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Design, synthesis and photoluminescent studies of new 1,5-benzodiazepines derivatives: Towards new ESIPT compounds

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ABSTRACT

A series of novel N_1-triazolo-4-(2-hydroxyphenyl)-1,5-benzodiazepin-2-ones **7a-e** and N_5-triazolo-4-(2-acetoxyphenyl)-1,5-benzodiazepin-2-ones **8a-e** were designed and synthesized in good yields *via* a Cu(I) catalyzed *1,3*-dipolar alkyne-azide coupling reaction (CuAAC) between the N_1- and N_5-propargyl-1,5-benzodiazepines **2** and **5** respectively and various arylazides **6a-e**. Photophysical properties were investigated for all the obtained triazolo-benzodiazepine hybrids by mean of absorption and fluorescence spectral techniques. Thus, a fluorescent emission was detected for the derivatives **7a-e** in aggregated state. On another hand, the *O*-acetylated derivatives **8a-e** were found to be not emissive. Finally, we have chosen a model reaction to demonstrate that upon deprotecting the -OAc group in the N_1, N_5-disubstituted benzodiazepine **8d** a moderate fluorescence reappeared in the obtained product **9d** proving that an ESIPT process can take place as long as the hydroxyl group remains free, allowing the OH/C=O proton transfer to occur. A computational study of compounds **7e** and **9d** in vacuo provide further details and arguments to rationalize the fluorescence of these compounds in aqueous mixtures.

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1. Introduction

Over the past decade, the fluorescence phenomenon has often been highlighted owing to the fact that a great number of researchers made a more frequent use of such spectroscopic technologies [1–4]. Indeed, the molecular fluorescence has proven to be attractive due to its efficiency in various fields of medicinal sciences research as an important diagnostic versatile tool [5–8]. Recently, the appearance of useful and well-designed fluorescent probes has accelerated exhaustively the development of new techniques in life science technology [9–12]. Among these probes, many privileged heterocyclic structures were found to exhibit fluorescence and have been successfully tested for their photoluminescent properties [13]. In this context, different sensing mechanisms such as photo-induced electron transfer (PET) [14], intramolecular charge transfer (ICT) [15], twisted intramolecular charge transfer (TICT) [16], fluorescence resonance energy transfer (FRET) [17], metal-ligand charge transfer (MLCT) [18], electronic energy transfer (EET) [19], and excited-state intramolecular proton transfer (ESIPT) [20] have been given as logical explanations especially when unexpected luminescent behaviors were detected.

As a part of our research program directed on the design and synthesis of molecular hybrids built around the 1,5-benzodiazepine (BZD) scaffold [21–24], H. Mtiraoui et al. [25], have recently explored the photoluminescent properties of some 1,5-benzodiazepin-2-one analogs finding that the synthesized analogs were emissive in the aggregated and solid state. As depicted below, an intramolecular O–H···N hydrogen-bonding within the heterocycle **1** enabled a proton transfer (ESIPT) process and was given by the authors as the main explanation for the photoluminescence occurring (Scheme 1).

Thereby, we have used the already described 4-(2-hydroxyphenyl)- 1,3-dihydro-1,5-benzodiazepin-2-one **1** [26], as a

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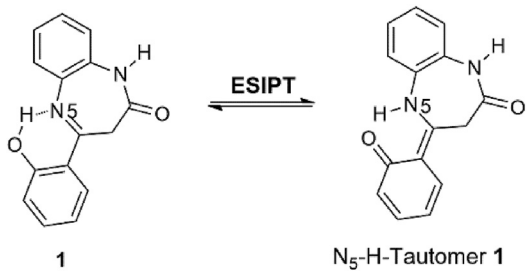


Scheme 1. The ESIPT process for compound **1**.

useful key-intermediate to develop synthetic routes to a series of N_1- or N_5-heteroaryl moieties, in particular triazole moieties, linked to the 1,5-benzodiazepine nucleus with the purpose to further study their photophysical properties. Indeed, triazole moieties linked to some derivatives have been well explored and investigated for their optical properties *via* different sensing mechanisms [27,28]. Thus, the particular purpose was to see to what extent, the structural modifications introduced on the BZD ring and the changing of the solvent's nature might affect the ESIPT process occurrence. The first idea was, then, to confirm what was previously described by H. Mtiraoui et al. [25], namely the systematic occurrence of an ESIPT process in the case of N_1-functionalized BZDs **1** analogs. The second goal was then to further develop the work with a view to study the fluorescence behaviors of the differently substituted synthesized BZD derivatives. Especially in the case of the N_5-functionalized BZD the changes in the fluorescence behaviors in relation to the availability (or not) of a free O—H group have been the subject of interesting studies. We describe herein the obtained results.

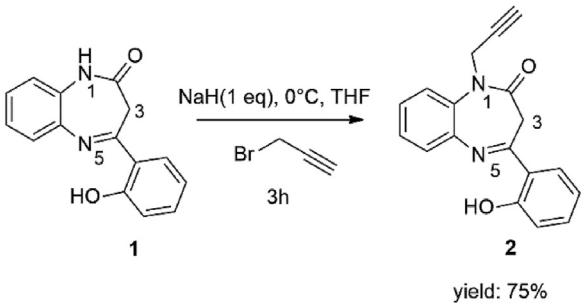
2. Results and discussions

Starting from the 1,5-benzodiazepine-one **1**, we have targeted novel hybrids linking the triazole moiety at different positions of the BZD ring. Consequently, since the well-known alkyne/azide Cu(I) catalyzed 1,3-dipolar cycloaddition reaction seemed then to be the most appropriate methodology for an easy access to such scaffolds [22,23], we first planned to perform regiospecific functionalizations (propargylation) of the amidic nitrogen (N_1) or the iminic one (N_5). To the best of our knowledge, the study of the selective propargylation from either of the two nitrogens in BZD **1** has not yet been described.

