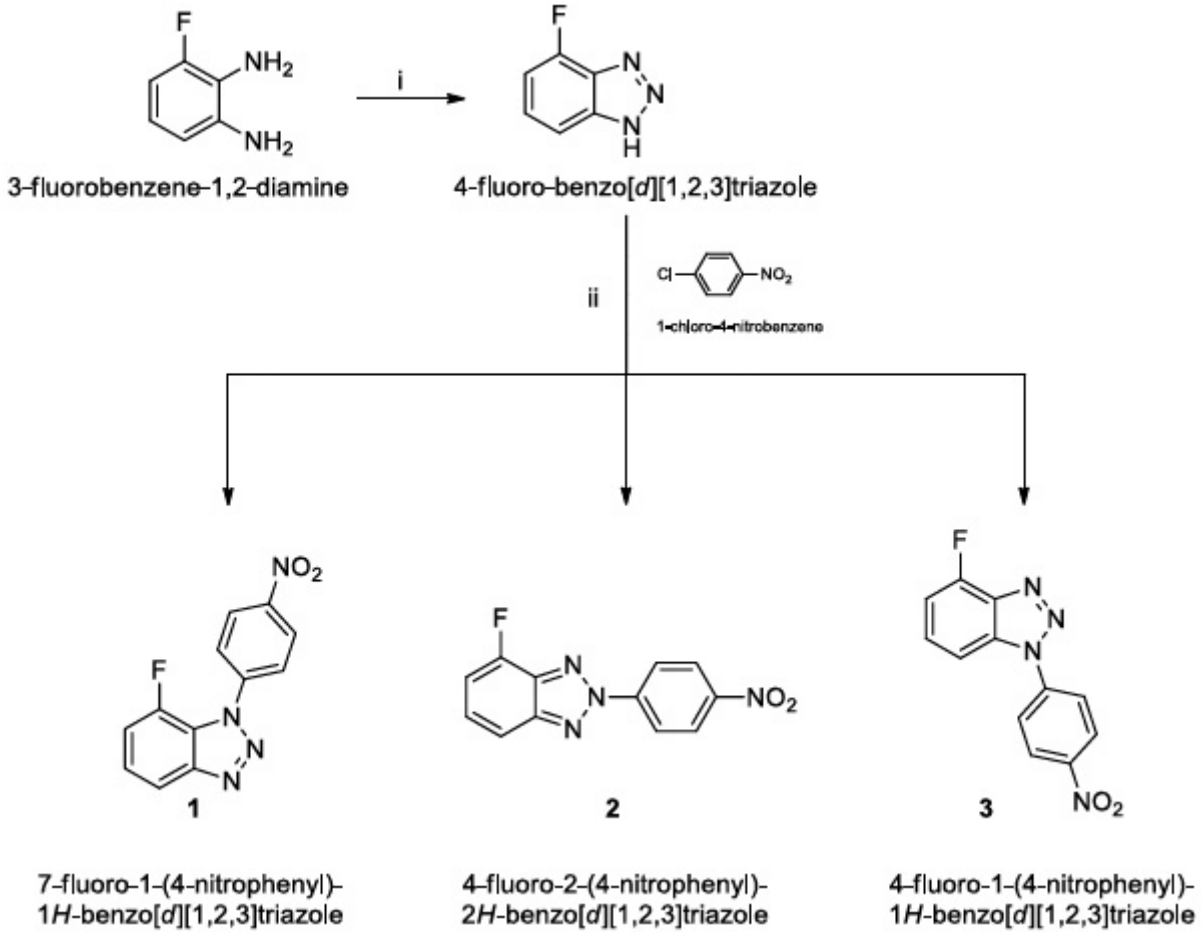

Fig. (1). Synthetic route to obtain the three geometric isomers 1, 2 and 3.

