

Mass spectroscopy of 3-arylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-diones and 3-aryl-7-thioxo-7,8-dihydro-6*H*-pyrimido[4,5-*c*]pyridazine-5-ones: Dimers containing water cluster and quasi-covalent hydrogen bond

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CHRONICLE

Article history:

Received March 25, 2013

Received in Revised form

July 27, 2013

Accepted 10 August 2013

Available online

12 August 2013

Keywords:

Electron impact mass spectroscopy

Water clustered

Dimer

Strong intermolecular H-bonding

Retro Diels-Alder

ABSTRACT

Electron impact (EI) mass spectrometer apparatus has been used to monitor the relative intensities of ion clusters of the type $X_n(H_2O)_n$ where X is 3-arylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-diones (**1a-d**), 3-aryl-7-thioxo-7,8-dihydro-6*H*-pyrimido[4,5-*c*]pyridazine-5-ones (**2a-d**) and $n = 1, 2$. The m/z of selected fragments obtained from **1a-d** and **2a-d** show a clustered water molecule due to strong intermolecular H-bonding between fragment and clustered water molecule.

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1. Introduction

The importance of fused pyrimidines as; pyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-diones, which are common sources for the development of new potential therapeutic agents, is well-known¹⁻⁵. Some of this class of compounds plays new heterocyclizations based on S_N^H -methodology as $N_{(2)}$ -oxide and 3-alkylamino derivatives of 6,8-dimethylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-dione^{6,7}.

Hydrogen bonding plays a key rule in biology, chemistry and remains a topic of intense current interest as judge by an enormous continuing amount of literatures. A few selected recent articles exemplify the general scope of the topic, ranging from the rule of H-bonding in: weak interaction in the gas phase⁸, supramolecular assemblies⁹, helical structure¹⁰, molecular rotors¹¹, through to

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measurement of H-bond acidity of organic compounds ¹², diastereoselective formation of centrosymmetric 18-membered ring ¹³ and etc.

Research investigations of the properties of clusters have been rapidly expanding in last two decades ¹⁴⁻²⁷. On account of the intrinsic nature of accurate measurement of molecular masses, mass spectrometry has become an indispensable tool to study noncovalent interactions for protein complexes or oligomers ²⁸⁻³¹. Mixed-clusters with water also have been reported with acetone ²⁵⁻²⁷, cyclopentanone ³², ammonia ³³, trimethylamine (TMA) ³⁴, etc. Herein, we report the formation of the monomeric and dimeric forms of 3-arylpyrimido[4,5-*c*]pyridazine-5,7(*6H,8H*)-diones (**1a-d**) and 3-aryl-7-thioxo-7,8-dihydro-6*H*-pyrimido[4,5-*c*]pyridazine-5-ones (**2a-d**) containing of H₂O cluster in structure by means of EI mass spectroscopy.

2. Results and Discussion

This paper presents results on the study of mass spectroscopy of 3-arylpyrimido[4,5-*c*]pyridazine-5,7(*6H,8H*)-diones **1a-d** and 3-aryl-7-thioxo-7,8-dihydro-6*H*-pyrimido[4,5-*c*]pyridazine-5-ones **2a-d**. The general formula structures of **1a-d** and **2a-d** is shown at Scheme 1. All mass fragments of these compounds and their corresponding natural abundances (in parenthesis) are summarized in Table 1. In addition to ¹H NMR data ³⁵, we found that the mass spectra of these compounds show strongly water clustered in the structure in ratio of 1:1. We assume the monomer and dimer structures of **1a-d** and **2a-d** as X_n(H₂O)_n where, X = heterocyclic compounds **1a-d** and **2a-d**, n = 1, 2 and thus, the structure of monomer and dimer containing of clustered water will be show as X₁(H₂O)₁ and X₂(H₂O)₂, respectively. The mass spectra of these compounds show the both water clustered monomer and dimer forms (Figures 1, 2 and Scheme 2). This observation indicated that there is a strong H-bond between monomer–water and weak H-bond between monomer–monomer species in gas phase. The strong H-bond not only exists between monomer-water species in solution (in DMSO as a suitable solvent) but also in gas phase in ionization chamber. The proposed water clustered dimer forms assigned as **I** and **II** structures is shown in Scheme 2. Interestingly, the fragmentation of these compounds in mass ionization chamber show some significant fragments that support the existence of X₁(H₂O)₁ and X₂(H₂O)₂ (monomer-H₂O and dimer-2H₂O species, respectively).