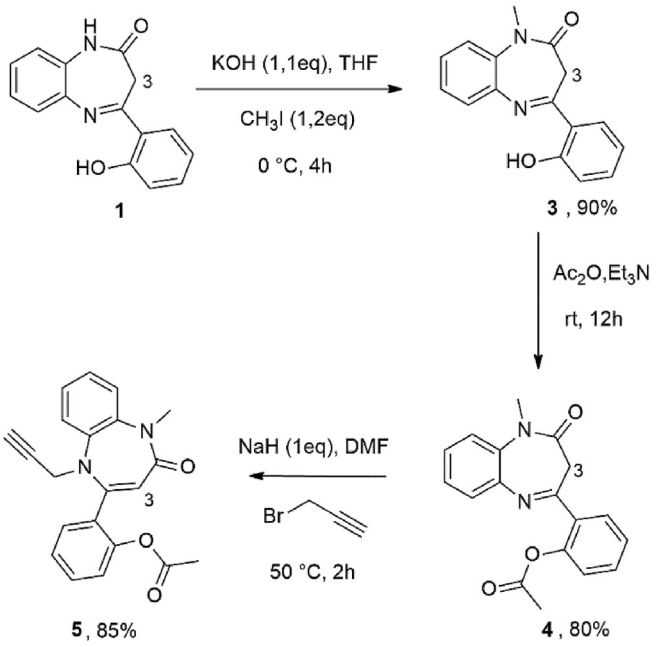
We have first achieved the N_1-propargylation of **1** using mild basic conditions (NaH in THF) [29]. Indeed, the use of such chemical conditions prevented the non-desired N_5-alkylation to take place. Undoubtedly, here the hydroxyl hydrogen is involved in an intramolecular hydrogen-bond with the iminic nitrogen N_5 and thereby dramatically reduces the nucleophilicity of this latter. The reaction, monitored by TLC, showed the formation of a sole product which was identified on the basis of its spectral data as the *N*-prop-2-ynyl- 1,5-benzodiazepin-2-one **2** (Scheme 2).

In the second stage of the work we had to develop an adequate methodology to perform a specific propargylation at the 5-position of BZD **1**. So as described in Scheme 3, a preliminary protective methylation of the amidic nitrogen was necessary. This reaction led quantitatively to the nitrogenated diazepine **3**. Here, the fact that we have not detected any trace of the side *O*-alkylation-product because of the reluctance of the oxygen atom to react can be rationalized in terms of the Hard and Soft Acid and Base principle [29].

The next step was then to deactivate the hydroxyl group in order



Scheme 2. N-alkylation of benzodiazepine **1**.

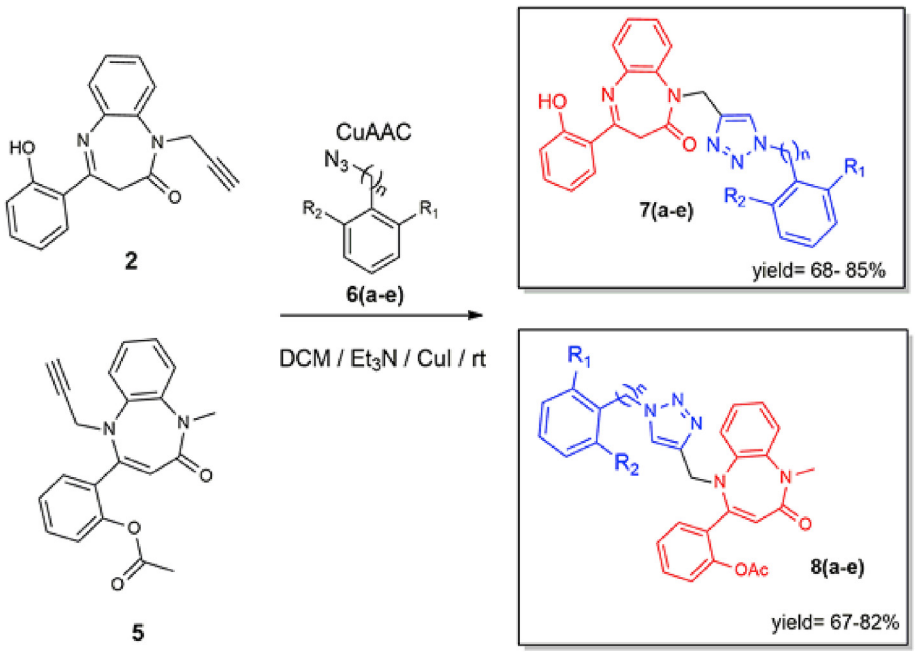


Scheme 3. Synthesis of compound **5**.

to increase the nucleophilicity of the nitrogen N_5. Thus, the *O*-acetylation was then achieved in the presence of an excess of acetic anhydride and trimethylamine allowing the reaction mixture to stir overnight at room temperature. Let's point out here that based on a TLC control, we have noticed that the fluorescence effect observed for compound **3** disappeared in the case of the acetylated analogs **4**. The suppression of the intramolecular O—H···N hydrogen-bond seems obvious since it suggests the impossibility of the establishment of an ESIPT process. In the next step, the deprotonation of the methylene at C_3 led to a mesomeric destabilized anionic form followed by a subsequent nucleophilic substitution of the negatively charged nitrogen N_5 on the propargyl bromide. The crude was purified on a chromatographic column (cyclohexane/ethyl acetate/ 6:4) and compound **5** was recovered in good yield as a pure form (Scheme 3).

Once prepared, both key-intermediates **2** and **5** were reacted following the CuAAC procedure [22,23] (Scheme 4) with a series of arylazides **6(a—e)** (*1,3*-dipoles) prepared according to the procedure described by Kamalraj et al. [30]. (Table 1). The % yield of each triazole product in Scheme 4 is depicted in Table 2.

At this stage of the work we were prompted to record the absorption and emission spectra for all prepared cycloadducts **7** and **8**. Our study was then firstly focused on the emission behavior of the N_1-triazolo-1,5-benzodiazepin-2-ones **7** in the aggregated



Scheme 4. Synthesis of compounds **7a-e** and **8a-e**.