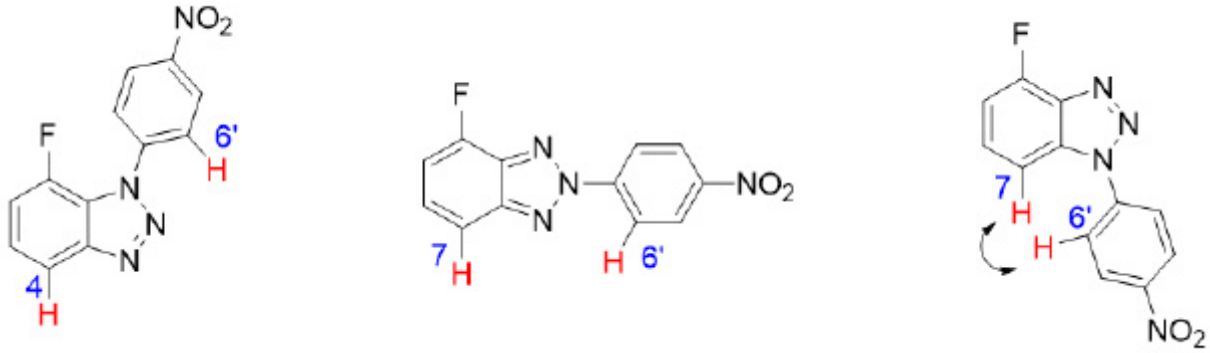

Fig. (2). Structure of derivatives 1, 2 and 3, with protons highlighted to show the protons investigated in the following NOESY spectra.

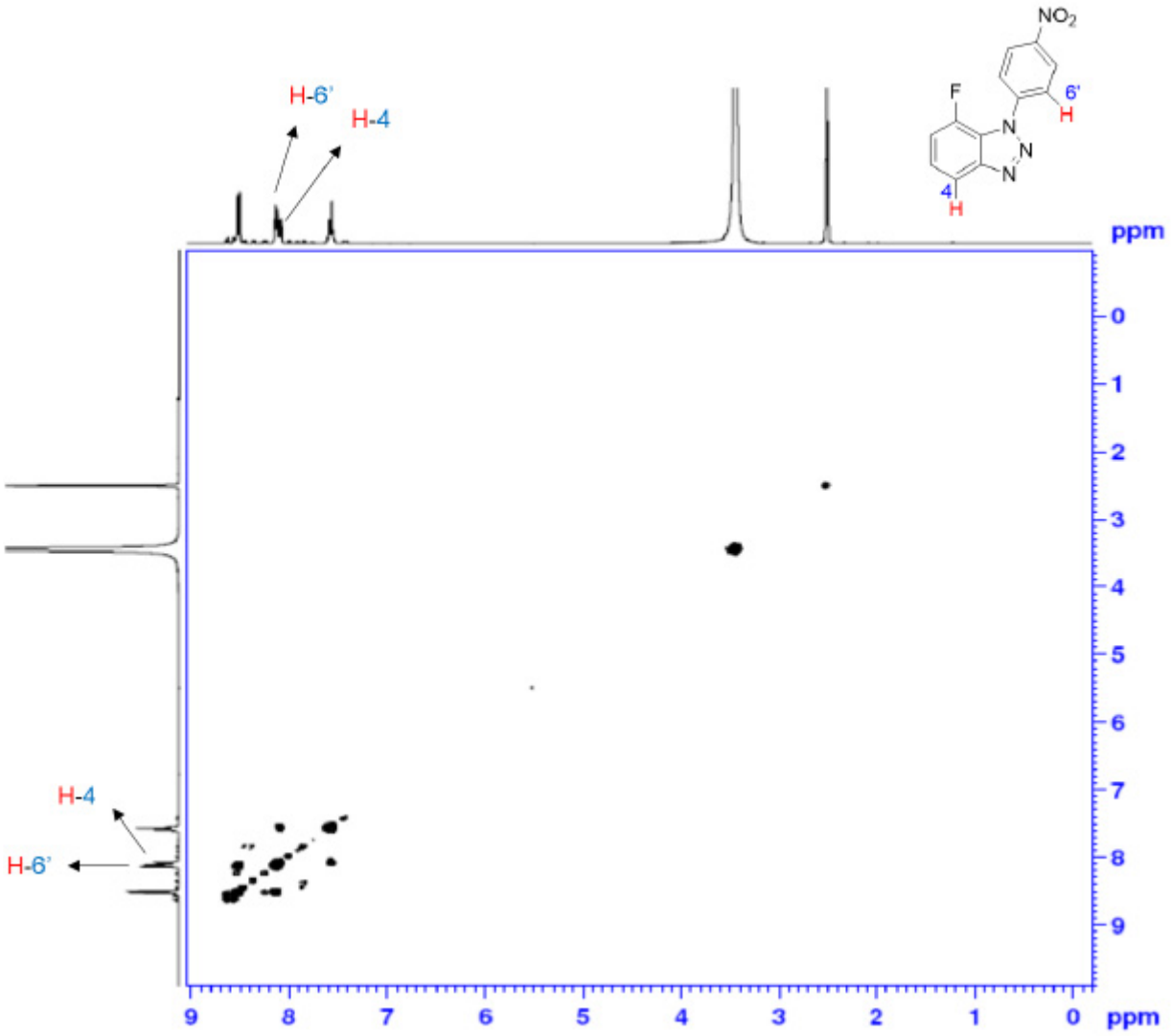

Fig. (3). NOESY spectra from derivative 1.