For instance, the proposed fragmentations of **1d** and **2d** are shown in Scheme 3. The peak of two clustered water ion molecular of dimer (X₂(H₂O)₂) and monomer (X₁(H₂O)₁) forms of **1d** appeared at *m/z* 552 ([M⁺+18]₂) in low intensity and at *m/z* 276 (M⁺+18) in 50% abundance, respectively. A peak at *m/z* 259 (M⁺+1) appeared as base peak (100% abundance) and corresponded to **D** and/or **E** fragments. Surprisingly, it seems that some other fragments also show the clustered water molecule and is shown in Scheme 3 and Figures 1 and 2. The X₁(H₂O)₁ (**B** form) was tautomerized to **C** then converted to **D** at *m/z* 259 with lose of water molecule and then captured hydrogen radical. The loss of hydroxyl radical from **C** can release the **E** form containing of a water clustered molecule. The capture of hydrogen radical by **E** was obtained **F** at *m/z* 260 (≈ 20%). The release of natural cyanic acid (HCN) from **F** obtained ion radical **G** containing of a water molecule at *m/z* 233 (33%). This form can convert to **H** then convert to **I** cation at followed by hydrogen radical loss. The instability of **I** forced to rearranged to 3-(4-fluorophenyl)oxazolo[4,5-*c*]pyridazine-6-ium ion (**J**) at *m/z* 232. Finally, the hydrogen radical capturing of **J** produced 3-(4-fluorophenyl)oxazolo[4,5-*c*]pyridazine (**3d**) at *m/z* 233 (33%). In parallel the fragmentation in the mentioned above, the peak at *m/z* 233 can be rationalized by retro Diels-Alder reaction on X₁(H₂O)₁ (**B** form) formed **K** involving HNCO loss, then cyclization of this form released β-lactam derivative containing of a clustered water (**L**). The **L** can tautomerize to **H** form (β-lactim). As demonstrates, the water molecule is appeared in many of the fragments and clustered to fragments by strong hydrogen-bonding (Scheme 3).

The fragment of 4-fluorobenzonitrile ion radical at *m/z* 121 (**5d**) can also arise from retro-Diels-Alder reaction of **1d** and **2d** on pyridazine ring moiety (Scheme 3). Fluorobenzene cation at *m/z* 95

generated from **5d** with loss of cyanide radical. Fluorobenzene cation can also be generated by heterolytic cleavage of the bond between C3-C9 in **1d** and/or **2d** molecule. The fragment of the fluorocyclobutadiene cation at m/z 69 generated from fluorobenzene cation with loss of acetylene and then loss of acetylene twice produced fluoroacetylene cation at m/z 43. This fragment converted to fluoroacetylene ion radical at m/z 44 by hydrogen radical capturing.

One of the important fragmentations on these compounds is the retro-Diels-Alder reaction on the pyrimidine ring moiety. This reaction generated the fragment of **M** with loss of HOCN in **1d** and HSCN in **2d** and then proton radical capturing produced ion radical of **N** at m/z 217. The ion radical of diazonium salt derivative (**O**) at m/z 190 generated from **N** with loss of neutral cyanic acid (HCN). Finally, the ion radical **O** generated the fragment of **P** at m/z 162 with loss of neutral nitrogen gas (N_2) (Scheme 3).

The significant peak of 4-fluorobenzonitrile (**5d**) at m/z 121 and ion radical intermediate (**Q**) (from **3d**) which arises through a retro-Diels-Alder reaction in the pyridazine ring moiety (Scheme 4). The hydrogen radical capturing of ion radical intermediate **Q** produces cation intermediate (**R**), then cyclized, produced cation intermediate (**S**). The cation intermediate **S**, rearranged to seven-membered ring cation intermediate (**T(i)**) (ring enlargement) is that of the resonance form of **T(ii)** (1,3,5-oxadiazepine-7-ium **6T(ii)**) at m/z 95 and its sulfur analogue **7(Tii)** at m/z 111). This fragmentation is similar to that of other compounds in this study (**1a-c** and **2a-c**) (Scheme 4). In parallel to the fragmentation mentioned above, 3-aryloxazolo[4,5-*c*]pyridazine (**3a-d**) and 3-arylthiazolo[4,5-*c*]pyridazine (**4a-d**) generate the aryl acetylenes (**8a-d**) at m/z 102 (**8a**), 181 (**8b**), 136 (**8c**) and 120 (**8d**), respectively, due to retro-Diels-Alder reaction on the pyridazine ring moiety (Scheme 4).

