A New Derivatives of Benzodiazepine, Imidazole, Isatin, Maleimide, Pyrimidine and 1,2,4-Triazole: Synthesis and Characterization

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Abstract

The synthesis of new benzodiazepine, imidazole, isatin, maleimide, pyrimidine and 1,2,4-triazole derived from 2-amino-4-hydroxy-1,3,5-triazine, *via* its cyclocondensation reaction with different organic reagents, is described.

FT-IR, ^{1}H-NMR and as well as ^{13}C-NMR spectra disclosed the structures of the precursors and heterocyclic derivatives formed.

Keywords: 1,3,5-Triazine, Isatin, 1,2,4-Triazole, Fused heterocyclic rings

Introduction

1,3,5-Triazine (or *s*-triazine) are class of compounds well known for a long time, and still continue the object of considerable interest, mainly due to their applications in different fields. Some 1,3,5-triazines display important biological properties; for example Melamine (2,4,6-triamino-1,3,5-triazine) are an important class of organic compounds since they demonstrated to have wide range of biological activities such as antianagiogenesis, antitumour activity for breast and ovarian cancer treatment[1], effective treatments for menopausal symptoms and postmenopausal osteoporosis, anti-metastatic activity, herbicidal effects, and many others[2]. In addition, some of them are also useful as chemoselective building blocks for dendrimers[3].

Schiff bases belong to a widely used group of organic intermediates important for production of specialty chemicals, e.g., pharmaceuticals, or rubber additives and as amino protective group in organic synthesis. They also use as liquid crystals, and in analytical, medicinal and polymer chemistry[4].

Isatin is an endogenous compound identified in humans that possess wide range of biological activities. Isatin has anxiogenic, anticonvulsant activity and acts as a potent antagonist on ortial natriuretic peptides receptors in vitro[5,6].

The incorporation of imidazole nuclei is an important synthetic strategy in drug discovery. Many imidazoles have been prepared as potentially pharmacological agents, including 2-nitroimidazole (Azomycine) (naturally occurring antibiotic), Clorimazole (an antimycotic agent), Miconazole (antifungal drug), Ergothionine (biologically active antihistamine), Clonidine and Moxonidine (exhibit antihypertensive activity)[7].

In addition, it was reported that compounds having triazole moieties, such as Vorozole, Letrozole and Anastrozole, have been used as nonsteroidal aromatase inhibitors in medicine for treating breast cancer. Moreover, 1,2,4-triazoles are a new class of antimicrobial agents. For instance, Fluconazole and Itraconazole are used as antimicrobial drugs in medicine[8]. Beside this, the synthesis of triazoles fused

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to another heterocyclic ring has attracted particular attention due to their diverse applications as antibacterial, antidepressant, antiviral, pesticides, herbicides, lubricants and analytical reagents[9]. A number of triazoles fused to triazines are incorporated into a wide variety of therapeutically important compounds[10].

Pyrimidines represent one of the most active classes of compounds, possessing a wide spectrum of biological activities, *viz.* significant in vitro activity against unrelated DNA and RNA viruses, diuretic, anti-HIV, cardiovascular, etc.[11].

Experimental

General

Melting points were determined on GallenKamp melting point apparatus and were uncorrected. The IR spectra of the compounds were recorded on Shimadzu FTIR-8300 spectrometer as KBr disc; results are given in cm^{-1}. ^{1}H-NMR and ^{13}C-NMR spectra were recorded at 300.131 and 75.47 MHz, respectively, in DMSO-d_6 for compounds **2**, **3**, **4**, **8**, **9** and **10**, in $CDCl_3$ for compounds **6**, **7**, **11** and **12,** on a Bruker AMX-400 NMR spectrometer. The chemical shifts are reported in part per million (ppm) downfield from internal tetramethylsilane (TMS) (chemical shift in δ values). ^{1}H- and ^{13}C-NMR were made at Centro de Química Física Molecular, Instituo Superior Técnico, Lisboa, Portugal and at Department of Chemistry, Chinese University of Hong Kong, Hong Kong, China.

2-Amino-4-hydroxy-1,3,5-triazine (**1**)

This material was obtained as synthetic material from Merck Chemical Company and used directly without further purification.