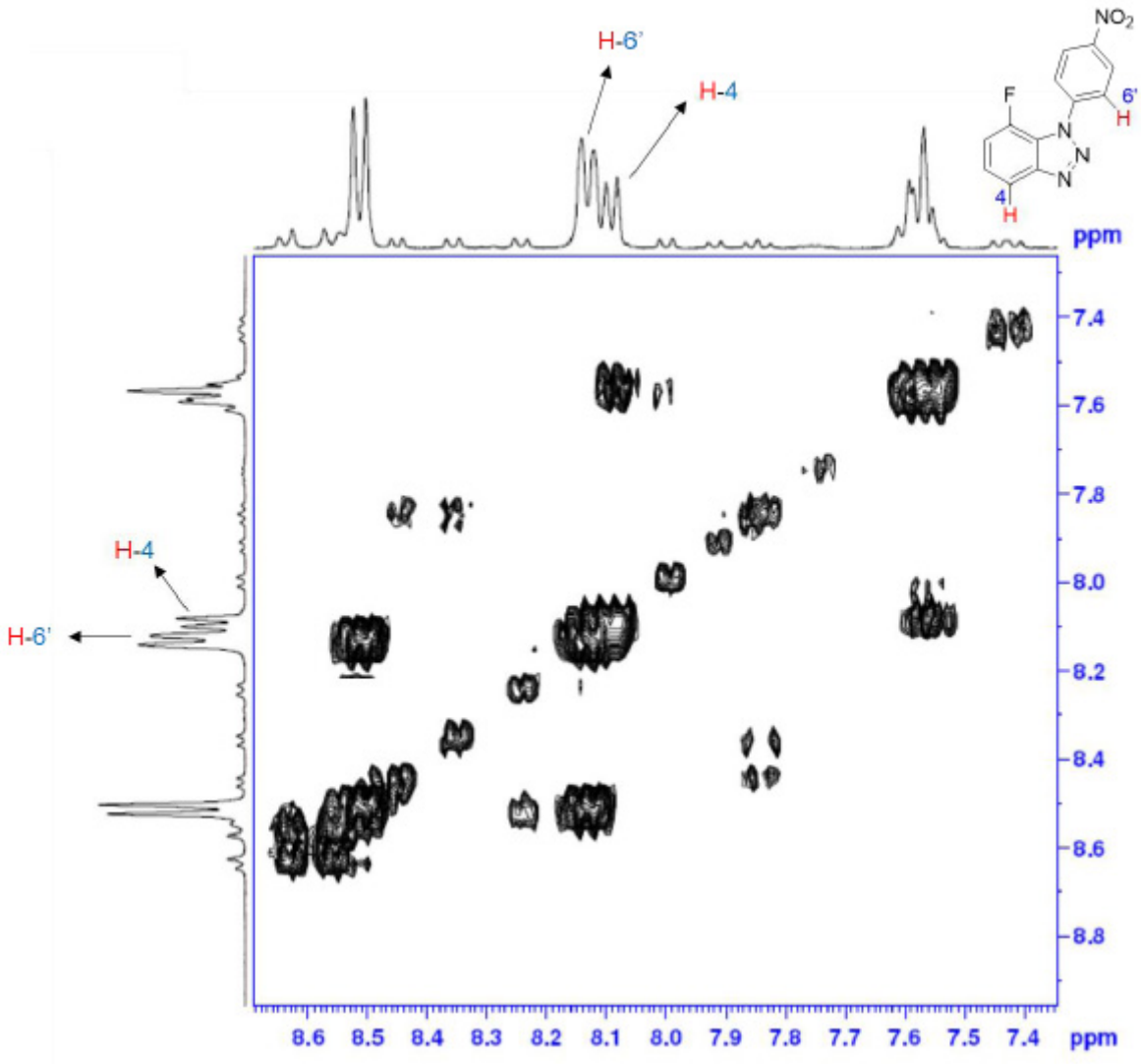

Fig. (4). NOESY spectra (zoomed 7.3-8.7 ppm) from derivative 1, proving no correlation between H-4 and H-6'.