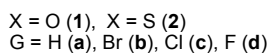
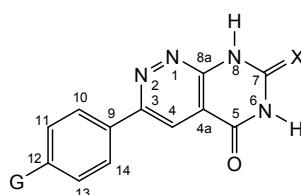
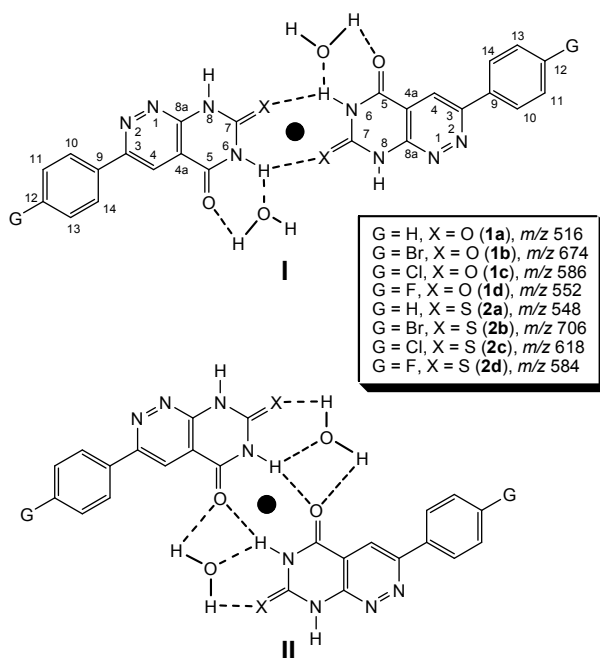
One of the most important phenomena in the fragmentation of these molecules (**1a-d** and **2a-d**) is the water-clustered molecule strongly attached to each fragment. It seems that the water molecule has made strong intermolecular H-bonding with the fluorine atom (F---H-O-H) and/or with polar functional groups as -OH, C=O, -NH, -N=N- and weakly with C=S and -SH in the corresponding fragment species in **1a-d** and **2a-d**.

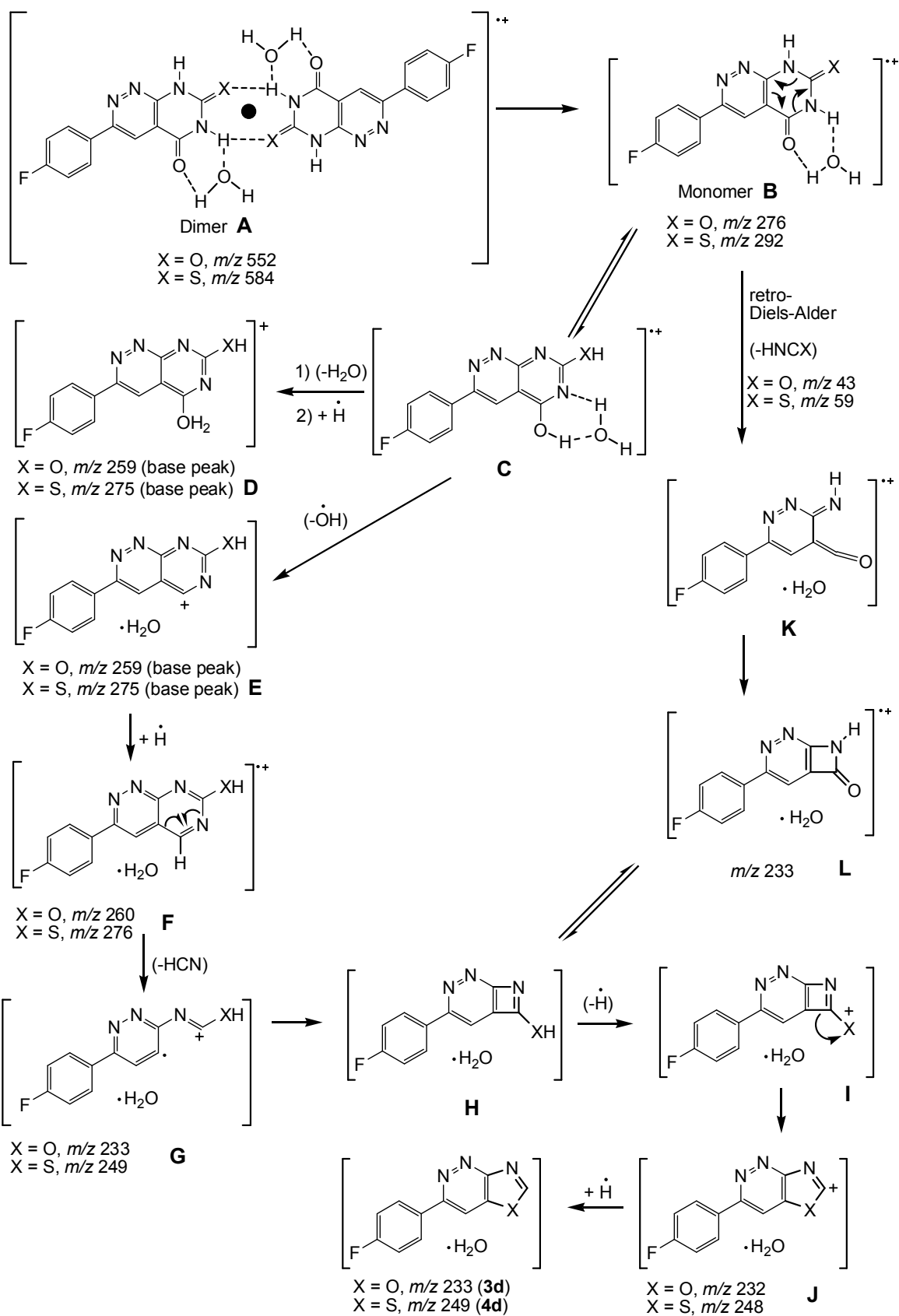
Another interesting, important and intricate phenomenon in the spectra of **1a-d** and **2a-d** are the masses of the fragments generated from the dimer form containing two clustered water molecules ($X_2(H_2O)_2$). The range of these mass fragments are at $276 < m/z < 552$ in **1d** and at $292 < m/z < 584$ in **2d** as representative (Table 1). The fragment of **L** (m/z 233) can also be generated by loss of HNCO and HNCS from **1d** and **2d**, respectively. The loss of water from **L** generated the fragment of **U** at m/z 215. The β -lactam **U** dimerized to fragment of **W** at m/z 430. In parallel, fragment of **L** generated the fragment **X** at m/z 190 by loss of HNCO. One of the other possible ways to obtaining of the m/z 121 (**Y**) is the loss of water and propionitrile molecules from **X** (Scheme 5).