Synthesis of 2-hydroxy-6H-pyrimido[1,2-a][1,3,5]triazine-6,8(7H)dione (**2**)

A mixture of compound **1** (0.012mol) and (0.012mol) of malonic acid in (25ml) absolute ethanol was heated under reflux for 24h. The reaction mixture was cooled and the formed precipitate was filtered off and recrystallized from benzene to give the desired products. M.P. >300˚C, Yield 70%.

2-Hydroxy-6-methyl-6,7-dihydro-8H-pyrimido[1,2-a][1,3,5]triazine-8-one (**3**)

The same procedure for synthesis of compound **2** but use crotonic acid instead of malonic acid. M.P. 205-208˚C, Yield 65%.

2,8-Dihydroxy-6(7H)-methylpyrimido[1,2-a][1,3,5]triazine (**4**)

The same procedure for synthesis of compound **2** but use acetyl acetone instead of malonic acid. M.P. 112-114˚C, Yield 55%.

Synthesis of 2-amino-4-hydrazino-1,3,5-triazine (**5**)

Hydrazine hydrate (0.01mol) was added to a solution of 2-amino-4-hydroxy-1,3,5-triazine (**1**) (0.01mol) in abs. ethanol (20ml) and the resulting mixture was refluxed for 6h. The solid that separated on cooling was filtered off and dried. M.P. >300˚C, Yield 80%.

Synthesis of 5-amino[1,2,4]triazolo[4,3-a][1,3,5]triazine-3-thiol (**6**)

To a warmed ethanolic sodium hydroxide solution prepared by dissolving of sodium hydroxide (0.01mol) and (0.01mol) of compound (**5**) in (25ml) abs. ethanol, (0.02mol) of carbon disulfide was added. The reaction mixture was refluxed for 13h, or until the evolution of H_2S ceased. The formed precipitate was filtered off and recrystallized from acetone. M.P. 187-189˚C, Yield 80%.).

Synthesis of 5-amino-3-(*p*-nitrophenyl)[1,2,4]triazolo[4,3-a][1,3,5]triazine (**7**)[12]

A mixture of compound **5** (0.015mol) and *p*-nitrobenzaldehyde

(0.015mol) in glacial acetic acid (25ml) was refluxed for 24h, the solvent was reduced to one third its volume under reduced pressure and then cooled. The solid that separated was recrystallized from suitable solvent to give the desired product. M.P. 150-152˚C, Yield 70%.

Synthesis of 5-amino-3-phenyl[1,2,4]triazolo[4,3-a][1,3,5]triazine (**8**)

Benzoyl chloride (0.015mol) was added to a solution of compound (**5**) (0.015mol) in abs. ethanol (20ml) and the resulting mixture was refluxed for 15h. The solid that formed was separated by filtration and recrystallized from benzene. M.P. 160-162˚C, Yield 77%.

Synthesis of 1-(4-hydroxy-1,3,5-triazin-2-yl)maleimide (**9**)

A mixture of compound (**1**) (0.015mol) and maleic anhydride (0.015mole) in acetic acid (25ml) was refluxed for 10h, the solvent was reduced to one third its volume under reduced pressure and then cooled. The solid that separated on cooling was recrystallized from ethanol to give the desired product. M.P. >300˚C, Yield 80%.

Synthesis of 3-[(4-hydroxy-1,3,5-triazin-2-yl)imino]-1,3-dihydro-2H-indol-2-one (**10**)

A mixture of compound (**1**) (0.01mol), distilled water (20ml) and isatin (0.01mol) were stirring at R.T. for 24h. The yellow powder was collected by filtration and dried then recrystallized from ethanol. M.P. 223-225˚C, Yield 73%.

Synthesis of 2-hydroxy-12,12a-dihydro[1,3,5]triazine[1,2-b][2,4] benzodiazepine -6,11-dione (**11**)[13]

Phthalic acid (0.015mol) dissolved in (25ml) abs. EtOH was added to compound (**1**) and the reaction mixture was refluxed for 42h. Then the mixture was poured on crushed ice, the formed solid product was filtered off and recrystallized from benzene. M.P. 260-262˚C, Yield 60%.