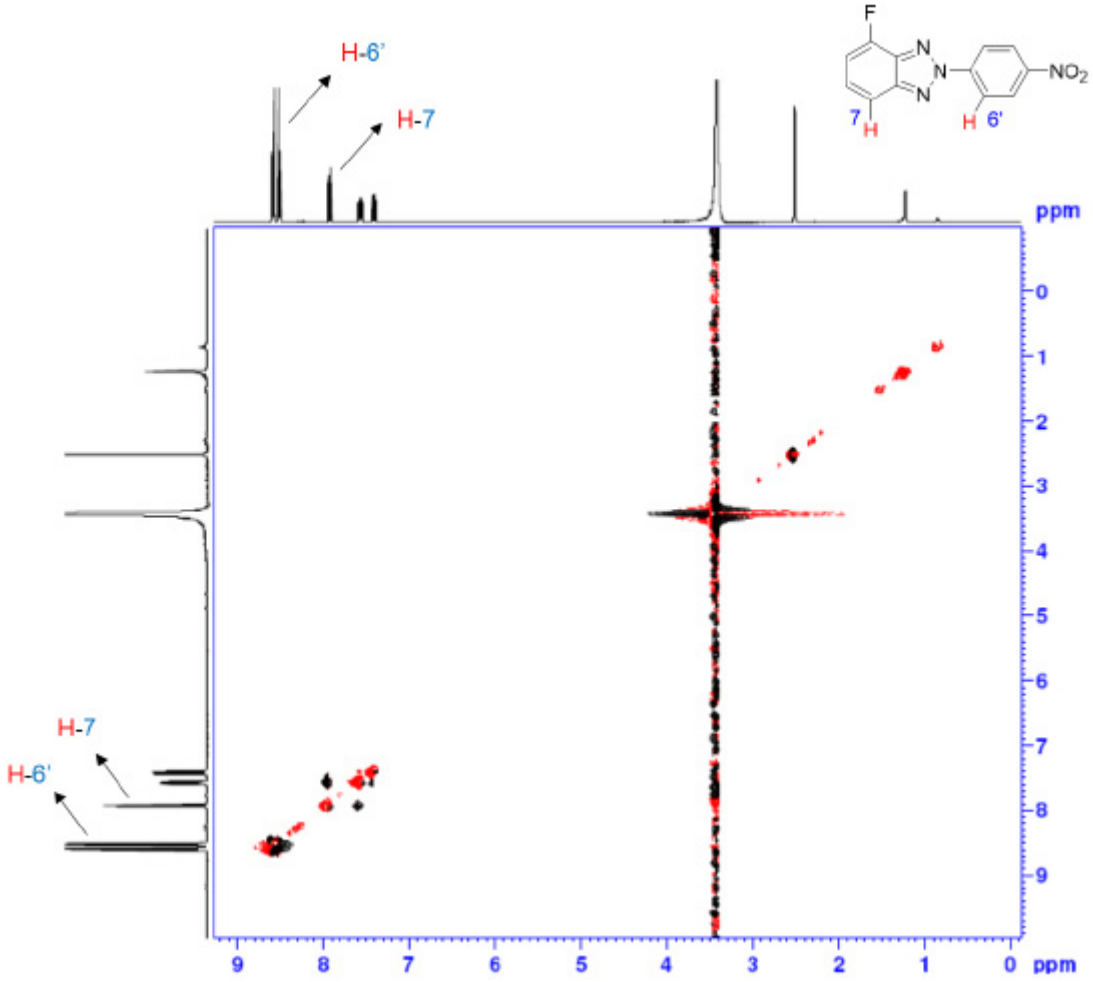

Fig. (5). NOESY spectra from derivative 2, proving no correlation between H-7 and H-6'.