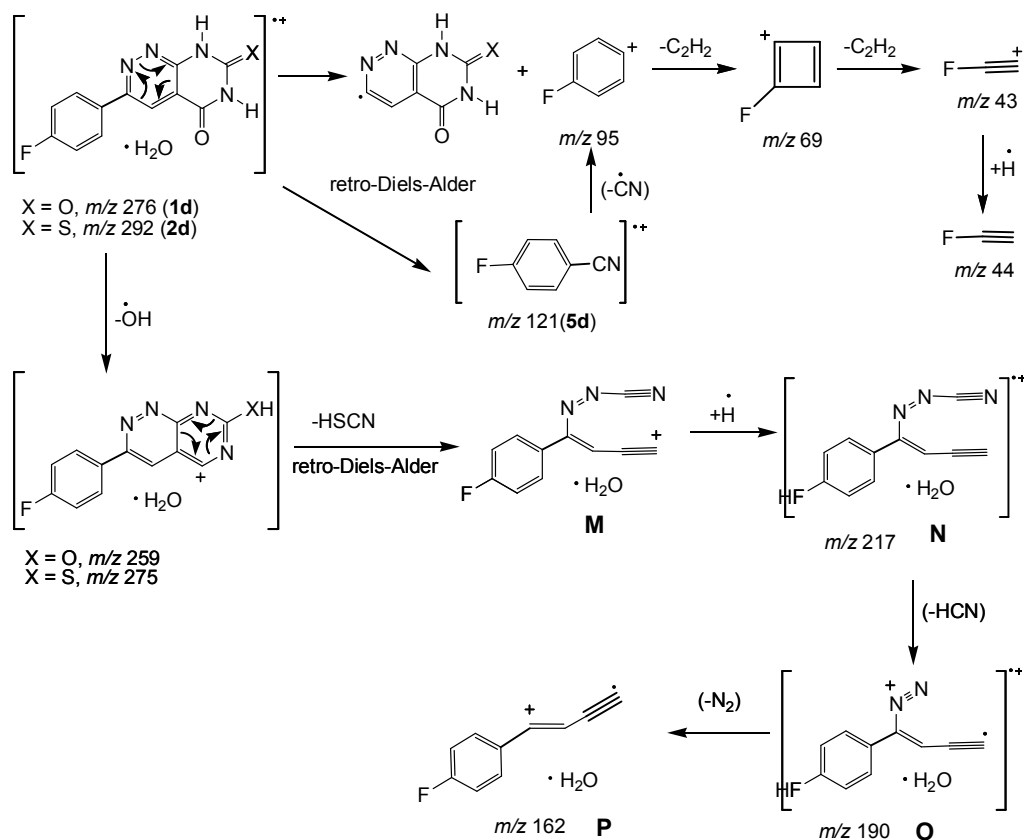
There are other pathways that may generate important fragments from dimers of **1d** and **2d** (Scheme 6). Dimer **A[i]** (lactam form) of **1d** and **2d** can tautomerize to dimer **A[ii]** (lactim form). The loss of two molecules of H_2S from dimer **A[ii]** of **2d** generated the centrosymmetric dimer (**Z**) at m/z 516. Dimer **Z** can exist in two tautomeric forms of lactim (**Z[i]**) and lactam (**Z[ii]**) forms (Scheme 6). The loss of H_2O , $2H_2O$, OH radical and 2OH radicals from the dimer form of **1d** (**A[i]**), generated the fragments of m/z 534, 516, 535 and 518, respectively. Unfortunately, an attempt to characterize the structures of these unknown fragments failed. Similarly, these fragmentations of **2d** generated the fragments of m/z 566, 548, 567 and 550, respectively. The fragments of m/z 516 (from **1d**) and m/z 548 (from **2d**) can be released via intramolecular rearrangement on the lactim dimer form (**A[ii]**). Representatively, the loss of SH radical from the lactim dimer form of **2d** (**A[ii]**) generated the fragment at m/z 551. It seems that this fragment generated via intramolecular rearrangement of the lactim dimer form of **2d** (**A[ii]**) (Scheme 6).