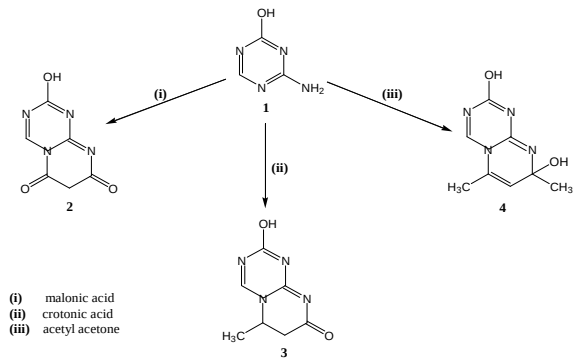
Synthesis of 6-aminoimidazo[1,2-a][1,3,5]triazine-2-ol (**12**)

2-Amino-5-hydroxy-1,3,5-triazine (**1**) (0.015mol) and chloroacetamide (0.015mol) was refluxed in (25ml) abs. ethanol for 12h. The reaction mixture was filtered off to obtain the crude product which then recrystallized from chloroform. M.P. 200-202˚C, Yield 60%.

Results and Discussion

In the present study, 2-amino-4-hydroxy-1,3,5-triazine (**1**) was chosen as the starting material due to its various biological activity. It is used for the synthesis of an interesting novel heterocyclic system through the reaction of its two reactive sides, amino and hydroxyl groups, with different organic reagents. These systems are known by their wide rang of applications and their chemistry has received considerable attention.

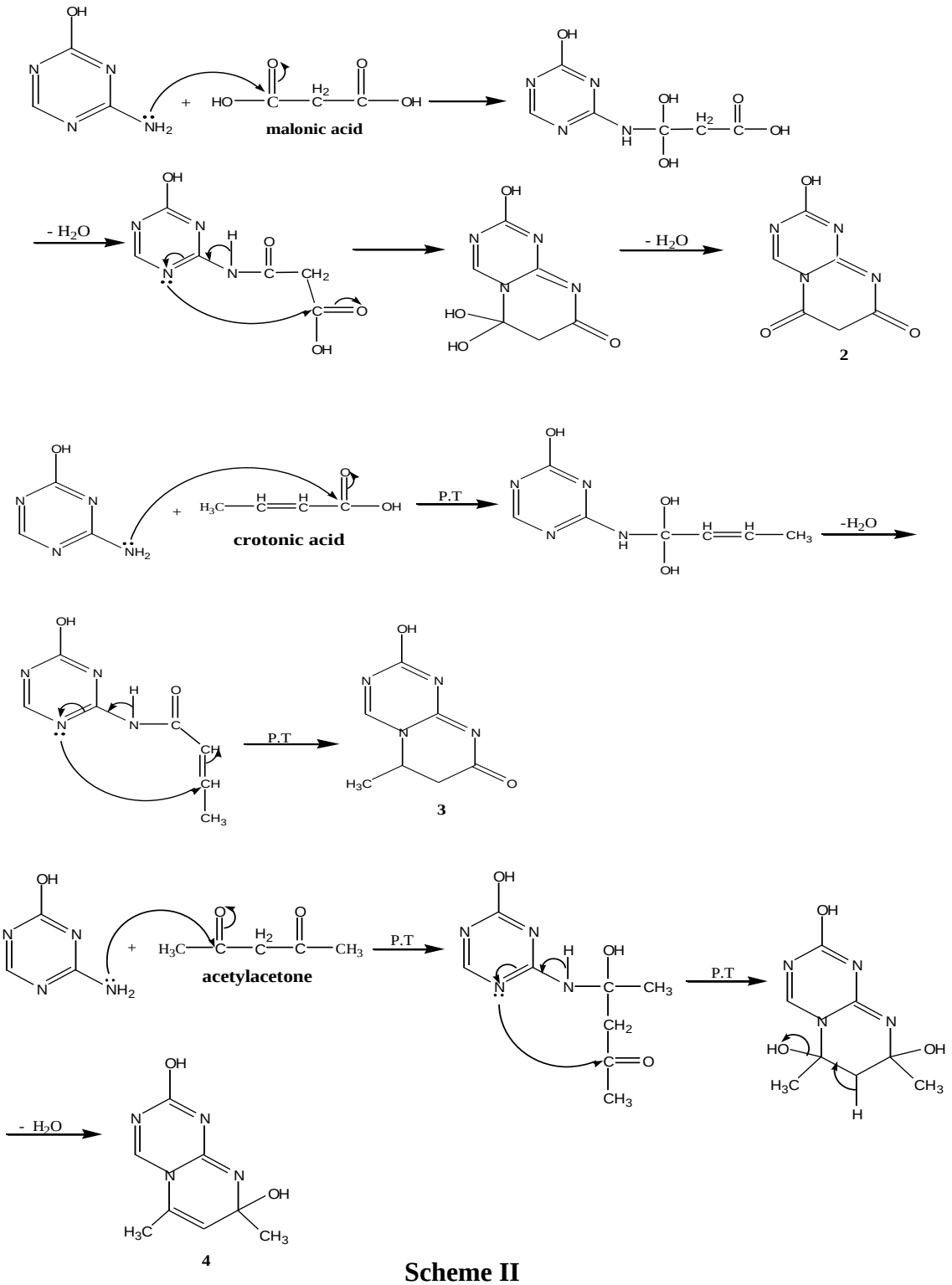
The cyclization of compound **1** was successfully achieved by its treatment with malonic acid, crotonic acid and acetyl acetone in refluxing EtOH to give 2-hydroxy-6H-pyrimido[1,2-a][1,3,5]triazine-6,8(7H)dione (**2**), 2-hydroxy-6-methyl-6,7-dihydro-8H-pyrimido[1,2-a][1,3,5]triazine-8-one (**3**) and 2,8-dihydroxy-6(7H)-methylpyrimido[1,2-a][1,3,5]triazine (**4**), respectively (**Scheme I**).



