Synthesis, Biological activity and Mass Spectral Fragmentation Patterns of some New Fused Phthalazine-1,4-dione Derivatives

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Síntesis, actividad biológica y patrones de fragmentación del espectro de masas de algunos nuevos derivados fundidos de ftalazina-1,4-diona

Síntesi, activitat biològica i patrons de fragmentació de l'espectre de masses d'alguns nous derivats fosos de ftalazina-1,4-diona

Recibido: 18 de septiembre de 2008; aceptado: 22 de octubre de 2008

RESUMEN

Se prepara 1,2,4-triazino[1,2-*b*]ftalazina-6,11-diona **(3)** y 1,2,4- triazino[1,2-*b*]ftalazina-5,10-diona **(4)** por reacción de 2-aminotiocarbonilftalazina-1,4-diona con cloropropionato de etilo y cloroacetato de etilo. La acetilación de **4** con Ac_2O da el correspondiente derivado monoacetilado (**5**), mientras que la acetilación de **4** con Ac_2O en presencia de AcONa da el correspondiente derivado diacetilado (**6**). El tratamiento de **4** con bromo en AcOH y aldehídos aromáticos rinde las correspondientes 1,2,4-triazino[1,2-*b*]ftalazina-5,10-dionas 3-substituidas (**7** y **8**). Se registran los espectros de masas de impacto electrónico de las dos series citadas de compuestos, y se discuten sus patrones de fragmentación.

Palabras clave: Síntesis, espectro de masas, derivados de ftalazinadiona

SUMMARY

1,2,4-Triazino[1,2-*b*]phthalazine-6,11-dione **(3)** and 1,2,4-triazino[1,2-*b*]phthalazine-5,10-dione **(4)** were prepared via the reaction of 2-aminothiocarbonylphthalazine-1,4-dione with ethyl chloropropionate and ethyl chloroacetate. Acetylation of **4** with Ac_2O gave the corresponding monoacetyl derivative **(5)**, while the acetylation of **4** with Ac_2O in the presence of AcONa gave the corresponding diacetyl derivative **(6)**. Treatment of **4** with bromine in AcOH and aromatic aldehydes afforded the corresponding 3-substituted-1,2,4-triazino[1,2-*b*]phthalazine-5,10-diones (**7** and **8**). The electron impact mass spectra of both of the above series of compounds have also been recorded and their fragmentation pattern is discussed.

Key words: Synthesis, mass Spectra, phthalazindione Derivatives

RESUM

Es prepara 1,2,4-triazina[1,2-*b*]ftalazina-6,11-diona **(3)** i 1,2,4- triazina[1,2-*b*]ftalazina-5,10-diona **(4)** per reacció de 2-aminotiocarbonilftalazina-1,4-diona amb cloropropionat d'etil i cloroacetat d'etil. L'acetilació de **4** amb Ac_2O dóna el corresponent derivat monoacetilat (**5**), mentre que l'acetilació de **4** amb Ac_2O en presència d'AcONa dóna el corresponent derivat diacetilat (**6**). El tractament de **4** amb brom en AcOH i aldehids aromàtics rendeix les corresponents 1,2,4-triazina[1,2-*b*]ftalazina-5,10-diones 3-substituïdes (**7** i **8**). Es registren els espectres de masses d'impacte electrònic de les dues sèries esmentades de compostos, i es discuteixen els seus patrons de fragmentació.

Mots clau: Síntesi, espectre de masses, derivats de ftalazinadiona

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INTRODUCTION

Various substituted nitrogen heterocycles have recently received significant importance because of their diverse pharmacological properties. These included analgesic, antiasthmatic diuretic, antihypertensive, anticholinergic, and antiinflammatory properties.[1-5]

In the course of recent investigation involving phthalic anhydride and thiosemicarbazide, it was found that 2-aminothiocarbonyl-phthalazine-1,4-dione (2) is converted into fused phthalzine-1,4-dione derivatives (3 and 4) by the action of ethyl chloro-propionate and ethyl chloroacetate under reflux. The fact that only limited information is available on the mass spectra of 2-aminothiocarbonyl-phthalazine-1,4-dione (2), along with the preparation of a novel fused phthalazine-1,4-dione, has prompted us to report their synthesis and study their electron impact (EI) mass spectral fragmentation.

RESULTS AND DISCUSSION

Chemistry

Condensation[6] of phthalic anhydride (1) with thiosemicarbazide in methanol under reflux, yielded the corresponding 2-aminothiocarbonyl-phthalazine-1,4-dione (2, Scheme I). The reaction of compound 2 with ethyl chloropropionate and ethyl chloracetate in the presence of fused sodium acetate in methanol under reflux led to the formation of 5-oxo-1-thioxo-2,3,4-trihydro-1,2,4-triazapino[1,2-b]-phthalazine-6,11-dione (3) and 4-oxo-1-thioxo-2,3-dihydro-1,2, 4-triazino[1,2-b]-phthalazine-5,10-dione (4, Scheme 1), respectively.

Acetylation[7] of compound 4 with acetic ahydride under reflux gave the corresponding 2-acetyl-1-thioxo-4-oxo-2,3-dihydro-1,2,4-triazino[1,2-b]phthalazine-5,10-dione (5), while the acetylation of compound 4 with acetic anhydride in the presence of fused sodium acetate under reflux led to the formation of 2,3-diacetyl-1-thioxo-4-oxo-2,3-dihydro-1,2,4-triazino[1,2-b]phthalazine-5,10-dione (6, Scheme 1).