Table 1. Selected mass fragments of **1a-d** and **2a-d**

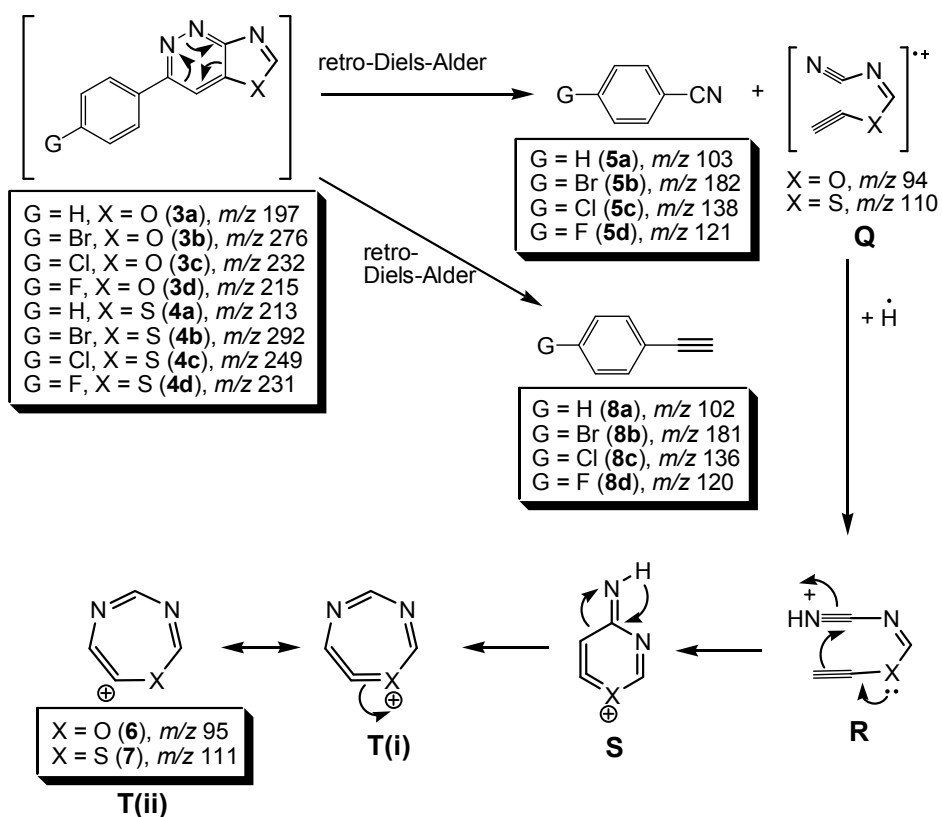
Compd.	Selected mass fragments, <i>m/z</i> (%)
1a	475 (3), 396 (5), 318 (2), 275 (2), 258 ([M ⁺ +18], 62), 241 ([M ⁺ +1], 100), 240 ([M ⁺], 4), 213 (18), 199 (30), 187 (25), 172 (25), 158 (20), 115 (42), 77 (26).
1b	579 (1), 551 (2), 537 (2), 523 (2), 498 (17), 455 (20), 397 (20), 383 (13), 368 (20), 353 (10), 338 ([M ⁺ +18], 42), 321 ([M ⁺ +2], 100), 319 ([M ⁺], 98), 295 (42), 241 (36), 227 (34), 183 (46), 115 (43), 97 (42), 83 (65), 57 (72), 43 (79)
1c	587 ([M ⁺ +18] ₂ , 0.5), 551 (1), 480 (1), 436 (1), 407 (2), 368 (1), 345 (2), 316 (3), 292 ([M ⁺ +18], 57), 277 ([M ⁺ +2], 50), 275 ([M ⁺], 100), 251 (33), 249 (100), 206 (39), 176 (18), 164 (17), 149 (50), 136 (68), 115 (65), 75 (40), 44 (47)
1d	552 ([M ⁺ +18] ₂ , trace), 535 (trace), 534 (trace), 518 (trace), 516 ([M ⁺] ₂ , trace), 464 (0.5), 355 (0.5), 276 ([M ⁺ +18], 50), 260 (20), 259 ([M ⁺ +1], 100), 233 (33), 217 (23), 190 (22), 133 (41), 120 (30)
2a	548 ([M ⁺ +18] ₂ , trace), 473 (2), 395 (3), 368 (3), 318 (2), 274 ([M ⁺ +18], trace), 256 ([M ⁺], 1), 230 (100), 199 (90), 172 (94), 143 (33), 115 (43), 100 (39), 77 (42), 51 (13)
2b	587 (2), 551 (3), 523 (4), 523 (5), 509 (3), 495 (3), 436 (2), 407 (5), 382 (2), 368 (24), 353 (6), 339 (5), 337 ([M ⁺ +2], 1), 335 ([M ⁺], 1), 310 (98), 308 (100), 279 (39), 277 (39), 252 (50), 250 (50), 223 (20), 221 (22), 183 (24), 142 (25), 113 (29), 57 (33), 43 (30)
2c	618 ([M ⁺ +18] ₂ , trace), 436 (1), 407 (2), 400 (3), 292 ([M ⁺ +2], 2), 290 ([M ⁺], 7), 266 (71), 264 (100), 235 (28), 233 (76), 208 (32), 206 (94), 177 (33), 149 (25), 137 (31), 113 (26)
2d	604 (3), 577 (7), 567 (2), 566 (4), 551 (10), 550 (5), 548 (4), 537 (5), 534 (2), 523 (5), 516 (0.5), 409 (2), 480 (2), 464 (3), 436 (5), 421 (2), 407 (9), 393 (4), 368 (10), 353 (5), 339 (8), 313 (20), 292 ([M ⁺ +18], 38), 275 ([M ⁺ +1], 100), 248 (73), 233 (28), 217 (28), 190 (41), 149 (35), 121 (34), 57 (34), 43 (34)