Table 1
One-pot synthesis of azides **6a** and **6(b–e)**.

Entry	n	R_1	R_2
6a	1	H	H
6b	0	H	CH_3
6c	0	CH_3	CH_3
6d	0	H	OCH_3
6e	0	H	Cl

Table 2
One-pot synthesis of 1,4-disubstituted 1,2,3-triazole **7**–**8**.

Entry	n	R_1	R_2	Yield (%)
7a	1	H	H	69
7b	0	H	CH_3	71
7c	0	CH_3	CH_3	82
7d	0	H	OCH_3	65
7e	0	H	Cl	83
8a	1	H	H	73
8b	0	H	CH_3	70
8c	0	CH_3	CH_3	64
8d	0	H	OCH_3	85
8e	0	H	Cl	78

Table 3
Photophysical data for compounds **7(a–e)** and **8(a–e)** in THF/H_2O mixture.

Entry	λabs (nm)	λem (nm)	Stokes Shift (nm)	Φ_F
7a	262	381	119	0,14[d]
7b	261	380	119	0,16[d]
7c	260	381	121	0,14[d]
7d	238	381	143	0,21[d]
7e	236	380	144	0,43[d]
8a	229	a	b	c
8b	236	a	b	c
8c	249	a	b	c
8d	238	a	b	c
8e	243	a	b	c

[a] not applicable.
[b] not determined.
[c] not fluorescent.
[d] Measurement determined at 25 °C by a relative method using quinine sulfate as standard ($\Phi_F = 0.52$ in 0.05 M H_2SO_4) [31].

state. It then turned out that all the derivatives are emissive and tend to exhibit an encouraging quantum yield ranging from 0.14 to 0.43 with a large stokes shift around 140 nm registered in water with 1% (v/v) of tetrahydrofuran (Table 3). Let us notice that under such conditions we have reach the highest intensity for the fluorescence emission. Indeed, H. Mtiraoui et al., have reported the fluorescence absorption and emission data for compound **1**, recorded in the solid state (quantum yield = 0.26 and stokes shift around 175 nm) and in different THF-water solution percentages. It has been determined that when using high water percentages, the emission of compound **1** would increase [25]. Same process for compounds **7(a–e)**, in an aqueous medium containing 1% (v/v) of THF, we have obtained the highest emission intensities. This is undoubtedly due to the formation of insoluble aggregates making them more emissive. Consequently, the luminescence here would therefore be related to an ESIPT mechanism initiated a strong internal hydrogen bond interaction N—HO in the aggregated state as driving force. Moreover, the rigidity of the conformations adopted by structures **7** presumably favored the formation of a radiative 6-membered ring H-bonding system responsible for the ESIPT effect.

As summarized in Table 2, in a THF/H_2O mixture, compounds **7a-e** were all emissive however displaying different bands' intensities that appear approximatively at the same λ_{em} (Fig. 1). Thus, while derivatives **7e** and **7d** were found to have the highest quantum yields: 0.43 and 0.21 respectively, compounds **7a**, **7b** and **7c** were less emissive exhibiting nearly the same quantum yields values. It is then thinkable that these yields variation are closely related to the electro-donating or electro-attracting nature effects of the R_1 and R_2 alkyl groups.

Contrary to the above described results, no fluorescence phenomena were detected for the *N_5*-triazolo-1,5-benzodiazepin-2-ones series **8a-e** neither in the aggregated state nor in solution. As anticipated above, the *O*-protective acetylation prevented here the establishment of hydrogen bonding to occur and consequently

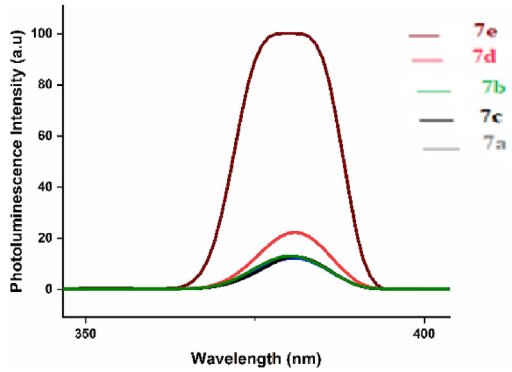


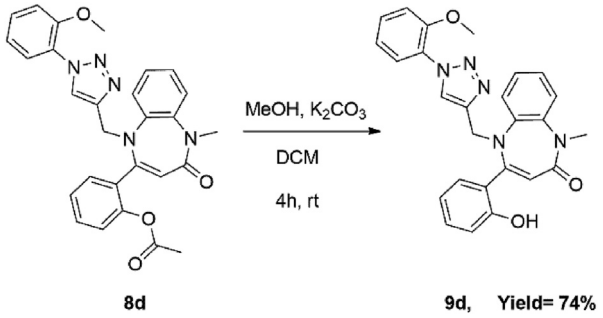
Fig. 1. Emission spectra of **7(a–e)** (c = 3x10E-5 mol/L) 1% (v/v) THF/H_2O at 25 °C upon an excitation from 236 to 262 nm.

avoided the ESIPT process. Consequently, we were prompted to realize the deacetylation reaction of compounds **8** with the aim to investigate the role of the hydroxyl group in the photoluminescent behavior of the molecule (Scheme 5).

The fluorescence spectra were recorded in anhydrous dichloromethane (DCM), EtOH and THF/H_2O mixtures. So while no emission was detected in DCM and EtOH, compound **9d** was fluorescent in the 1% (v/v) THF-water mixture, however the quantum yield was lower compared to analogs **7a-e**.