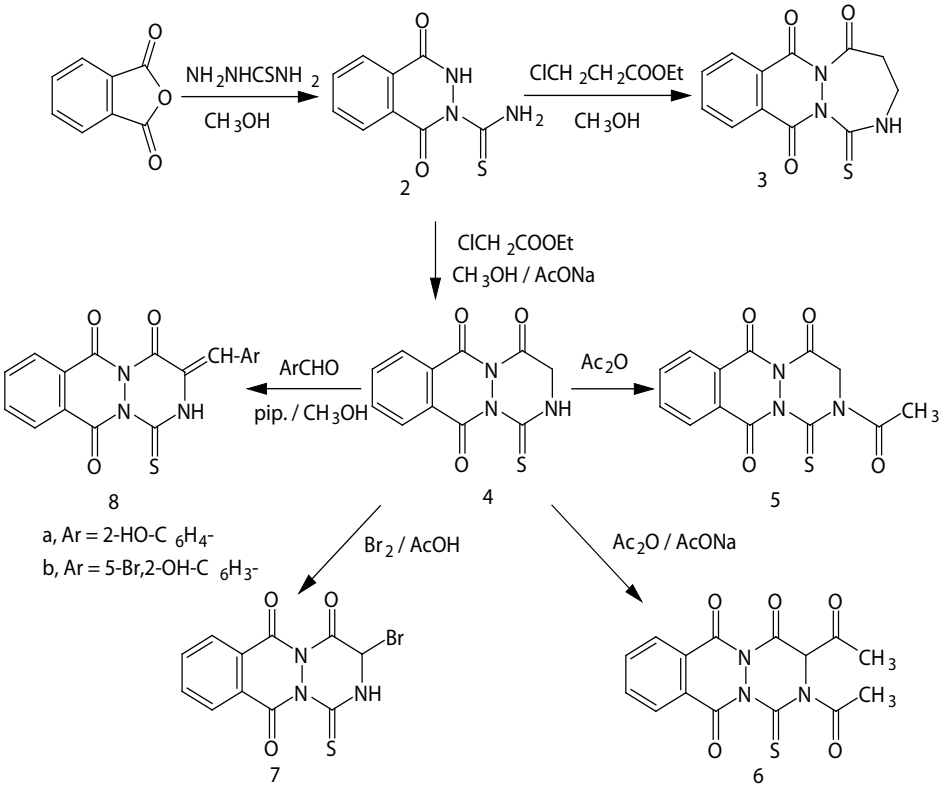
Bromination[8] of 1-thioxo-4-oxo-2,3-dihydro-1,2,4-triazino[1, 2-b]phthalazine-5,10-dione 4 with one mole from the bromine in glacial acetic acid at room temperature gave the corresponding 3-bromo-4-oxo-1-thioxo-2,3-dihydro-1,2,4-triazino[1,2-b]-phthalazine -5,10-dione (7). Condensation of compound 4 with aromatic aldehydes (such as 2-hydroxybenzaldehyde and 5-bromo-2-hydroxybenzaldehyde) in the presence of piperidine under fusion led to the formation of 4-oxo-3-arylidene-1-thioxo-1,2,4-triazino[1,2-b]phthalazine-5,10-dione (8a, b; Scheme 1).

Mass Spectrometry

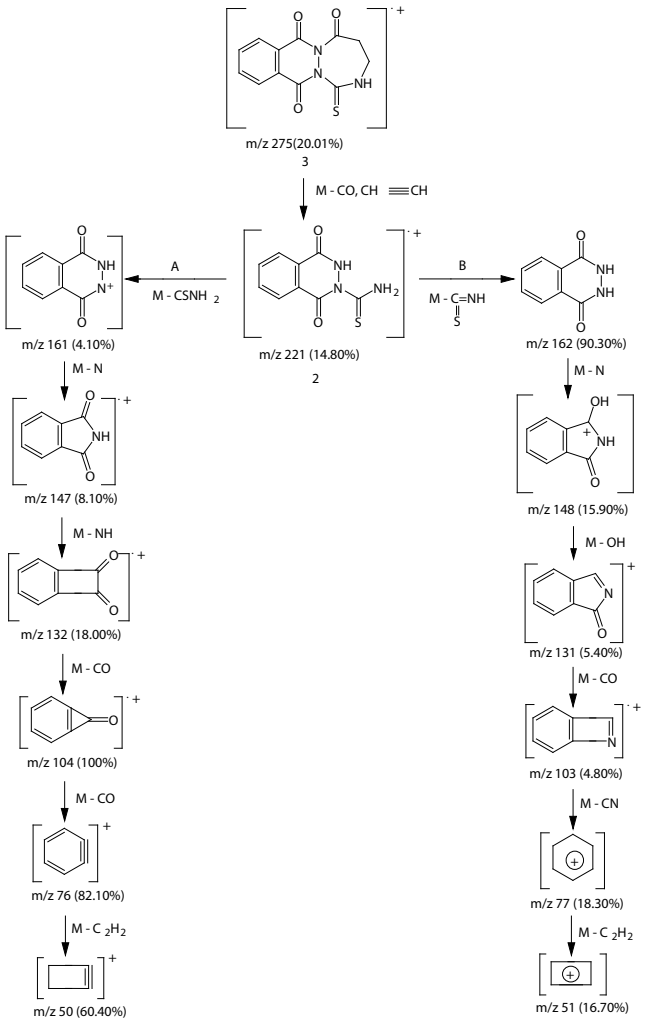
All the spectra showed characteristic common fragmentation pathways[9-12] with intense molecular ion peaks in most cases. Table 1 list the m/z (relative abundance, %) values should be principal fragments of some synthesized compounds, while fig. 1, 2, 3, 4, 5 and 6 illustrate, the mass spectra of compounds 2, 3, 4, 6, 7 and 8b, respectively.