Scheme I

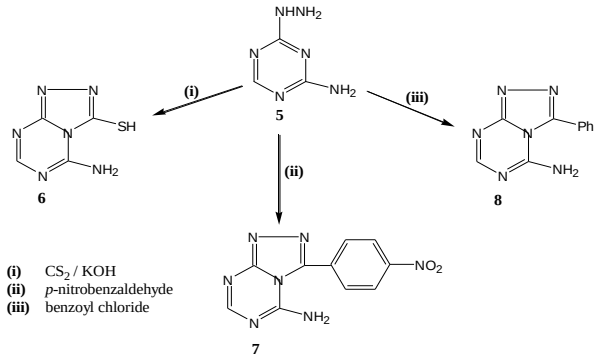
The IR spectra of compounds (**2**, **3** and **4**) were characterized by the disappearance of the absorption bands of

NH_2 group at 3300-3200cm^{-1}. The ^{1}H-NMR spectra showed characteristic signals at 3.005 (s, 2H, CH_2), 1.737 (s, 3H, CH_3) and 2.143 (s, 3H, CH_3) which were assigned for CH_2 and CH_3 groups of compounds **2**, **3** and **4**, respectively. The ^{13}C-NMR spectra showed signals at 180.02 (1C, C=O), 128.43 (1C, CH_2) and 17.26 (1C, CH_3) corresponding to compounds **2**, **3** and **4**, respectively, **Fig. 1** show ^{13}C-NMR spectrum of compound **4**. The mechanism of the above mentioned reactions are outlined in (**Scheme II**).