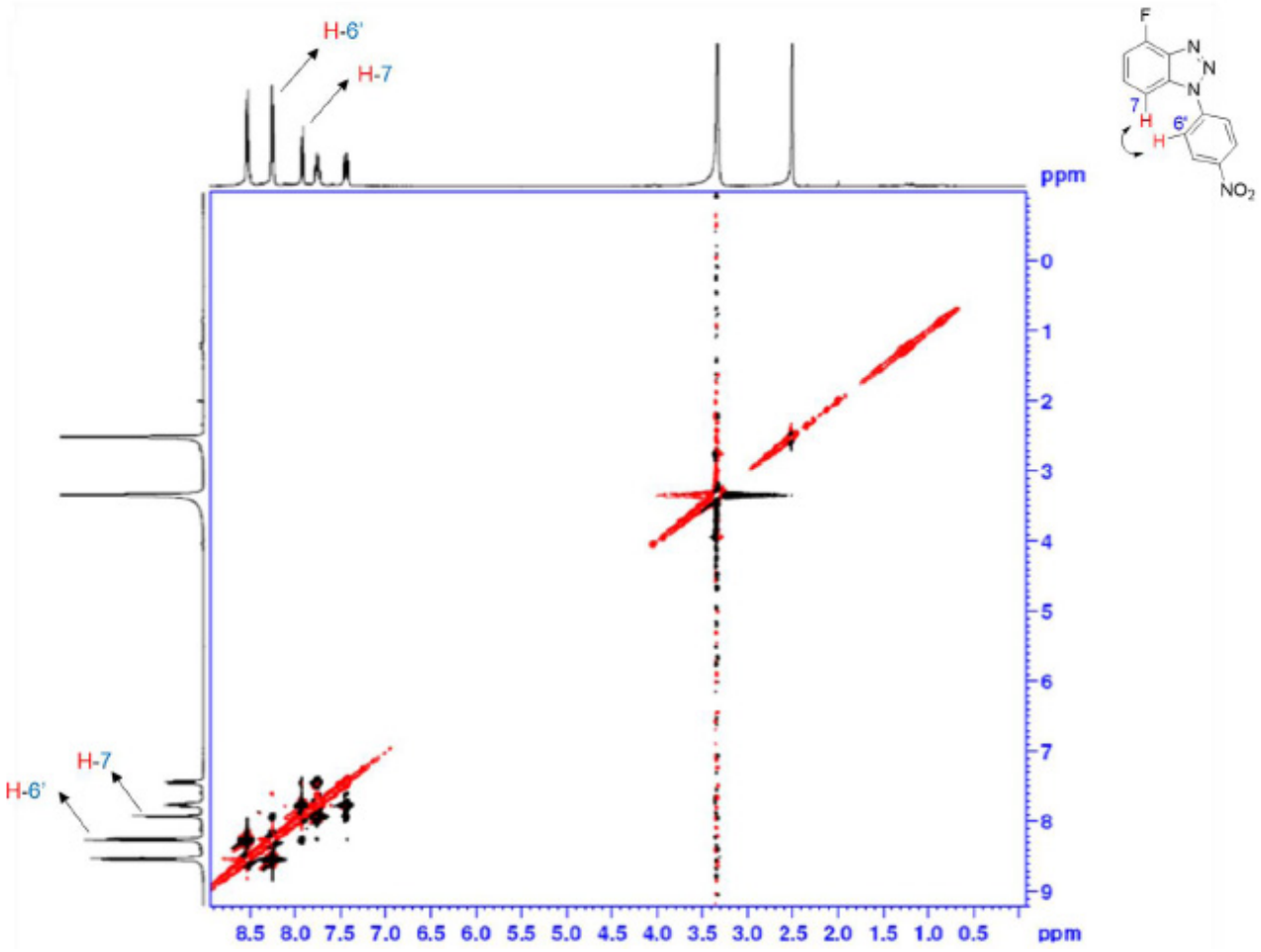

Fig. (6). NOESY spectra from derivative 3.