Compounds 2 and 3

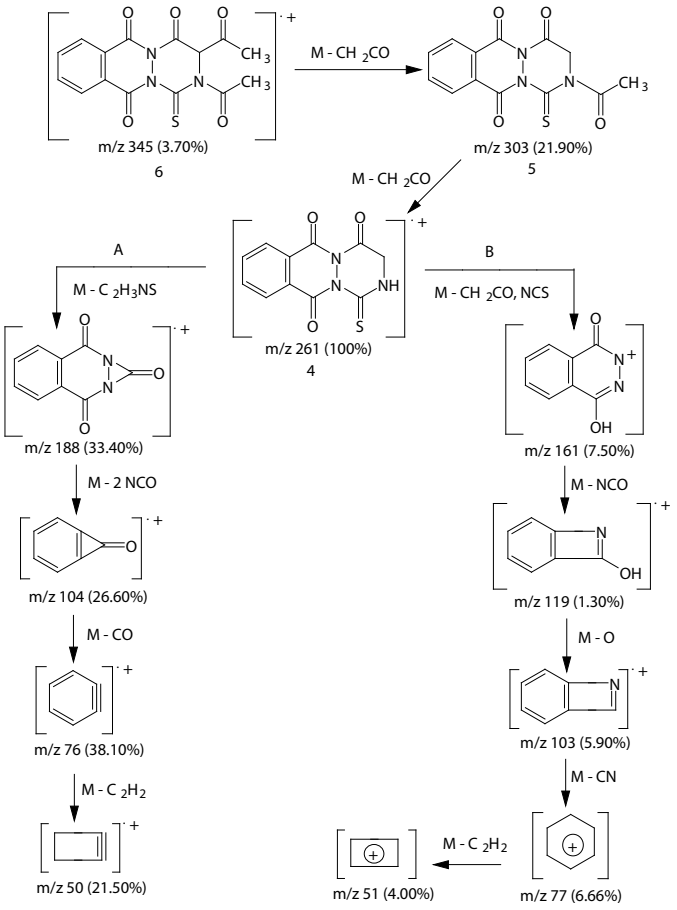
The mass spectra of the compounds 2 (fig. 1) and 3 (fig. 2) showed intense molecular ion peaks at m/z 221 and m/z 275, consistent with the molecular formula $C_9H_7N_3O_2S$ and $C_{12}H_9N_3O_3S$, respectively. The molecular ion of compound 2 and 3 fragmented further and involved two pathways as illustrated in Scheme 2. the molecular ion of m/z 221 fragmented via the pathway A to give peak at m/z 161 by losing $CSNH_2$ group. The ion of m/z 161 underwent fragmentation produce ion of m/z 147, corresponding to the molecular ion of phthalamide by losing nitrogen atom. This



Scheme 1



Scheme 2. Main fragmentation pathway of compounds 2 and 3



Scheme 3. Main fragmentation pathway of compounds 4, 5, 6

fragmentation led to ion of m/z 132, 104, 76 and m/z 50, respectively. Accordingly, the same molecular ion of m/z 221 fragmented via the pathway B by a cleavage hydrogen isothiocyanate group to give peak at m/z 162, corresponding to the molecular ion of phthalazine-1,4-dione, which lost nitrogen atom to give peak at m/z 148. It further underwent loss of OH, CO, CN and C_2H_2 to give peaks at m/z 131, 103, 77 and m/z 51, respectively.

Compound 3

From the study of mass spectra of the compound 3, had fragmented to give ion of m/z 221, corresponding to the molecular ion of compound 2 by losing carbon monoxide and acetylene molecule. The ion of m/z 221 underwent cleavage via pathway A and B in the same fragmentation processes which was observed for compound 2.

Compounds 4, 5 and 6

The mass spectra of compounds 4 (Fig. 3), and 6 (Fig. 4) are fully consistent with the assigned structures. In most cases, intense molecular ion peak were observed. Thus, compound 4 showed an intense molecular ion peak at 261, corresponding to the molecular formula $C_{11}H_7N_3O_3S$. The molecular ion of compound 4 (m/z 261) fragmented via the pathway A to give peak at m/z 188. further it underwent loss of two group from isocyanate (NCO) and carbon monoxide molecule to give stable peak at m/z 76.

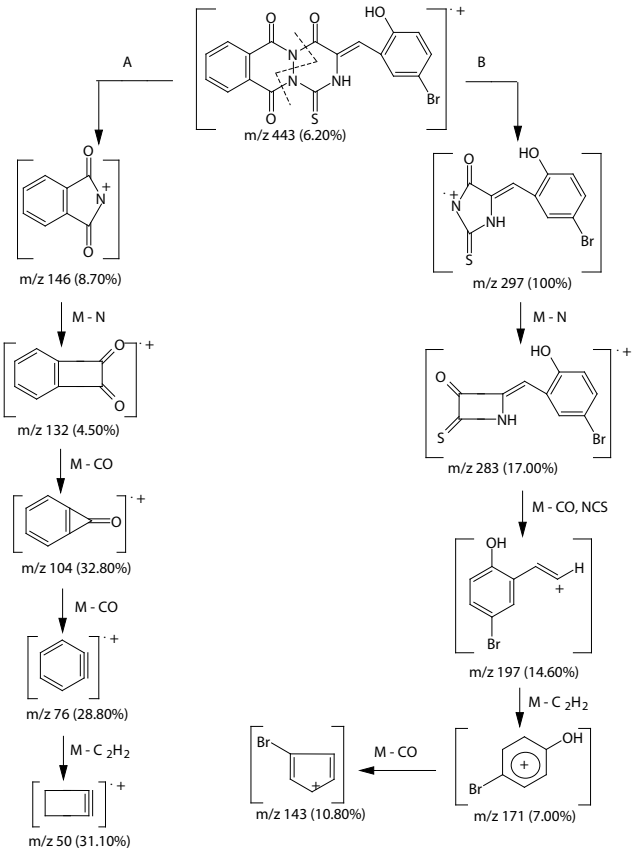
Subequently, the molecular ion of m/z 261 fragmented via the pathway B by a cleavage of methylene carbonyl and isothiocyanate groups (CH_2CO, NCS) to give the peak at m/z 161, which lost thiocyanate (NCO) to give peak at m/z 119. It further underwent loss of oxygen atom, cyano group and acetylene molecule to give peaks at m/z 103, 77 and m/z 51, respectively.