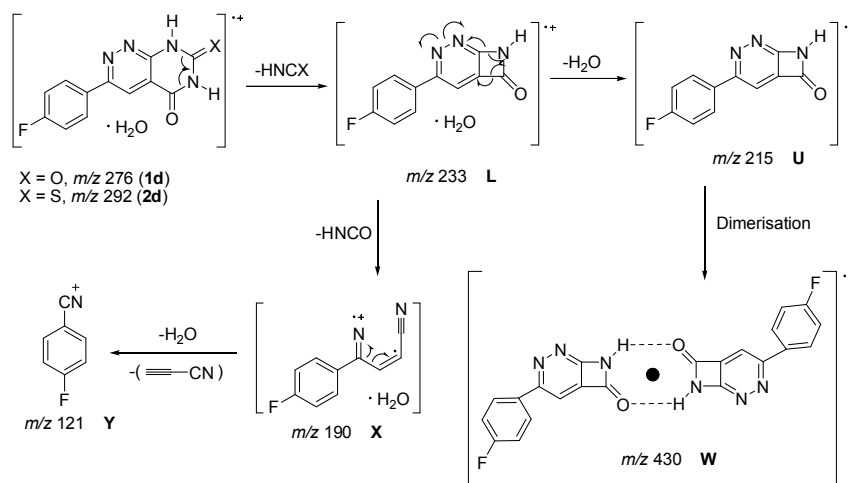
**Scheme 1.** Formula structures of **1a-d** and **2a-d**.**Scheme 2.** Possible proposed centrosymmetric dimer forms of **1a-d** and **2a-d** containing of two clustered water molecule in gas phase is shown as X₂(H₂O)₂ in the text (the centre of symmetry assigned by dot (•)).

Scheme 3. Possible mass fragmentation patterns of **1d** and **2d**.