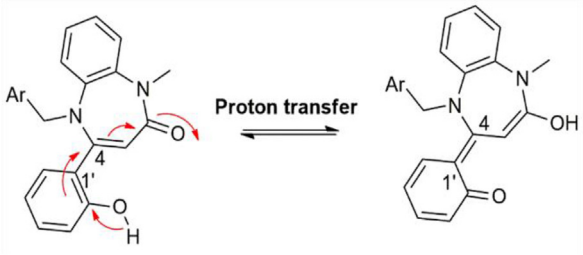
In a THF/H_2O mixture, the fluorescence reappeared nevertheless with a relative decrease of intensity compared to that observed for derivatives **7(a–e)**. It is thinkable that the steric hindrance caused by the presence of the triazolyl moiety at N_5 is at the origin of the fluorescence phenomenon. Indeed, the C_4–$C_{1'}$ rotation while being prevented places the hydroxyl group close to the carbonyl one. In this conformation, the hydrogen of the hydroxyl group (donor) and the oxygen of the carbonyl group (acceptor) were able to interact following an intramolecular reversible proton-transfer causing a sudden change in the luminescence behavior and a loss of the mesomeric π-electron-delocalization within the phenyl ring. (Scheme 6).

A computational study on compounds **7e** and **9d** in vacuo has been conducted in order to rationalize the observed fluorescence in **9d** The proton transfer between the two forms involved in ESIPT mechanisms as described in Schemes 1 (for **7e**) and 6 (for **9d**) have been explored by total energy optimization to find possible stationary molecular structures. For **7e**, a single minimum energy structure M1 has been found and characterized and a short H-bond between the Ph-O-H and proximal N atom of imino group stabilizes a planar conformation of this part of the molecule, as expected. A simple geometry scan to mimic the proximal proton transfer O–H···N< ↔ O- … H–N+< by reducing the N···H distance from



8d **9d, Yield= 74%**

Scheme 5. Deacetylation reaction of compound **8d**.



Scheme 6. The ESIPT mechanism for compound **9d** (less fluorescent than analogs **7(a–e)**).

M1 to 1.01 Å shows that this process requires less than 3–4 kcal·mol-1 suggesting that this transfer is thermally accessible, as required for the ESIPT mechanism. In the case of compound **9d** we have characterized two different minimum energy conformers M1 and M2, connected by a transition state TS to represent the Ph-O-H…O=C< proton transfer depicted in Scheme 6. A detailed inspection of the structure of M1 suggests that distal Ph-O-CH_3 ether group rests close to the region where the proton transfer should occur and can stabilize assist the proton transfer process by H-bonding, as described in Fig. 2. Detail of the optimized structure of M1 structure of **9d** is shown in Fig. 2 where the distances between the three oxygen atoms and the proton transferred are shown.

This intramolecular proton transfer from M1 to M2 in vacuo has an energy barrier of 24 kcal·mol-1 (TS) to reach the minimum energy conformer M2, which is 22 kcal·mol-1 less stable than M1. This energy profile is too high to be thermally accessible but can be strongly reduced by the assistance of a water molecule which provide a Grotthuss-like proton transfer mechanism as

Ph-O-H…OH–H···O=C< ↔ Ph-O- … H–OH···H–O + -C≤

Both the distances and the angles of this intermediate structure are plausible and provide a mechanism to stabilize the excited state required in the ESIPT process and explains the fluorescence response of compound **9d** described in Table 4. From this model it is expected that the presence of water in the solvent is required to be activate the fluorescence, as observed. Also, the longer path justifies the lower emission quantum yield compared to **7e**.

The larger distance for the proton transfer in **9d** explains the absence of fluorescence in anhydrous media and the lower quantum yield observed for this compound in THF/H_2O mixtures

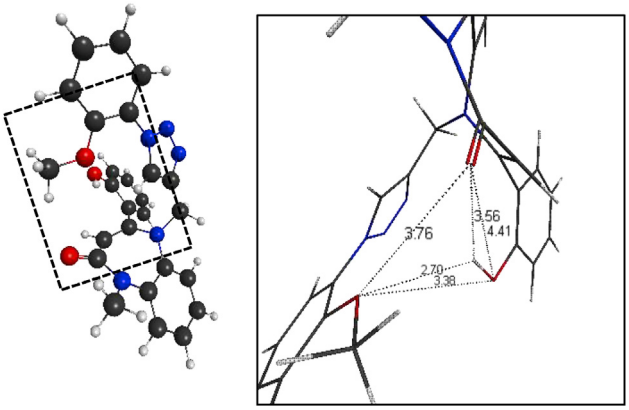


Fig. 2. Detail of the M1 minimum energy optimized structure of **9d** around the groups involved in the proton transfer proton transfer.

Table 4
Photophysical data for compound **9d**.

Entry	Compd	Solvent	λabs (nm)	λem (nm)	Stokes (nm)	ΦF
1	**9d**	THF/H_2O	235	381	146	0,11
		DCM	238	a	b	c
		EtOH	238	a	b	c

[a] not applicable.
[b] not determined.
[c] not fluorescent.

compared to **7e**. Another mechanism that can be invoked to interpret fluorescence disappearance in anhydrous DCM and EtOH can be rationalized in terms of the formation of hydrogen-bonded dimers (excimers) with an excited-state double proton transfer (ESDPT) process [32] that break conjugation of the phenyl ring. However, this mechanism seems to be effective for fluorescence quenching only at high concentration of the compounds, which is not the present case.

3. Conclusion

In conclusion, in this work, we have described two efficient regiospecific synthetic routes towards N_1 and N_5-triazolo-1,5-benzodiazepin-2-ones **7** and **8** using a Cu(I) catalyzed procedure as the key synthetic step. Compounds **7** and **8** were evaluated for their photophysical properties giving a set of interesting information that could potentially make them very interesting probes for technological applications. The observations resulting from our studies of the fluorescence behavior of the N-triazolo-1,5-benzodiazepin-2-ones scaffold bearing a 2-hydroxyphenyl group at 4-position led us to state that the fact of keeping free the hydroxyl group is indispensable for the photoluminescent emission (in which the hypothesized mechanism is ESIPT) occurrence in THF/H_2O mixtures and its absence in anhydrous EtOH and DCM solution. On another hand, we have demonstrated that even when both N1 and N5 are functionalized and as long as the hydroxyl group remains free, the ESIPT process will take place as a result of the OH/C═O proton transfer. Results from a computational study of compounds **7e** and **9d** in vacuo provide further details and arguments to reinforce this conclusion.