The molecular ion peak of compound 5 was observed at m/z 303, corresponding to the molecular formula $C_{13}H_9N_3O_4S$. The loss of methylene carbonyl molecule from the molecular ion peak at m/z 303 gave a base peak at m/z 261 (molecular ion of compound 4). The molecular ion peak of diacetl derivative (6) was observed at m/z 345, corresponding to the molecular formula $C_{15}H_{11}N_3O_5S$. The loss of methylene carbonyl molecule from the molecular ion peak at 345 gave a fragment ion of m/z 303, corresponding to the molecular ion of compound 5.

The fragment ion at m/z 303 underwent fragmentation to produce a stable peak at m/z 261, corresponding to the molecular ion of compound 4 by losing methylene carbonyl molecule. The stable ion of m/z 261 which has further broken via similar way of compound 4 (Scheme 3).

Compounds 7 and 8

The mass spectra of compound 7 (Fig. 5) showed an intense molecular ion peak at 339, corresponding to the molecular formula $C_{11}H_6N_3BrO_3S$. The M+2 was observed



Scheme 4. Main fragmentation pathway of compounds 8b

along with the molecular ion peak due to the presence of isotopes bromine atom in the compound. The formation of a stable ion m/z 260 could be explained due to loss of bromine atom from the molecular ion peak (M-Br). The possible fragmentation pathway of compound 7 was summarized in table 1.

The molecular ion peak of compound 8a and 8b was observed at m/z 365 and m/z 443 (Fig. 6), corresponding to the molecular formula $C_{18}H_{11}N_3O_4S$ and $C_{18}H_{10}N_3BrO_4S$. From study the mass spectra of the compounds 8a, 8b, it was found that the molecular ion for all these compounds fragmented further into involved to pathways as illustrated in Table 1 and Scheme 4.

The molecular ion of compound 8b (m/z 443) fragmented via the pathway A to give peak at m/z 146, corresponding to the molecular ion radical cation of phthalamide. It further underwent loss of nitrogen atom, carbon monoxide and acetylene to give peaks at m/z 132, 104, 76 and m/z 50, respectively.

Accordingly , the same molecular ion of m/z 443 fragmented via the pathway B by a cleavage phthalamide radical cation molecule to give the stable fragment ion at m/z 297. The stable fragment ion at m/z 297 underwent fragmentation to produce peaks at m/z 283, 197, 171, 143 and m/z 63 by losing nitrogen atom, carbon monoxide, isothiocyanate, acetylene, carbon monoxide and hydrogen bromide, respectively .

Biological activity

Some synthesized compounds were assayed against Gram positive bacteria (such as Bacillus Subtilis, Streptococcus Penumonia and Staphylococcus Aureus), Gram negative bacteria (such as Escherishia Coli and Pesudomonas Sp.) and Fungi (namely, Aspergillus Nigaer and Penicillium Sp.) following agar-diffusion technique.[13,14]

The compounds were tested at 100 µg /mL concentration and the activity was determined by measuring the zone of inhibition (Table 2) .

All compounds showed activity against bacteria , while compounds No. 3 and 7 did not exhibit any activity against Staphylococcus Auraes and Streptococcus Penumonia . Also , All compounds were active against Fungi, except compounds No. 7 and 8b were non active against Aspergillus Nigaer.

Experimental

NMR spectra were recorded on a General Electric QE300 instrument and chemical shifts were given with respect to TMS. IR spectra were recorded on a perkin-Elmer 1420 spectrometer and a Biorad FTS7(KBr). Mass spectra were recorded on GC/MS with CI (chemical ionization) and a Hewlett-Packard MS-Engine Thermospray and ionization by electron impact to 70 eV. The accelerating voltage was 6KV, the the temperature of the ion source was ≅ 200°C and the emission current ≅ 100 mA.

Microanalyses were conducted using an elemental analyzer 1106. Melting points were determined on MEL.TEMPII melting point apparatus and uncorrected.