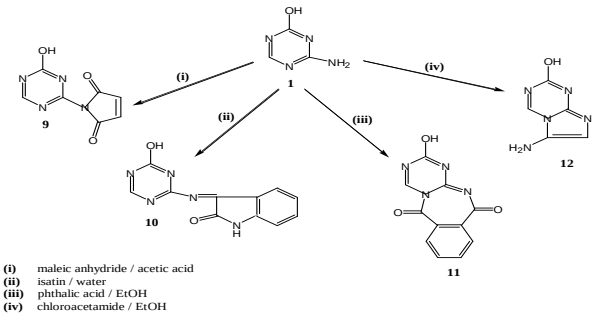
Scheme II

Heating of compound **1** with hydrazine hydrate resulted 2-amino-4-hydrazino-1,3,5-triazine (**5**), which represent the key intermediate for the synthesis of 1,2,4-triazole derivatives. Cyclocondensation of **5** with CS_2, *p*-nitrobenzaldehyde and benzoyl chloride gave **5**-amino[1,2,4]triazolo[4,3-a][1,3,5]triazine-3-thiol (**6**), 5-amino-3-(*p*-nitrophenyl)[1,2,4]triazolo[4,3-a][1,3,5]triazine (**7**) and 5-amino-3-phenyl[1,2,4]triazolo[4,3-a][1,3,5]triazine (**8**), respectively, in good yield (**Scheme III**). ^{1}H-NMR spectrum of compound (**6**) showed signal at δ 8.632 (s, 1H) corresponding to the SH group proton, which was further characterized by disappearance with D_2O exchange. The ^{1}H-NMR spectra of compound (**7**) and compound (**8**) showed characteristic signals at about 7.051-8.700 ppm confirmed to aromatic protons. The IR spectra exhibited the characteristic absorption bands of SH, aromatic *p*-substituted and aromatic *mono* substituted at 2526, 842, 775 and 678 cm^{-1} for compounds (**6**), (**7**) and (**8**), respectively. The results are in agreement with their ^{1}H-NMR spectra.



Scheme III

Furthermore, we decide to synthesis new Schiff base of isatin in water. We allowed to 2-amino-4-hydroxy-1,3,5-triazine (**1**) to condensed with isatin, the corresponding 3-[(4-hydroxy-1,3,5-triazin-2-yl)imino]-1,3-dihydro-2H-indol-2-one (**10**) was formed cleanly and efficiently in a water suspension medium without using any acid catalyst or organic solvent and the yellow powder was isolated simply by filtration (**Scheme IV**). The structure of compound **10** was characterized by its IR, ^{1}H-NMR and ^{13}C-NMR spectra. The IR spectrum of this compound showed the disappearance of NH_2 absorption band, whereas the characteristic absorption band for C=N of imine compounds appeared at 1618. The ^{1}H-NMR spectrum exhibited the presence of the protons of the aromatic ring at 6.886-7.591ppm. The aromatic carbons of this compound appeared at 122.73-138.34 in ^{13}C-NMR spectrum, **Fig. 2** show ^{1}H-NMR spectrum of compound **10**.



Scheme IV

Compounds **9**, **11** and **12** were successfully formed by treatment of **1** with maleic anhydride, phthalic acid and chloroacetamide, respectively, (**Scheme IV**). The IR spectrum of compound **9** and **11** were characterized by the absorption band of C=O at about 1700cm^{-1}, while the IR spectrum of compound **12** showed absorption band at 3300-3200 due to NH_2 group.

The ^{1}H-NMR spectrum of compound **9** displayed multiple signals at 6.634-7.299ppm belonging to =CH- protons of maleimide ring together with –N=CH- proton of triazine ring. ^{1}H-NMR spectra of compounds **11** and **12** showed characteristic signals at 6.850-7.942 (m, 4H) due to aromatic protons and at 8.575 (s, 2H) corresponding to NH_2 protons which was further characterized by D_2O exchange, respectively. ^{13}C-NMR spectra

exhibited characteristic signals at 182.91 for C=O carbon of compound **11** and at 87.35, 89.42 assigned for carbon atoms of imidazole ring of compound **12**. **Table I** summarizes the physical properties of the synthesized compounds; **Table II** shows the spectral data of these compounds.

Table I: Physical properties of compounds (2-12)

Compound No.	M.P/ ˚C	%Yield
2	>300	70
3	205-208	65
4	112-114	55
5	>300	80
6	187-189	80
7	150-152	70
8	160-162	77
9	>300	80
10	223-225	73
11	260-262	60
12	200-202	60

Table II: Spectral data for compounds (2-12)