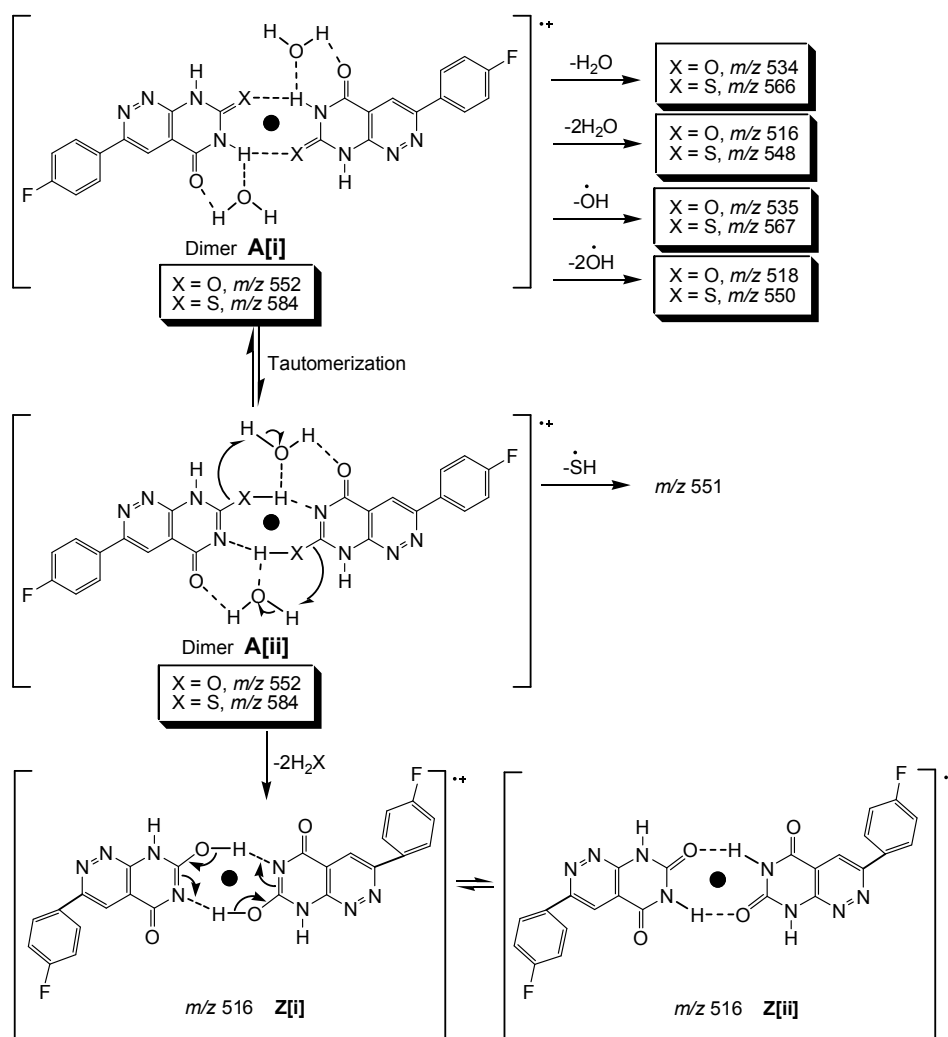


Scheme 3. (Continued).

Scheme 4. Possible mass fragmentation patterns of 3-aryloxazolo[4,5-c]pyridazine (**3a-d**) and 3-arylthiazolo[4,5-c]pyridazine (**4a-d**) formed from **1a-d** and **2a-d** in mass spectrometry, respectively.



Scheme 5. Possible proposed mass fragmentation and dimerization of **1d** and **2d** as representative.



Scheme 6. Possible proposed mass fragmentation, dissociation and dimerization of **1d** and **2d** as representative.

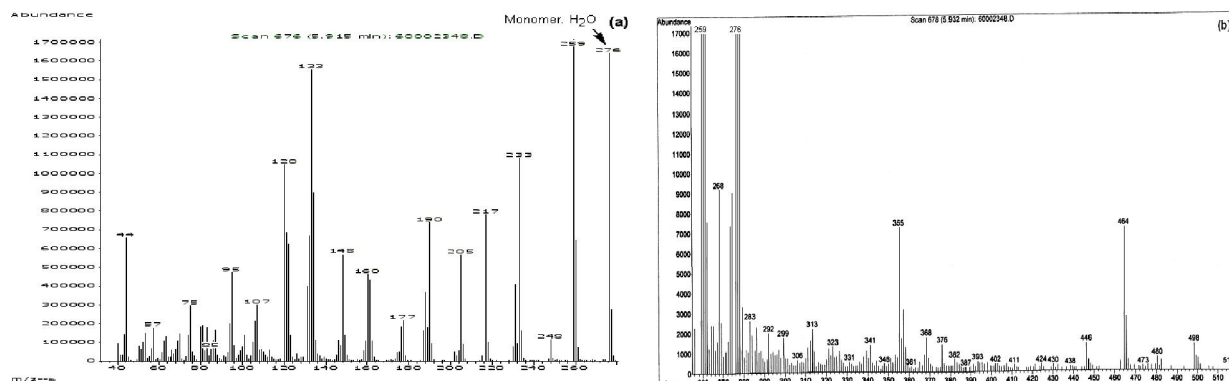


Fig. 1. Mass spectrum of **1d** (a) and its expanded spectrum (b)