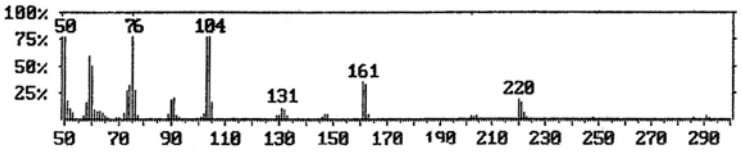


Figure 1: 70 ev mass spectrum of compound 2

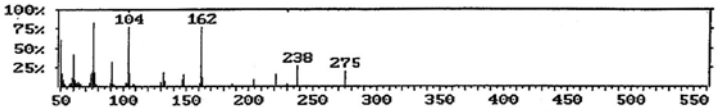


Figure 2: 70 ev mass spectrum of compound 3

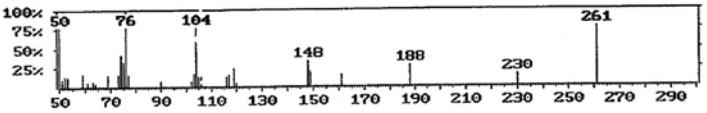


Figure 3: 70 ev mass spectrum of compound 4

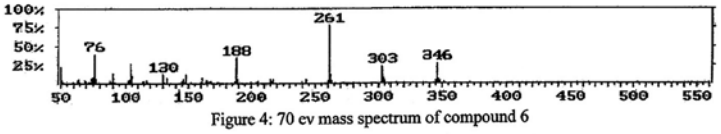


Figure 4: 70 ev mass spectrum of compound 6

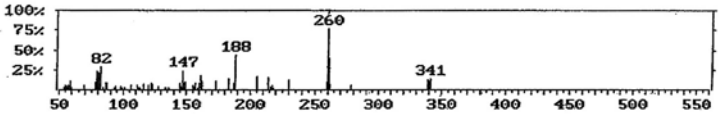


Figure 5: 70 ev mass spectrum of compound 7

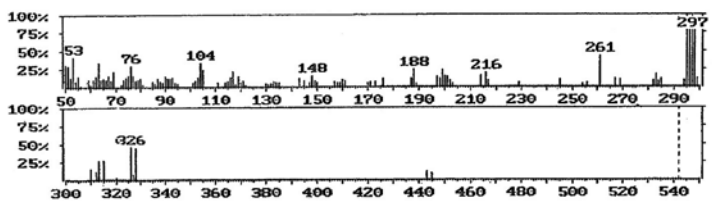


Figure 6: 70 ev mass spectrum of compound 8b

Table 1: EI Mass spectra (70 eV) of compounds 2-8, m/z creative intensity, %)