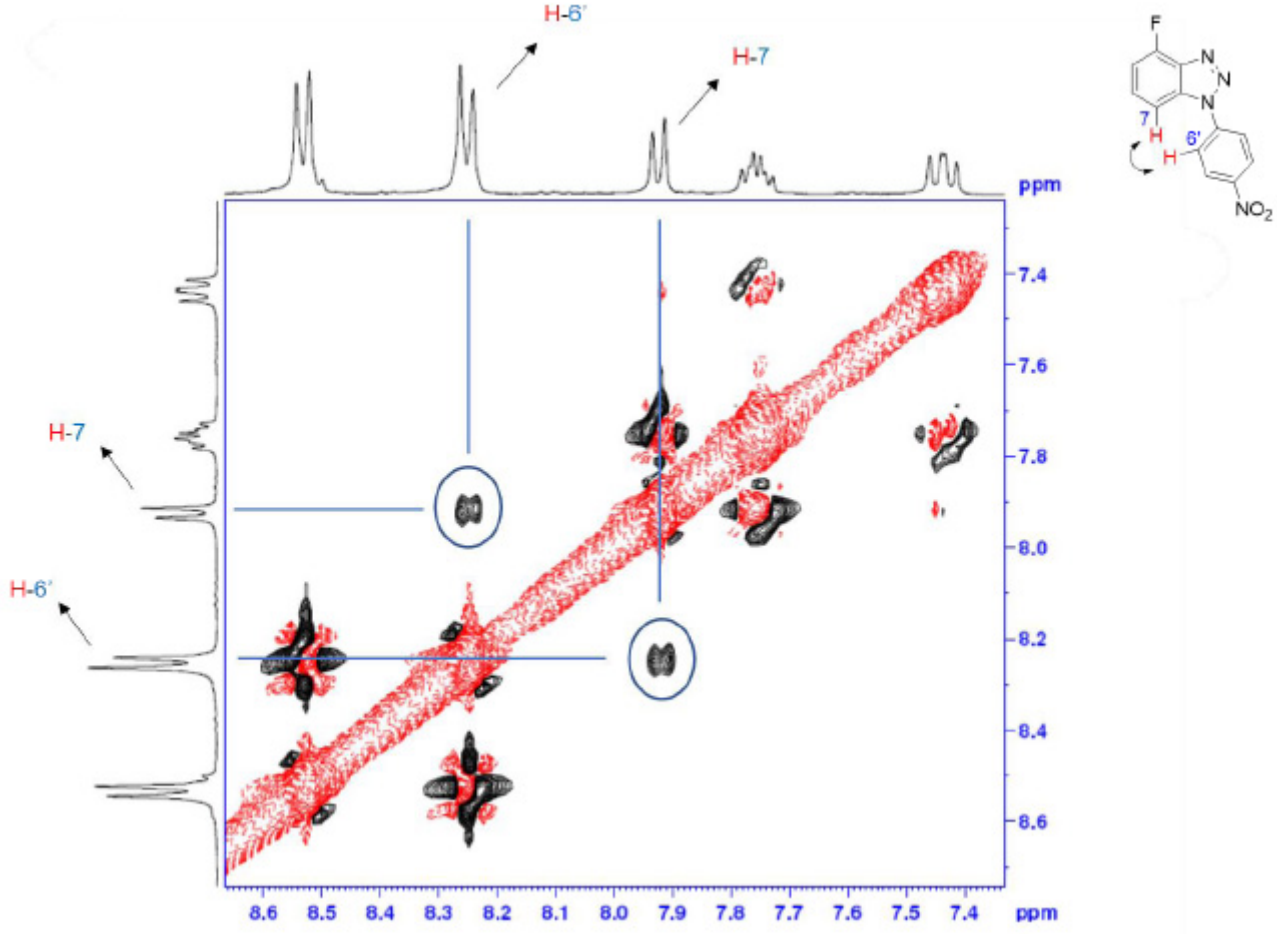

Fig. (7). NOESY spectra (zoomed 7.3-8.7 ppm) from derivative 3, highlighting correlation between H-6' and H-7.

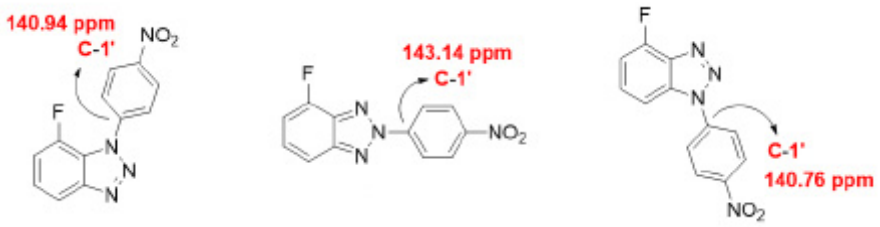

Fig. (8). Structure of derivatives 1, 2 and 3, with C-1' highlighted to show the carbon studied in the following HMBC spectra.