Comp. No.	FT-IR	^{1}H-NMR	^{13}C-NMR
2	IR: 3384 (OH), 3178 (NH_{taut}), 2920 and 2850 (CH), 1660(C=N), 1700(C=O)	3.005 (s, 2H, CH_2), 6.872 (s, 1H, -N=C<u>H</u>-), 7.716 (s, 1H, NH) (D_2O exchange, disappear), 10.687 (s, 1H, OH) (D_2O exchange, disappear)	132.01 (1C, CH_2), 154.42-160.51 (3C, triazine), 180.02, 180.66 (2C, C=O)
3	3400 (OH), 3176 (NH_{taut}), 2923 and 2800 (CH), 1662 (C=N), 1705 (C=O)	1.737 (s, 3H, CH_3), 4.042 (d, 2H, CH_2), 6.544 (t, 1H, -C<u>H</u>-CH_3), 7.009 (s, 1H, -N=C<u>H</u>-), 7.556 (s, 1H, NH) (D_2O exchange, disappear), 11.214 (s, 1H, OH) (D_2O exchange, disappear)	20.23 (1C, CH_3), 30.65 (1C, <u>C</u>-CH_3), 128.43 (1C, CH_2), 155.30-159.12 (3C, triazine), 178.54, 179.01(2C, C=O)
4	3350 (OH), 3176 (NH_{taut}), 3080 (=CH-), 2910 (CH), 1665 (C=N), 1550 (C=C)	2.143 (s, 6H, CH_3), 4.602 (s, 1H, =C<u>H</u>-), 7.415 (s, 1H, -N=C<u>H</u>-), 8.014 (s, 1H, NH) (D_2O exchange, disappear), 10.397 (s, 2H, OH) (D_2O exchange, disappear)	17.26, 17.88 (2C, CH_3), 95.22 (1C, -CH=), 78.33, 78.52 (2C, -<u>C</u>(CH_3)), 157.02-162.32 (3C, triazine)
5	3300-3150 (NH_2, -$NHNH_2$), 1662 (C=N)	4.567 (s, 2H, NHN<u>H</u>$_2$) (D_2O exchange, disappear), 6.235 (s, 1H, N<u>H</u>NH_2) (D_2O exchange, disappear), 6.325 (s, 1H, -N=C<u>H</u>), 7.755 (s, 2H, NH_2) (D_2O exchange, disappear)	-
6	3327-3250 (NH_2), 2526 (SH), 1633 (C=N)	5.632 (s, 1H, SH) (D_2O exchange, disappear), 6.511 (s, 1H, -N=C<u>H</u>-), 6.855 (s, 2H, NH_2) (D_2O exchange, disappear)	132.01 (1C, triazole), 160.51-164.09 (3C, triazine)
7	3310-3230 (NH_2), 1633 (C=N)	6.503 (s, 1H, -N=C<u>H</u>-), 6.771 (s, 2H, NH_2) (D_2O exchange, disappear), 7.078-7.805 (m, 4H, aromatic protons)	122.20-125.13 (6C, aromatic carbons), 140.41 (1C, triazole), 158.09-161.33 (3C, triazine)
8	3300-3220 (NH_2), 1639 (C=N) , 775 and 678 (aromatic *mono* substituted)	6.315 (s, 1H, -N=C<u>H</u>-), 7.021 (s, 2H, NH_2) (D_2O exchange, disappear), 7.551-8.692 (m, 5H, aromatic protons)	126.04-130.15 (6C, aromatic carbons),135.62 (1C, triazole), 154.85-158.25 (3C, triazine)
9	3350 (OH),3032(=CH-), 1700 (C=O), 1630 (C=N)	6.434-7.299 (m, 3H, =C<u>H</u>-), 8.019 (s, 1H, NH) (D_2O exchange, disappear), 10.409 (s, 1H, OH) (D_2O exchange, disappear)	-
10	3400 (OH), 3186 (NH), 3080 (CH), 1710 (C=O), 1618 (C=N)	6.886-7.591 (m, 5H, aromatic protons and -N=C<u>H</u>-), 7.975, 8.218 (s, 2H, NH) (D_2O exchange, disappear), 11.020 (s, 1H, OH) (D_2O exchange, disappear)	122.73-138.34 (6C, aromatic carbons), 150.69-159.33 (3C, triazine), 160.02 (1C, -<u>C</u>=N- imine), 180.36 (1C, C=O)
11	3400 (OH), 3200 (NH), 3080 (CH), 1705 (C=O), 1630 (C=N), 765 (aromatic *o*-substituted)	6.023 (s, 1H, -N=C<u>H</u>-), 6.850-7.442 (m. 4H, aromatic protons), 8.309 (s, 1H, NH) (D_2O exchange, disappear). 11.020 (s, 1H, OH) (D_2O exchange, disappear)	132.84-136.06 (6C, aromatic carbons), 152.88-155.71 (3C, triazine), 181.12, 182.91 (2C, C=O)
12	3400 (OH), 3300-3200 (NH_2), 3027 (CH), 1662 (C=N)	5.018 (s, 1H, =C<u>H</u>-), 6.632 (s, 1H, -N=C<u>H</u>-), 7.313 (s, 1H, NH) (D_2O exchange, disappear), 8.475 (s, 2H, NH_2) (D_2O exchange, disappear), 10.041 (s, 1H, OH) (D_2O exchange, disappear)	87.35 and 89.42 (2C, imidazole), 160.50-163.41 (3C, triazine)