Comp	M+	Pathway A		Pathway B		Other ions
		-M	m/z	-M	m/z	
2	$[C_{12}H_7N_3O_2S]^+$ 221(3.90)	$CSNH_2$ N NH CO CO C_2H_2	$[C_9H_5N_3O_2]$+ 161(34.80) $[C_8H_7NO_2]$+ 147(4.10) $[C_8H_5O_2]$+ 132(8.30) $[C_7H_5O]$+ 104(89.60) $[C_6H_4]$+ 76(100) $[C_4H_3]$+ 50(90.50)	CSNH N OH CO CN C_2H_2	$[C_8H_6N_2O_2]$+ 162(32.00) $[C_8H_8N_2O_2]$+ 148(3.70) $[C_8H_6NO]$+ 131(10.10) $[C_7H_5N]$+ 103(79.20) $[C6H_3]$+ 77(28.80) $[C_4H_3]$+ 51(17.00)	222(M+1, 1.30), 220(4.50), 203(1.40),163(4.50), 149 (1.30), 146(1.40), 133(3.20) , 130(3.10), 118(1.20), 117(1.10), 105(15.70), 102(3.40), 92(2.70), 91(19.30), 90(18.40), 78 (2.50), 75(87.0), 74 (31.30), 73(26.60), 63 (7.30), 62(7.20), 61(8.80), 60(50.20), 59(59.10), 58(15.30), 52(9.30)
3	$[C_{12}H_9N_3O_3S]^+$ 275(20.01)	CO, C_2H_2 $CSNH_2$ N NH CO CO C_2H_2	$[C_9H_7N_3O_2S]^+$ 221(14.80) $[C_8H_6N_2O_2]^+$ 161(4.10) $[C_8H_6NO_2]^+$ 147(8.10) $[C_8H_5O_2]^+$ 132(18.00) $[C_6H_4O]^+$ 104(100) $[C_6H_4]^+$ 76(82.10) $[C_4H_3]^+$ 50(60.40)	CO, C_2H_2 S=C=NH N OH CO CN C_2H_2	$[C_9H_7N_2O_2S]^+$ 221(14.80) $[C_8H_6N_2O_2]^+$ 162(90.30) $[C_8H_6NO_2]^+$ 148(15.90) $[C_8H_6NO]^+$ 131(5.40) $[C_7H_5N]^+$ 103(4.80) $[C_6H_5]^+$ 77(18.30) $[C_4H_3]^+$ 51(16.70)	276(M+), 2.10), 204(7.90) , 187(2.40), 163(11.50), 133(6.70), 108(3.30), 105 (17.00), 102(3.70), 93 (2.10), 92(2.50), 91(31.10) , 90(4.70), 78(3.50), 75 (17.80), 74(15.20), 73 (4.20), 62(4.60), 61(8.50), 60(41.80), 59(11.50), 52(8.60).
4	$[C_{11}H_7N_3O_2S]^+$ 261(42.70)	C_2H_3NS 2NCO CO C_2H_2	$[C_9H_6N_2O_2]^+$ 188(13.80) $[C_7H_5O]^+$ 104(89.90) $[C_6H_4]^+$ 76(100) $[C_4H_3]^+$ 50(79.80)	CH_2CO, NCS NCO O CN C_2H_2	$[C_8H_6N_2O_2]^+$ 161(7.30) $[C_7H_5NO]^+$ 119(11.90) $[C_7H_5N]^+$ 103(17.00) $[C_6H_5]^+$ 77(14.70) $[C_4H_3]^+$ 51(9.60)	230(7.80), 149(9.60), 148(16.50), 120(1.80), 119(7.30), 116(6.40), 105(12.80), 102(6.90), 90(7.30), 75(31.20), 74(40.80), 73(14.70), 64(15.60), 64(4.60), 63(7.30), 61(5.50), 59 (16.50), 53(12.40), 52 (13.80).
5	$[C_{13}H_9N_3O_3S]^+$ 303(6.23)	CH_2CO C_2H_3NS 2NCO CO C_2H_2	$[C_{11}H_7N_3O_2S]^+$ 261(100%) $[C_8H_7N_2O_3]$ 188(2.30) $[C_7H_4O]^+$ 104(19.10) $[C_6H_4]^{+\cdot}$ 76(17.20) $[C_4H_3]^+$ 50(19.10)	CH_2CO CH_2CO, NCS NCO O CN C_2H_2	$[C_{11}H_7N_3O_2S]^+$ 261(100%) $[C_8H_6N_2O_3]$ 161(57.40) $[C_7H_5NO]$ 119(13.20) $[C_7H_5N]^+$ 103(13.20) $[C_6H_5]^+$ 77(4.30) $[C_4H_3]$ 51(6.40)	304(2.30), 262(5.20), 260(58.20), 149(57.40), 147(23.40), 132(34.00), 131(46.80), 130(8.50), 113 (23.40), 112(36.20), 111(44.70), 86(10.60), 84(14.90), 66(12.80), 57(17.00).
6	$[C_{15}H_{11}N_3O_5S]^{+\cdot}$ 345(3.70)	CH_2CO CH_2CO C_2H_3NS 2NCO CO C_2H_2	$[C_{13}H_9N_3O_3S]^{+\cdot}$ 303(21.90) $[C_{11}H_7H_3O_3S]^{+\cdot}$ 261(100) $[C_8H_6N_2O_3]^{+\cdot}$ 1188(33.40) $[C_7H_5O]^{+\cdot}$ 104(26.60) $[8H_4]^{+\cdot}$ 76(38.10) $[C_4H_3]^{+\cdot}$ 50(21.50)	CH_2CO CH_2CO CH_2CO, NCS NCO O CN C_2H_2	$[C_{13}H_9N_3O_3S]^{+\cdot}$ 303(21.90) $[C_{11}H_7H_3O_3S]^{+\cdot}$ 261(100%) $[C_8H_6N_2O_2]^{+\cdot}$ 161(7.50) $[C_7H_5NO]^{+\cdot}$ 119(1.30) $[C_7H_5N]^{+\cdot}$ 103(5.90) [8H5]+ 77(6.60) $[C_4H_3]^+$ 51(4.00)	346($M^{+\cdot}$,`, 25.80), 304(7.40), 302(1.40), 262(12.60), 260(4.00) 217(5.10), 215(5.90), 184(5.60), 187(3.10), 160(1.50), 148(10.60), 146(6.00), 131(1.60), 130(10.60), 118(1.70), 118(1.70), 117(3.80), 105(11.50), 102(4.30), 90(14.40), 75(8.30), 64(5.10), 63(4.10), 59(1.50), 52(1.50).
7	$[C_{11}H_6N_3BrO_3S]^+$ 339(11.9)	-Br CH=NH CS CO	$[C_{11}H_6N_3O_3S]^+$ 260(100) $[C_8H_6N_3O_2]^+$ 188(44.10) $[C_8H_6N_2O_2]^+$ 60(8.10)	-HBr CO, CN CS N	$[C_{11}H_6N_3O_3S]^+$ 259(10.10) [C9H5N2O2S]+ 205(16.80) $[C_8H_6N_2O_2]^+$ 161(17.40) $[C_8H_6NO_2]^{+\cdot}$ 147(24.10)	341($M^{+\cdot}$2, 13.60), 278(5.20), 261(40.0), 230(13.00), 214(14.8), 187(8.70), 183(13.30), 173(11.30), 162(11.30), 159(2.90), 149(9.90), 148(7.80), 146(4.60), 136(2.60), 134(3.50), 133(3.20), 123(6.70), 122(9.00), 116(7.00), 111(5.20), 98(4.60), 82(29.30), 81(20.40), 80(22.3), 79(23.20)
8a	$[C_{18}H_{11}N_3O_4S]^{+\cdot}$ 365(2.30)	$C_{10}H_7N_2O_2S$ N CO CO C_2H_2	$[C_8H_4NO_2]^+$ 146(18.76) $[C_8H_4O_2]^+$ 132(6.80) $[C_7H_5O]^{+\cdot}$ 104(31.20) $[C_6H_4]^{+\cdot}$ 76(12.0) $[C_4H_3]^+$ 50(14.50)	$C_8H_4NO_2$ N CO, NCS C_2H_2 O C_2H_2	$[C_{10}H_7N_2O_2S]^+$ 219(100) $[C_{10}H_7NO_2S]^{+\cdot}$ 205(12.30) $[C_7H_5O]^+$ 119(49.30) $[C_7H_5O]^+$ 93(23.50) $[C_6H_5]$+ 77(48.00) $[C_4H_3]$+ 51(36.70)	366($M^{+\cdot}$1, 1.30), 364(9.20), 218(52.1), 218(43.20), 188(8.20), 187(1.90), 161(2.30), 160(6.90), 148(12.30), 147(5.20), 133(3.50), 131(2.90), 120(21.20), 118(17.20), 45(28.10), 92(14.50), 91(28.10), 78(44.30), 66(16.70), 65(45.70), 64(29.90), 63(48.40), 54(25.8), 58(25.80), 53(15.90)
8b	$[C_{18}H_{10}N_3BrO_4S]^+$ 443(6.20)		$[C_8H_4NO_2]^+$ 146(5.70) $[C_8H_4O_3]^{+\cdot}$ 132(4.50) $[C_7H_5O]^{+\cdot}$ 104(32.80) $[C_6H_4]^{+\cdot}$ 76(28.80) $[C_4H_3]^{+\cdot}$ 50(31.10)	$C_8H_4NO_2$ N CO, NCS C_2H_2 CO HBr	$[C_{10}H_6N_2BrO_2S]^+$ 297(100) $[C_{10}H_6NBrO_2S]^{+\cdot}$ 283(17.00) $[C_6H_6BrO]^+$ 197(14.60) $[C_6H_6BrO]^+$ 171(7.00) $[C_4H_4Br]^+$ 143(10.80) $[C_5H_3]^+$ 63(33.30)	445(5.20), 328(11.20), 327(1.70), 326(11.40), 315(26.10), 313(25.40), 312(11.70), 310(15.50) 299(11.70), 298(83.90), 296(86.90), 295(98.30), 285(11.60), 284(7.40), 282(9.10), 216(18.80), 214(15.30), 199(22.40), 198(11.40), 189(4.90), 188(23.50), 187(11.70), 173(6.60), 148(15.50), 147(5.90), 145(8.70), 119(13.60), 117(20.60), 105(23.90), 103(13.10), 93(12.30), 91(11.20), 77(15.70), 75(15.70), 69(20.80), 64(10.40), 62(14.00), 59(10.20), 55(13.30), 53(40.70), 51(29.40).