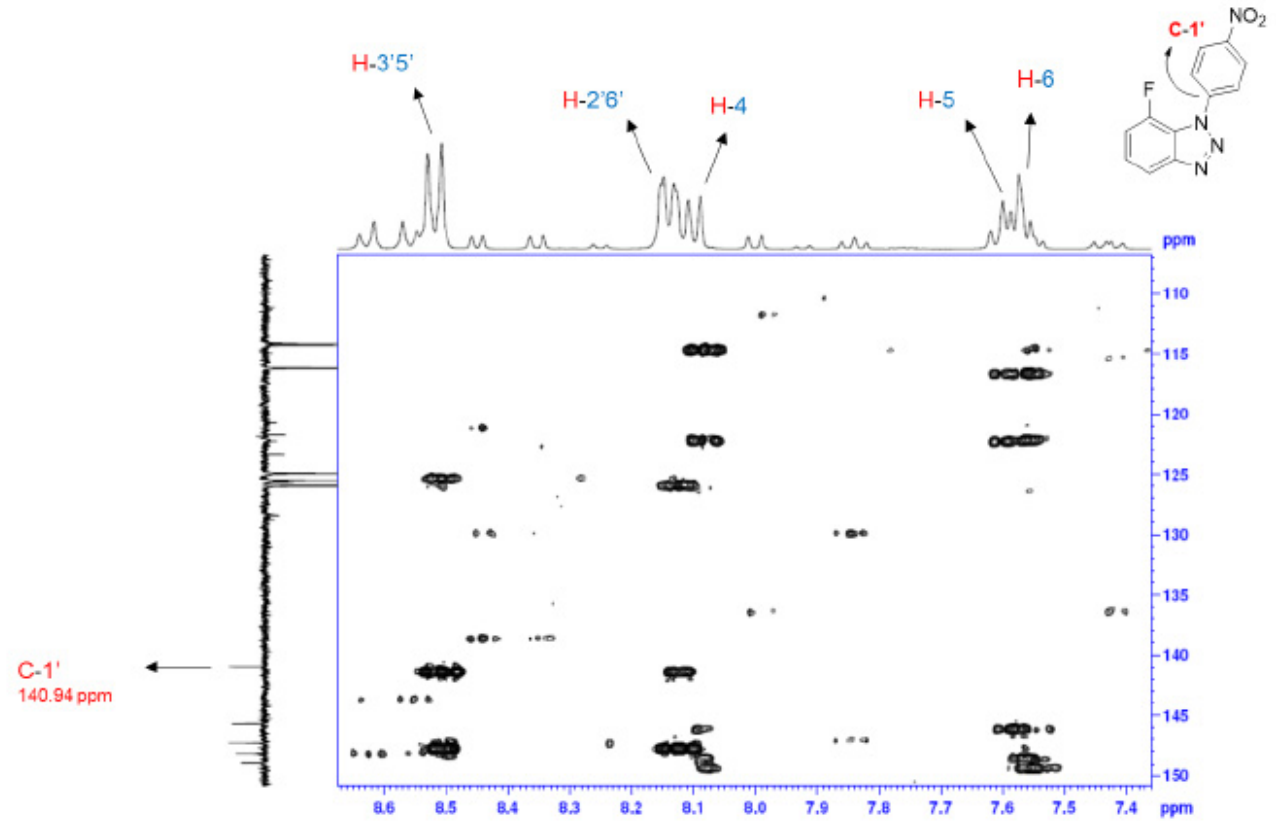

Fig. (9). HMBC spectra from derivative 1.