4. Experimental section

Chemical reagents and solvents were purchased from commercial suppliers (Merck, Aldrich, and Fluka) and were used as received without further purification. All reactions involving air and moisture sensitive reagents were per-formed under Argon using syringe septum cap technique. All the melting points were determined in open glass capillaries and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded in DMSO [d_6] or $CDCl_3$ on 'Brucker Avance 300 MHz' spectrophotometer with TMS as internal stand-ard in which chemical shifts are expressed in δ ppm coupling constants (J) are reported in Hertz (Hz). High-resolution mass spectra (HRMS) were obtained using an orthogonal acceleration time-of-flight (oa-TOF) mass spec-trometer equipped with an electrospray source and in the positive and negative modes ($ESI^+/^-$). The reactions were monitored by thin-layer chromatography (TLC) on silica gel G plates in the solvent system cyclohexane/ethyl acetate mixture (6:4) and the spots were visualized with UV light. UV−visible spectra were obtained using a UV-3100PC Spectrophotometer. Fluorescence spectroscopic studies were determined with an instrument Spectrofluorimeter flx-Xenius, with an excitation and emission band widths of 10 nm. Fluorescence quantum yields in THF/H_2O were measured at 25 °C by a relative method according to the literature using quinine sulfate (Φ_F = 52% in 0.05 M H_2SO_4) as a standard [31]. The following equation was used to determine the relative fluorescence quantum yield in solution:

$$\Phi F(x) = (A_S/A_X)(F_X/F_S)(n_X/n_S)^2\ \Phi F(s)$$

where A is the absorbance (in the range of 0.01−0.1 A.U.), F is the area under the emission curve, n is the refractive index of the solvents (at 25 °C) used in measurements, and the subscripts s and x represent standard and unknown, respectively.

4.1. General procedure for the synthesis of BZDs *1*–*5*

4-(2-hydroxyphenyl)-3H-1,5-benzodiazepin-2-one (**1**) was prepared according to the literature [26].

4.1.1. Preparation of 1-prop-2-ynyl-4-(2-hydroxyphenyl)-3H-1,5-benzodiazepin-2-one (*2*)

1g of benzodiazepinone **1** (4 mmol) and NaH (1 eq) in 40 mL of THF were stirred for 15 min. Then 1.2 eq of propargyl bromide were added and the mixture was stirred under reflux at 80 °C for 3 h. After filtration, the mixture was purified by chromatography on a silica column using cyclohexane-ethyl acetate 60:40 as eluent. Expected compounds **2** was obtained in 75% yield. Mp = 143−145 °C. ^{1}H NMR (300 MHz, DMSO [d_6]) δ ppm: 3.14 (d, J = 15Hz, 1H), 3.24 (t, J = 3Hz, 1H), 3.36 (d, J = 15Hz, 1H), 4.64−4.67 (dd, J = 6Hz, 3Hz, 2H), 6.98−7.05 (m, 2H), 7.36−7.51 (m, 4H), 7.74−7.77 (m, 1H), 7.94−7.97 (dd, J = 9Hz, J = 3Hz, 1H), 13.86 (s, 1H); ^{13}C NMR (75 MHz, DMSO [d_6]) δ ppm: 36.4, 37.8, 74.8, 79.5, 117.6, 117.8, 119, 122.2, 125.9, 126.8, 127.3, 130, 133.9, 134.2, 138.2, 161.3, 164.6, 164.8.

4.1.2. Preparation of 4-(2-hydroxyphenyl)-1-methyl-1H ben-zo[b][1,4]diazepin-2(3H)-one (*3*)

To a solution of compound **1** (1.01 g, 4 mmol) in THF (50 mL), was added KOH (0.295 g, 1.1 eq) at 0 °C. The mixture was stirred for 15 min before the addition of methyl iodide (8 mmol, 1.2 eq). The mixture was allowed to stir for 4 h at 0 °C before filtration through celite. The solvent was then evaporated off under reduced pressure and the crude material was purified by column chromatography (cyclohexane/ethylacetate 60:40). Compound **3** was obtained with 90% yield. Mp = 172−174 °C. ^{1}H NMR (300 MHz, DMSO [d_6]) δ ppm: 3.05 (d, J = 12Hz, 1H) 3.32 (s, 3H), 4.30 (d, J = 15 Hz, 2H) 7.33−7.49 (m, 4H) 7.56−7.59 (dd, J = 8.4 Hz, J = 1.5 Hz 1H); ^{13}C NMR (75 MHz, DMSO [d_6]) δ ppm: 34.8, 37.9, 117.6, 117.8, 118.6, 119, 122.5, 125.3, 126.6, 127.2, 129.9, 134.0, 135.7, 137.7, 161.3, 164.8, 165.3.

4.1.3. Preparation of 2-(1-methyl-2-oxo-2,3-dihydro-1H-benzodiazepin-4-yl) phenyl acetate (*4*)

To a solution of compound **3** (2g, 8 mmol) in 30 mL of acetic anhydride was added (1 mL, 1.1 eq) of Et_3N. The mixture was allowed to stir for 12 h at room temperature. After removing the solvent under reduced pressure, the crude material was poured into distilled water and extracted with dichloromethane. The organic layers were combined and dried over anhydrous $MgSO_4$, then filtered and the filtrate concentrated at reduced pressure. The crude material was purified by column chromatography on silica gel (cyclohexane/ethyl acetate) 60:40 Compound **4** was obtained in 80% yield. Mp = 168−170 °C. ^{1}H NMR (300 MHz, DMSO [d_6]) δ ppm: 2.83 (s, 3H), 3.10 (s, 1H), 3.44 (s, 3H), 3.96 (s, 1H), 7.16−7.19 (m, 6H), 7.92 (d, J = 6Hz, 1H); ^{13}C NMR (75 MHz, DMSO [d_6]) δ ppm = 20.4, 34.4, 41.4, 120.9, 122.7, 124.3, 125.3, 125.7, 125.7, 126.5, 129.9, 130.4, 130.9, 134.3, 140.3, 147.9, 159.9, 165.9, 168.5.