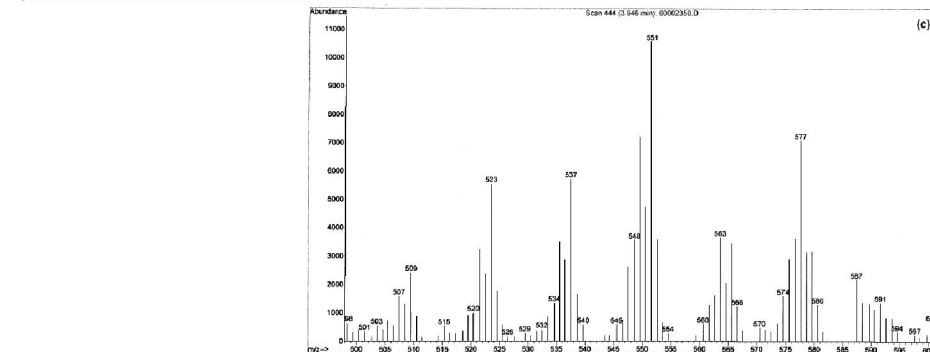
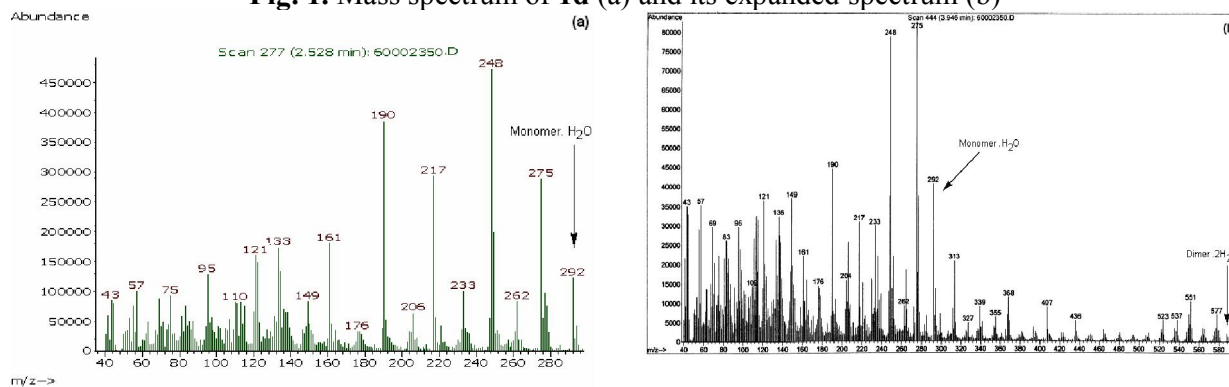


Fig. 2. Mass spectrum of **2d** (a) and its expanded spectrum of high mass fragmentation region (b and c)

3. Conclusion

In summary, the mass fragmentations of the new compounds **1a-d** and **2a-d** were studied by electron impact (EI) mass spectroscopy. All these compounds showed ion clusters of the type $X_1(H_2O)_1$ (in high natural abundance) and $X_2(H_2O)_2$ (in low natural abundance) where X is 3-arylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-diones (**1a-d**) and 3-aryl-7-thioxo-7,8-dihydro-6*H*-pyrimido[4,5-*c*]pyridazine-5-ones (**2a-d**). The water molecule strongly clustered in monomer molecules by strong intermolecular H-bonding. Many of the fragments of **1a-d** and **2a-d** show water clustered via strong intermolecular H-bonding.

Acknowledgements

We thank the Urmia University Research Council for supporting this work.

4. Experimental

The experiments were performed with the instrument specifications: Manufacturer Company; Agilent Technology (HP) type, MS Model; 5973 network mass selective detector Electron Impact (EI) spectrometer, Analyzer; quadrupole. The vapor species were ionized with electrons of energy 70 eV. The temperature range measurements were 50-350 °C, ion source and analyzer temperatures was 230 °C.

The novel synthesis of the compounds 3-arylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-diones **1a-d** and 3-aryl-7-thioxo-7,8-dihydro-6*H*-pyrimido[4,5-*c*]pyridazine-5-ones **2a-d** has been synthesized by our research group³⁵.

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