Table 2 Antimicrobial activity of some prepared compounds 2-8

(-) No Clearing Zone (+) Small Clearing Zone
(++) Medium Clearing Zone (+++) Large Clearing Zone

Comp No.	Antifungal Activity		Antimicrobial activity				
			Gram Negative Bacteria		Gram Positive Bacteria		
	Penicillium Sp.	**Aspergillus** *Nigaer*	*Pesudomo-nas Sp.*	*E.Coli*	*Staphylococcus Aureas*	*Streptococcus Penumonia*	*Bacillus Subtilis*
2	+	+++	++	+++	+	+++	+++
3	++	+	+	+++	-	+	+++
4	+	+	++	++	++	+	++
7	++	-	+++	+	++	-	+++
8b	++	-	+	+++	+	+	+

2-Aminothiocarbonyl-phthalazine-1,4-dione (2)
A mixture of 1 (0.01 mol) and thiosemicarbazide (0.01 mol) in methanol (50 mL) was heated under reflux for 2 h, then colled. The solid obtained was filtered off, washed with methanol, dried and purified by acetic acid to give 2 as colourless crystals, yield 87%, m.p. 185°C. IR spectrum (KBr): 3336, 3191 (NH_2), 3264 (NH), 1685(C=O), 1622, 1585 (C=C), 1393 (C=S) cm^{-1}. ^1H NMR spectrum (DMSO-d_6) δ: 3.92(s, 2H, NH_2), 7.36-8.06(m, 4H, ArH), 10.35 (s, 1H, NH). ^{13}C-NMR (DMSO-d_6) δ: 183.27(C=S), 167.87(C=O), 136.72, 132.30, 129.64, 128.65, 128.09(C aryl).
Anal.Calcd for $C_9H_7N_3O_2S$: C, 48.87; H, 3.17; N, 19.00; S, 14.48. Found: C, 48.63; H, 3.09; N, 18.86, S,14.24.

5-Oxo-1-thioxo-2,3,4-trihydro-1,2,4-triazapino[1,2-b] phthalazine -6,11-dione (3).
4-Oxo-1-thioxo-2,3-dihydro-1,2,4-triazino[1,2-b]-phthalazine-5, 10-dione (4).
A mixture of 2 (0.01 mol), ethyl chloropropionate and ethyl chloroacetate (0.01 mol) in methanol (50 mL) in presence of fused sodium acetate (0.03 mol) was heated under reflux for 4h, then cooled and poured into water. The resulting solid was filtered off, washed with water, dried and purified by recrystallization from a suitable solvent to give 3 and 4.

Compound 3 was obtained as colourless crystals, yield 53%, m.p. 200°C. IR spectrum (KBr): 3282(NH), 1728, 1685 (C=O), 1623, 1596, 1533 (C = C), 1389 (C = S) cm^{-1}. ^1H NMR spectrum (DMSO-d_6) δ: 3.32-3.51(br.m, 4H, $NHCH_2CH_2CO$), 7.23-8.12(m, 4H, ArH), 10.35(s, 1H, NH). ^{13}C-NMR spectrum (DMSO-d_6) δ: 182.33(C=S), 167.86, 165.23(C=O), 136.86, 132.32, 129.68, 128.77, 128.12 (C-aryl), 38.6, 40.26 ($2XCH_2$). Anal. Calcd for $C_{12}H_9N_3O_3S$: C, 52.36; H, 3.27; N, 15.27; S, 11.64. Found: C, 52.07; H, 3.11; N, 15.09; S, 11.36.

Compound 4 was obtained as colourless crystals, yield 67%, m.p. 270°C. IR spectrum (KBr): 3213 (NH), 1720, 1695 (C=O), 1614, 1582 (C=C), 1392 (C=S) cm^{-1}. ^1H NMR spectrum (DMSO-d_6) δ: 4.20(s, 2H, $NHCH_2CO$), 7.23-7.89(m, 4H, ArH), 10.35(s, 1H, NH). ^{13}C-NMR Spectrum (DMSO-d_6) δ: 184.30(C=S), 167.31, 163.70(C=O), 136.62, 132.35, 129.59, 128.71, 128.12(C-aryl), 52.10 (NCH_2CO). Anal. Calcd for $C_{11}H_7N_3O_3S$: C, 50.57; H, 2.68; N, 16.09; S, 12.26. Found: C, 50.45; H, 2.49; N, 15.83; S, 12.01.

2-Acetyl-4-oxo-1-thioxo-2,3-dihydro-1,2,4-triazino[1,2-b] phthalazine-5,10-dione (5)
A solution of 4 (0.01 mol) in acetic anhydride (25 mL) was heated under reflux for 2 h, then cooled and poured onto ice-water. The resulting solid was filtered off, washed with water, dried and purified by recrystillazation form ethanol to give 5 as colourless, yield 51%, m.p. 150°C. IR spectrum (KBr): 1720, 1689 (CO), 1610, 1505, 1583 (C=C), 1398 (C=S) cm^{-1}. ^1H NMR. Spectrum (DMSO-d_6) δ: 2.60(s, 3H, $COCH_3$), 4.01(s, 2H, NCH_2CO), 7.31-7.92 (m, 4H, ArH). ^{13}C-NMR spectrum (DMSO-d_6) δ: 182.81(C=S), 167.32, 165.20(C=O), 135.92, 134.61, 129.21, 127.63, 124.58(C-anyl), 53.20(NCH_2CO), 26.32($\underline{C}H_3CO$). Anal. Calcd for $C_{13}H_9N_3O_4S$: C, 51.48; H, 2.97; N, 13.86; S, 10.56. Found : C, 51.27; H, 2.71; N, 13.63; S, 10.33.