*4.1.4. Preparation of 2-(5-methyl-4-oxo-1-(prop-2-yn-1-yl)-4,5k-dihydro-1H-benzodiazepin-2-yl) phenyl acetate (**5**)*

To a solution of compound **4** (1g, 3 mmol) in DMF (10 mL), sodium hydride NaH (1 eq, 3 mmol, 120 mg) was added. After 15 min, propargyl bromide was added (1.1 eq, 350 mL). The mixture was stirred at 50 °C for 3 h then filtered through celite before removing the solvent under reduced pressure. The crude material was purified by flash column chromatography on silica gel (cyclo-hexane/ethyl acetate from 100:0 to 70:30). Compound **5** was obtained in 85% yield, Mp = 173–179 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ: 1.93 (s, 3H), 2.54 (t, J = 3Hz, 1H), 3.51 (s, 3H), 4.78 (s, 2H), 6.37 (s, 1H), 7.06–7.64 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$): δ: 166.6, 166, 155.3, 139.9, 138.1, 131.1, 130.1, 129.1, 128.4, 128.4, 128.3, 126.4, 125.3, 125.2, 122.1, 121.9, 120.9, 113.2, 56, 35.9, 30.9, 22.6. HRMS (ESI^+): $C_{21}H_{18}N_2O_3$; Calculated for $[M+H]^+$ = 347.1396, obtained for $[M+H]^+$ = 347.1390.

*4.2. General procedure for the synthesis of 1,3-dipoles (**6a-e**)*

The arylamine (0.072 mol) was dissolved in a solution of hydrochloric acid-water (1 M) (52 mL) while maintaining stirring. The temperature of the reaction should be maintained between 0 and 5 °C. (Solution 1). Sodium nitrite $NaNO_2$ (0.072 mol) was dissolved in ice-cold water (25.65 g) then poured in small portions into the solution 1. On the other hand, NaN_3 (0.072 mol) was dissolved in water (56.7 mL) and added to the reaction mixture and stirred for 2 h. The precipitate obtained was dissolved with di-chloromethane. The organic layer was washed with water and then dried over anhydrous sodium sulfate. Finally, the dichloromethane was removed under reduced pressure. Five different 1,3-dipoles were obtained with good yields (79–85%). The preparation of these azides was based on the literature [28].

*4.3. General procedure for the synthesis of BZDs (**7a-e**), (**8a-e**) and (**9d**)*

In a 50 mL flask, dipolarophile **2** (0.300 g, 1 mmol) was introduced into 20 mL of dichloromethane and the mixture was stirred at room temperature for 5 min. One equivalent of azide **6a-e**, triethylamine (2 mL) and 5 mol% Cu (I) copper iodide were added. The reaction mixture was stirred at room temperature for 8 h. Then the solvent was evaporated off under reduced pressure and the crude formed compound was purified by chromatography on silica gel using cyclohexane/ethyl acetate (60:40) as eluent.

*4.3.1. 1-((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)-4-(2-hydroxyphenyl)- 1H-benzodiazepin-2(3H)-one (**7a**)*

Yield 71%, Mp = 186–191 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ ppm: 3.05 (d, J = 12 Hz, 1H) 4.26 (d, J = 12 Hz, 1H), 4.89 (d, J = 15 Hz, 1H), 5.15 (d, J = 15 Hz, 1H), 5.48 (d, J = 12 Hz, 1H) 5.50 (d, J = 12 Hz, 1H), 7.10 (q, 2H) 7.35 (m, 9H) 7.60 (s, 1H) 7.85 (d, J = 8.1 Hz, 1H) 8.10 (d, J = 8.1, 1H); ^{1}^{3}C NMR (75 MHz, $CDCl_3$, 25 °C) δ ppm: 38.2, 44.7, 54.2, 118.2, 119.07, 123.3, 126.0, 126.9, 127.5, 128.1, 128.7, 129.1, 129.3, 134.0, 162.3, 118.0, 124.1, 125.9, 134.2, 138.3, 164.0, 164.9; HRMS (ESI^-): $C_{25}H_{21}N_5O_2$ calculated for $[M-H]^-$ = 422.1617, obtained for $[M-H]^-$ = 422.1621.

*4.3.2. 1-((1-(2,6-dimethylphenyl)-1H-1,2,3-triazol-4-yl)methyl)-4-(2-hydroxyphenyl)-1H-benzodiazepin-2(3H)-one (**7b**)*

Yield 82%, Mp = 181–188 °C. ^{1}H NMR (300 MHz, $CDCl^3$, 25 °C) δ ppm: 1.18 (s, 6H), 3.00 (d, J = 12 Hz, 1H), 4.20 (d, J = 12Hz, 1H), 5.09 (d, J = 15 Hz, 1H), 5.14 (d, J = 15 Hz, 1H), 7.00 (q, 2H), 7.10 (d, J = 6Hz, 1Hz), 7.45 (m, 5H), 7.55 (s, 1H), 7.80 (d, J = 4.5, 1H), 8.00 (d, J = 4.5, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ ppm: 17.2, 38.2, 44.4, 118.2, 119.1, 123.5, 124.2, 125.7, 126.1, 126.9, 127.5, 128.4, 129.3, 129.9, 134.1, 118.0, 124.4, 134.9, 135.3, 135.7, 138.7, 143.5, 162.1, 164.3, 165.08; HRMS (ESI^+): $C_{26}H_{23}N_5O_2$ calculated for $[M+Na]^+$ = 460.1749, obtained for $[M+Na]^+$ = 460.1763.