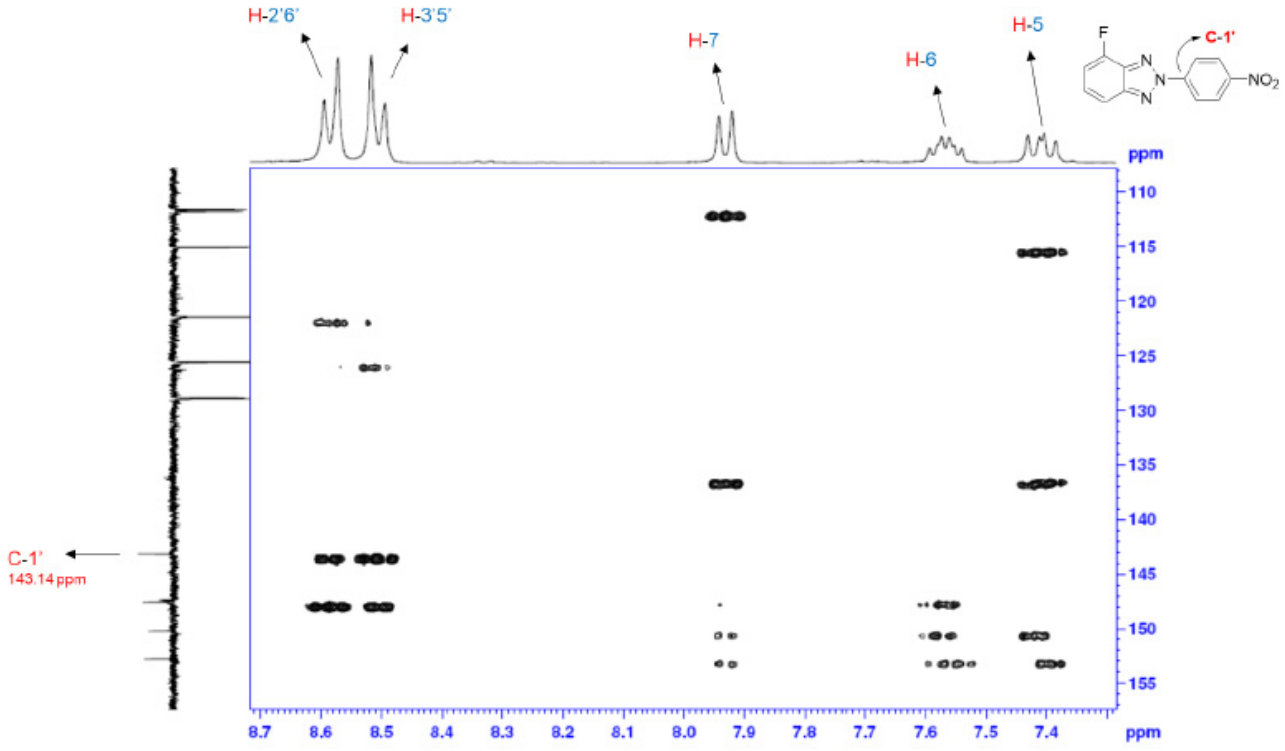

Fig. (10). HMBC spectra from derivative 2.

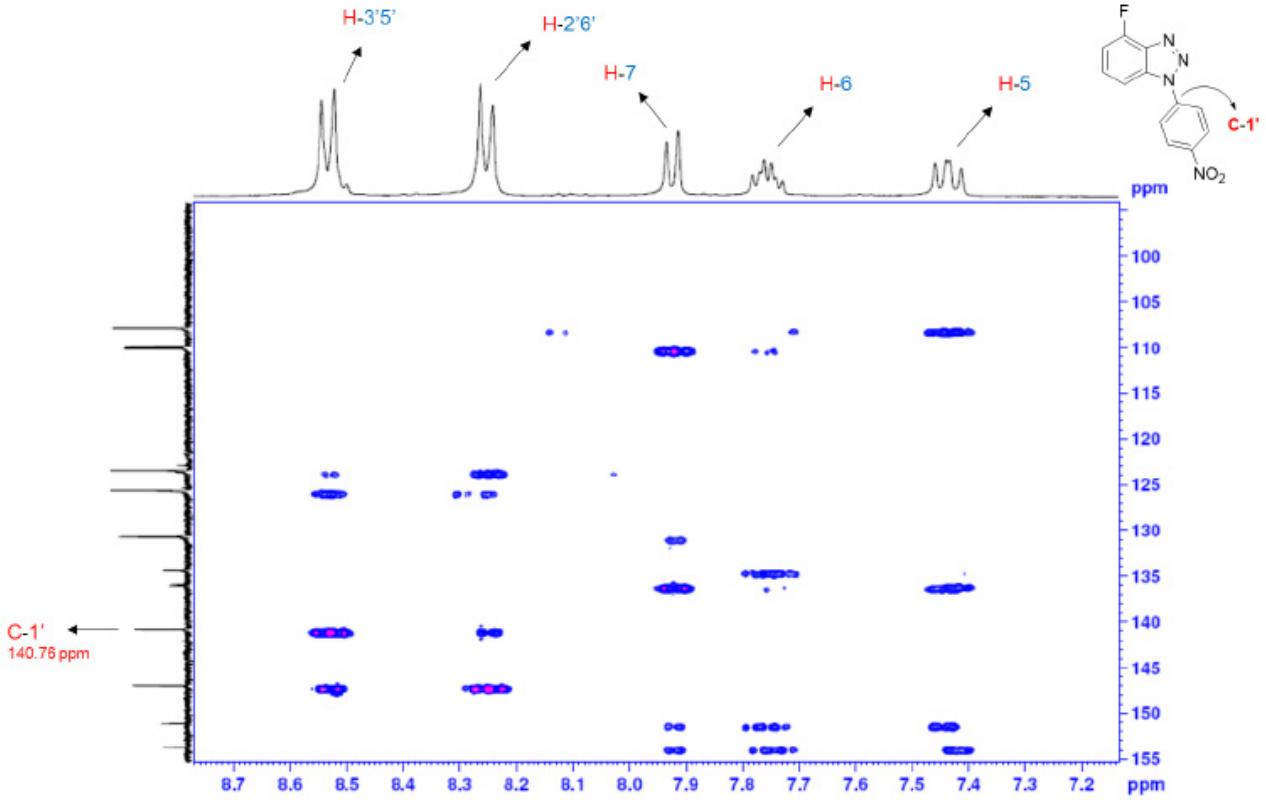

Fig. (11). HMBC spectra from derivative 3.