2,3-Diacetyl- 4 -oxo- 1 -thioxo-2,3-dihydro-1,2,4-triazino[1,2-b]- phthalazine-5,10-dione (6)
A mixture of 4 (0.01 mol) and fused sodium acetate (0.02 mol) in acetic anhydride (25 mL) was heated under reflux for 3 h, then cooled and poured into ice-diluted hydrochloric acid, the resulting product was filtered off, washed with water, dried and purified by recrystallizaiton with ethanol to give 6 as colourless, yield 62%, m.p. 160 °C. IR spectrum (KBr): 1718-1705 (br. CO), 1689 (C=O), 1612, 1585 (C=C), 1399 (C=S) cm^{-1}. ^1H NMR spectrum (DMSO-d_6), δ: 2.30(s, 3H, $COCH_3$), 2.55(s, 3H, $COCH_3$) 7.01(s, 1H, $NCH(CO)_2$), 7.42-8.01(m, 4H, ArH), ^{13}C-NMR (DMSO-d_6), δ: 187.20(C=S), 167.30, 165.28, 163.38(C=O), 135.92, 134.69, 133.10, 129.13, 127.65, 123.54(C-aryl), 26.48 (CH_3), 20.22 (CH_3). Anal- Calcd. For $C_{15}H_{11}N_3O_5S$: C, 52.17; H, 3.19; N, 12.17, S, 9.27. Found : C, 51.93; H, 3.02; N, 11.97; S, 9.01.

3- Bromo - 4- oxo - 1- thioxo - 2, 3-dihydro -1, 2, 4- triazino [1, 2-b] phthalazine -5, 10 - dione (7)
A solution of 4 (0.01 mol) in glacial acetic acid (30 mL). was added to a solution of bromine (0.01 mol) in glacial acetic acid (10 mL) with stirring at room temperature for 2h, the solid obtained was filtered off, washed with water, dried and purified by recrystallization with ethanol to give 7 as pale yellow crystals, yield 64%, m.p. 290°C. IR spectrum (KBr): 3218 (NH), 1738-1705 (br. C=O), 1612, 1582 (C=C), 1397 (C=S) cm^{-1}. ^1H NMR spectrum (DMSO-d_6), δ: 6.5 (s, 1H, COCHBr), 7.41-8.01(m, 4H, ArH), 10.42 (s, 1H, NH). ^{13}C-NMR spectrum (DMSO-d_6), δ: 183.20(C=S), 167.20, 163.62(C=O), 139.20, 134.78, 131.31, 129.97, 123.38(C-

aryl), 53.20(-CHBr). Anal-Calcd for $C_{11}H_6N_3BrO_3S$: C, 38.93; H, 1.77; N, 12.39; Br, 23.30; S, 9.44. Found : C, 38.67; H, 1.52; N, 12.12; Br, 23.03; S, 9.29.

3-Arylidene - 4- oxo - 1- thioxo - 1, 2, 4- triazino [1, 2-b] phthal-azine-5,10-dione (8)

A mixture of 4 (0.01 mol), aromatic aldehydes (namely 2-hydroxybenzaldehyde and 5-bromo-2-hydroxylbenzaldehyde, 0.01 mol) and piperidine (1 mL) was fused on a hot plate at 120-125°C.

The reaction mixture was cooled and acidified with dilute hydrochloric acid (2 N). The crude product was filtered off, washed with water, dried and purified by recrystallization with ethanol to give 8.

3-(2-Hydroxy)benzaldehyde-4-oxo-1-thioxo-1, 2, 4-triazino[1, 2-b]phthalazine-5,10-dione (8a) as yellow crystals, yield 71%, m.p. 285°C. IR spectrum (KBr): 3192 (NH), 3350-2653 (br.OH), 1719-1695(br. C=O), 1605, 1566 (C=C), 1401 (C=S), 1200, 1115 (C-O) cm^{-1}. ^1H NMR(DMSO-d_6), δ: 7.01-8.12(m, 9H, ArH and olefinic proton), 10.32(s, 1H, NH), 11.43(s, 1H, OH). Anal. Calcd for $C_{18}H_{11}N_3O_4S$: C, 59.18; H, 3.01; N, 11.51; S, 8.77. Found: C, 59.02; H, 2.84; N, 11.37; S, 8.49.

3-(5-Bromo-2-hyaroxy)-benzaladehyde-4-oxo-1-thioxo-1, 2, 4- triazino[1,2-b]phthalazine-5,10-dione (8b) as pale yellow crystals, yield 73%, m.p. 230 °C. IR spectrum (KBr): 3352-2741 (br. OH), 3209 (NH), 1723-1698 (br. C-O), 1617, 1585 (C = C), 1413 (C = S), 1179, 1114 (C – O) cm^{-1}. ^1H-NMR spectrum (DMSO-d_6), δ: 6.98-8.01(m, 8H, ArH and olefinic proton), 10.36(s, 1H, NH), 11.42(s, 1H, OH). Anal. Calcd for $C_{18}H_{10}N_3BrO_4S$: C, 48.76; H, 2.26; N, 9.48; Br, 17.83; S, 7.22. Found : C, 48.50; H, 2.07; N, 9.22; Br, 17.61; S, 7.01.

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