*4.3.3. 4-(2-hydroxyphenyl)-1-((1-(o-tolyl)-1H-1,2,3-triazol-4-yl) methyl)-1H-benzodiazepin-2(3H)-one (**7c**)*

Yield 69%, Mp = 177–181 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 2.08 (s, 3H), 2.95 (d, J = 12 Hz, 1H), 4.25 (d, J = 12Hz, 1H), 4.95 (d, J = 15Hz, 1H), 5.20 (d, J = 15Hz, 1H), 6.85 (q, 2H), 7.40 (m, 8H), 7.7 (s, 1H), 7.85 (d, J = 6.9, 1H), 8.10 (d, J = 6.9, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 17.8, 38.2, 44.6, 118.2, 119.1, 123.4, 125.8, 126.0, 126.8, 126.9, 127.5, 129.3, 129.8 131.4, 134.1, 118.0, 33.4, 135.2, 136.3, 138.4, 143.5, 162.2, 164.1, 165.0; HRMS (ESI^-): $C_{25}H_{21}N_5O_2$ calculated for $[M-H]^-$ = 423.1617, obtained for $[M-H]^-$ = 422.1618.

*4.3.4. 4-(2-hydroxyphenyl)-1-((1-(2-methoxyphenyl)-1H-1,2,3-triazol-4-yl)methyl)-1H-benzodiazepin-2(3H)-one (**7d**)*

Yield 71%, Mp = 180–189 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 3.05 (d, J = 12Hz, 1H), 3.86 (s, 3H), 4.30 (d, J = 12Hz, 1H), 4.98 (d, J = 15Hz, 1H), 5.35 (d, J = 15Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 38.2, 44.6, 55.9, 118.2, 119.1, 121.1, 123.4, 125.3, 126.0, 126.2, 126.4, 126.9, 127.6, 129.3, 130.1, 134.1, 112.2, 118.0, 135.2, 138.3, 143.1, 151.1, 162.2, 164.2, 164.9; HRMS (ESI^-): $C_{25}H_{21}N_5O_3$; calculated for $[M-H]^-$ = 438.1566, obtained for $[M-H]^-$ = 438.1565.

*4.3.5. 1-((1-(2-chlorophenyl)-1H-1,2,3-triazol-4-yl)methyl)-4-(2-hydroxyphenyl)-1H-benzodiazepin-2(3H)-one (**7e**)*

Yield 84%, Mp = 189–195 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 3.10 (d, J = 12Hz, 1H), 4.35 (d, J = 12Hz, 1H), 5.10 (d, J = 15Hz, 1H), 5.30 (d, J = 15Hz, 1H), 8.08 (s, 1H), 7.10–8.20 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 38.2, 44.6, 118.2, 119.1, 123.3, 126.1, 126.3, 126.9, 127.2, 127.8, 129.3, 129.5, 130.5, 130.7, 130.8, 118.0, 126.0, 127.6, 134.1, 134.8, 135.1, 138.4, 143.5, 162.2, 165.0; HRMS (ESI^+): $C_{24}H_{18}ClN_5O_2$; calculated for $[M+H]^+$ = 444.1227, obtained for $[M+H]^+$ = 444.1234.

*4.4. General procedure for the synthesis of BZDs **(8a-e)***

A solution of **5** (0.300 g, 1 mmol) in 20 mL of dichloro-methane was stirred at room temperature for 5 min. Then, one equivalent of azide, triethylamine (2 mL) and 5 mol % of Cu (I) copper iodide were added. The reaction mixture was stirred at room temperature for 8 h. Then the solvent was evaporated off under reduced pressure and the crude compound was purified by chromatography on silica gel eluting with cyclohexane/ethyl acetate/methanol (60:30:10).

*4.4.1. 2-(1-((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)-5-methyl-4-oxo-4,5-dihydro-1H-benzodiazepin-2-yl)phenylacetate (**8a**)*

Yield 78%, Mp = 192–197 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ ppm: 1.78 (s, 3H), 3.50 (s, 3H), 5.32 (s, 2H), 5.56 (s, 2H), 6.40 (s, 1H), 7.20 (m, 9H), 7.30 (s, 1H), 7.04 (s, 2H), 7.18 (s, 1H), 7.55 (d, J = 7.5, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ ppm: 22.5, 35.9, 29.6, 54.5, 113.4, 121.6, 122.2, 125.4, 128.3, 128.7, 129.0, 131.6, 113.0, 121.1, 124.9, 127.8, 128.5, 131.16, 134.0, 137.5, 155.5, 165.6. HRMS (ESI^+): $C_{28}H_{25}N_5O_3$; calculated for $[M+H]^+$ = 480.2036, obtained for $[M+H]^+$ = 480.1957.

*4.4.2. 2-(5-methyl-4-oxo-1-((1-(o-tolyl)-1H-1,2,3-triazol-4-yl) methyl)-4,5-dihydro-1H-benzodiazepin-2-yl)phenylacetate (**8b**)*

Yield 87%, Mp = 195–199 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ ppm: 1.90 (s, 3H), 2.26 (s, 3H), 2.40 (s, 3H), 5.40 (d, J = 12Hz, 1H), 5.50 (d, J = 12Hz, 1H), 6.49 (s, 1H), 7.10 (d, J = 6.9, 1H), 7.30 (dd, J_1 = 17.4, J_2 6.9Hz, 4H), 7.45 (m, 5H), 7.55 (d, J = 7.8 Hz, 1H), 7.68 (d, J = 7.5 Hz, 1H), 8.07 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ ppm: 25.3, 29.9, 43.3, 70.3, 120.8, 128.3, 129.0, 129.5, 132.7, 133.2, 134.19,

136.2, 136.6, 137.1, 138.8, 127.3, 132.0, 136.2, 140.8, 143.7, 145.3, 150.8, 173.3. HRMS (ESI^+): $C_{28}H_{25}N_5O_3$; calculated for $[M+H]^+ = 480.2036$, obtained for $[M+H]^+ = 480.2047$.