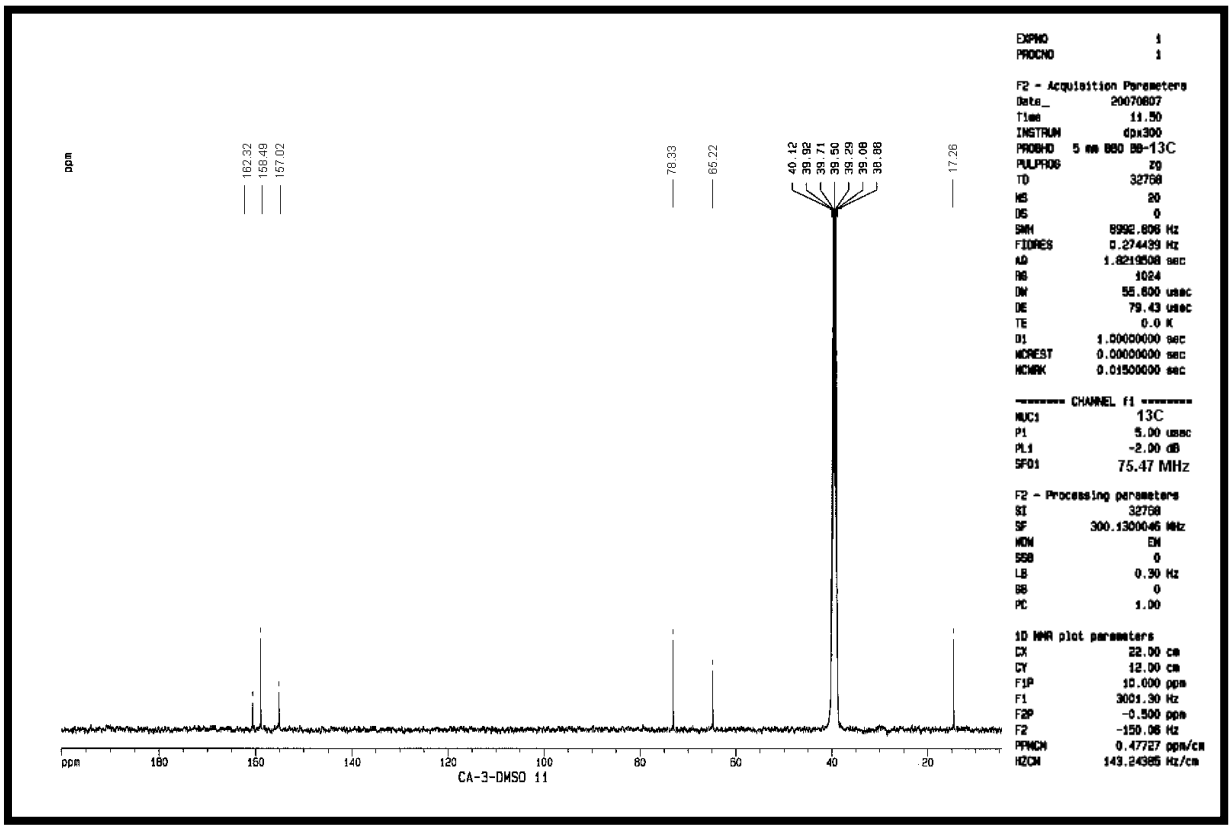


Fig. 1 ^{13}C-NMR spectrum of compound **4**

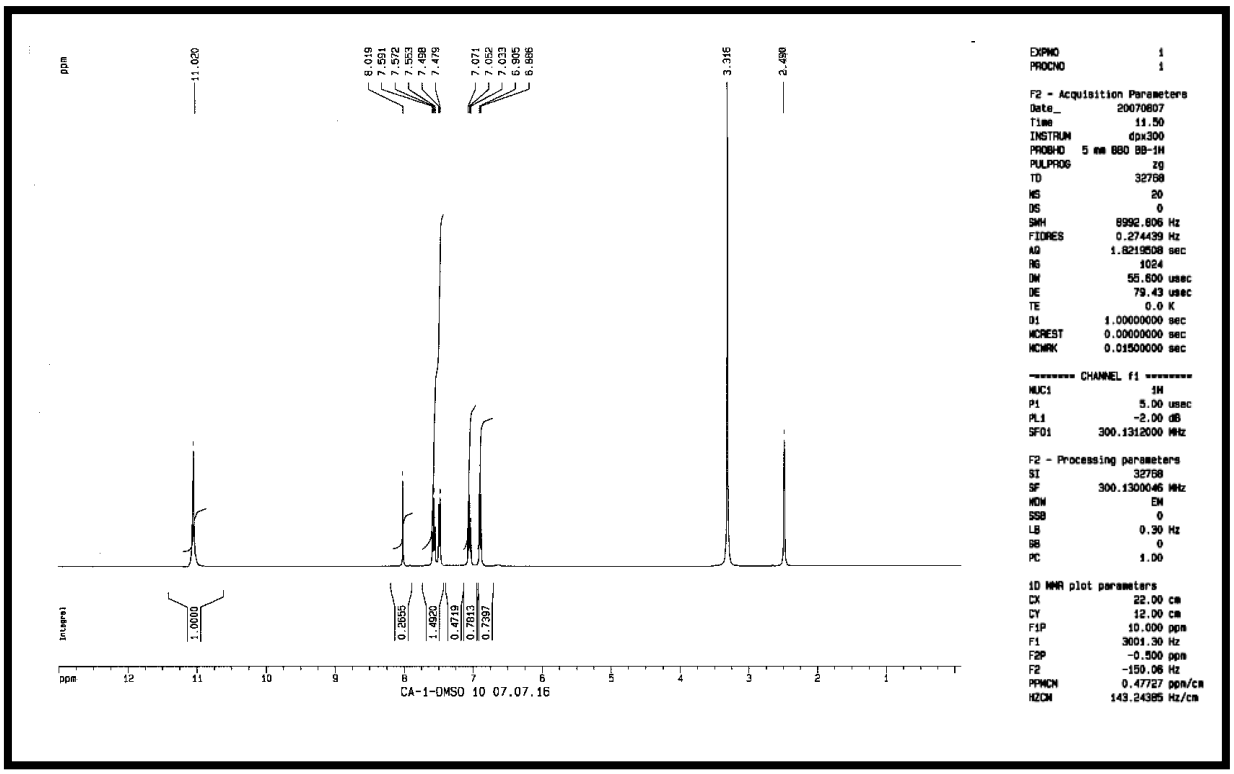


Fig. 2 ^{1}H-NMR spectrum of compound **10**

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مشتقات جديدة من البنزودايايزأبين, ايميدازول, أيساتين, مالأيماید, بايريمدين و ١,٢,٤-ترايازول: تحضير وتشخيص

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الخلاصة:

تم في هذا البحث تحضير عدد من المعوضات الجديدة لمشتقات البنزودايايزأبين, ايميدازول, أيساتين, مالأيماید, بايريمدين و ١,٢,٤-ترايازول وذلك من خلال تفاعل ٢-أمينو-٤-هيدروكسي-١,٣,٥-ترايزين مع عدد من الكواشف العضوية المختلفة. شخصت المادة الأساس وكذلك جميع المركبات المحضرة بالطرق الطيفية FT-IR ، ^{1}H- NMR ، ^{13}C-NMR.