*4.4.3. 2-(1-((1-(2,6-dimethylphenyl)-1H-1,2,3-triazol-4-yl)-methyl)-5-methyl-4-oxo-4,5-dihydro-1H-benzodiazepin-2-yl) phenylacetate (**8c**)*

Yield 81%, Mp = 191–196 °C. ^1H NMR (300 MHz, $CDCl_3$, 25 °C) δ ppm: 1.88 (s, 3H), 1.90 (s, 3H), 2.10 (s, 6H), 5.47 (s, 2H), 6,47 (s, 1H), 7.06 (s, 1H), 7.16 (d, $J = 7.5$Hz, 1H), 7.25 (t, $J_1 = 7.5$Hz, $J_2 = 5.1$ Hz, 4H), 7.35 (d, $J = 6.9$, 2H), 7.50 (d, $J = 8.1$Hz, 1H), 7.60 (d, 7.2Hz, 1H), 7.87 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ ppm: 17.3, 22.6, 35.9, 62.9, 113.5, 114.4, 121.0, 121.7, 122.2, 124.8, 125.4, 128.4, 128.8, 129.2, 130.0, 131.6, 120.0, 135.38, 135.8, 138.0, 143.5, 146.7, 156.1, 166.0, 169.7. HRMS (ESI^+): $C_{29}H_{27}N_5O_3$; calculated for $[M+H]^+ = 494.2192$, obtained for $[M+H]^+ = 494.2197$.

*4.4.4. 2-(1-((1-(2-methoxyphenyl)-1H-1,2,3-triazol-4-yl)methyl)-5-methyl-4-oxo-4,5-dihydro-1H-benzodiazepin-2-yl)phenylacetate (**8d**)*

Yield 68%, Mp = 189–193 °C. ^1H NMR (300 MHz, $CDCl_3$, 25 °C) δ ppm: 1.95 (s, 3H), 2.15 (s, 3H), 3.86 (s, 3H), 5.43 (s, 2H), 6.44 (s, 1H), 7.40 (m, 10H), 7.58 (d, $J = 1.5$Hz, 1H), 7.61 (d, $J = 1.5$Hz, 1H), 8,45 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ ppm: 22.7, 36.0, 55.9, 62.6, 111.8, 112.3, 113.1, 120.4 121.1, 121.6, 122.1, 124.7, 124.9, 125.2, 125.4, 125.7, 128.3, 128.5, 129.0, 129.1, 130.2, 137.4, 150.7, 165.5. HRMS (ESI^+): $C_{28}H_{25}N_5O_4$, calculated for $[M+H]^+ = 496.1985$, obtained for $[M+H]^+ = 496.1931$.

*4.4.5. 2-(1-((1-(2-chlorophenyl)-1H-1, 2,3-triazol-4-yl)methyl)-5-methyl-4-oxo-4,5-dihydro-1H-benzodiazepin-2-yl)phenylacetate (**8e**)*

Yield 75%, Mp = 193–197 °C. ^1H NMR (300 MHz, $CDCl_3$, 25 °C) δ ppm: 1.25 (s, 3H), 2.20 (s, 3H), 5.43 (s, 2H), 6.45 (s, 1H), 7.1 (t, $J = 7.1$Hz, 1H), 7.40 (m, 11H), 8.20 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ ppm: 22.7, 36.0, 62.7, 121.7, 122.1, 125.3, 127.7, 127.9, 130.8, 130.8, 113.1, 121.2, 124.8, 127.2, 128.3, 129.0, 130.3, 134.3, 137.4, 165.5, HRMS (ESI^+): $C_{27}H_{22}ClN_5O_3$; calculated for $[M+Na]^+ = 522.1309$, Obtained for $[M+Na]^+ = 522.1324$.

*4.5. Preparation of compound (**9d**)*

A solution of **8d** (1 mmol) in a mixture of 10 mL of dichloromethane and 20 mL of methanol was stirred at room temperature for 5 min. Then (1 mmol, 1 eq) of K_2CO_3 was added and the mixture was stirred at room temperature for 4 h. Solvent was evaporated off under reduced pressure. The crude material was purified by chromatography on silica gel eluting with cyclohexane/ethyl acetate (70:30).

*4.5.1. 4-(2-hydroxyphenyl)-5-((1-(2-methoxyphenyl)-1H-1,2,3-triazol-4-yl)methyl)-1-methyl-1H-benzo[b] [1,4]diazepin-2(5H)-one (**9d**)*

Yield 74%, Mp = 194–198 °C. ^1H NMR (300 MHz, $CDCl_3$, 25 °C) δ ppm: 2.00 (s, 3H), 3.29 (s, 3H), 3.32 (s, 3H), 3.77 (s, 2H), 7.45 (m, 13H), 8.57 (s, 1H), ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ ppm: 26.81, 35.14, 56.48, 62.17, 113.46, 113.86, 121.32, 121.40, 122.50, 125.22, 126.06, 126.16, 126.74, 126.98, 127.38, 128.97, 130.78, 131.19, 132.26, 134.93. HRMS (ESI^+): $C_{26}H_{23}N_5O_3$; calculated for $[M+Na]^+ = 476.1699$, Obtained for $[M+Na]^+ = 476.1721$.

5. Computational studies

The origin of the unexpected fluorescence response of compound **9d** compared to compounds **7a-e** has been investigated by means of electronic structure calculations and density functional theory (DFT) based methods. We have performed B3LYP [33,34] calculations on structures **9d** and **7e** in vacuo using standard 6-31+G* all-electron basis sets [35] as implemented in the GAMESS package [36,37]. Finally, it can be useful to further interpret the ESIPT mechanism by inspection of the HOMO-LUMO energy differences (ΔEH-L) as an approximation of the of the emission from the excited state: for **7e**, ΔEH-L = 4.05 eV for M1 and 3.40 eV for the structure with N–H bond at 1.01 Å, and for **9d**, ΔEH-L = 4.19 eV for M1 and 3.48 eV for M2. Interestingly enough, in both compounds the expected emission energy at M1 should be significantly lower than that from the structure with the proton transferred to the N-atom, as implied by the ESIPT mechanism, with similar values for **7e** and **9b** as compared to the experimental values (380 nm (3.26 eV) and 381 nm (3.25 eV), respectively). These results provide further support to the action of ESIPT mechanism in compound **9d** and the interpretation of the fluorescence in this family of compounds.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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