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UTILIZATION OF DIBEZOBARRELENE IN SYNTHESIS OF NEW POLYNUCLEAR HETEROCYCLIC NITROGEN COMPOUNDS

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ABSTRACT

Phthalazinediones 2_{a-d}, 5_{a-c} and 7 were yielded from the reaction of dibenzobarrelene **1** with hydrazides. 2_d was acetylated and sulphonated to get **3** and **4**, respectively. Reaction of **5a-c** with formaldeyde in acetic acid gave polynuclear heterocyclic compounds **6a-c**. 7 was reacted with cyclic ketones and aromatic aldehydes to produce thiopheno and acrylonitrile derivatives **8** and **9**, respectively. Benzoimidazole **10** and isoindoledione derivative **11** were yielded from reaction of **1** with *o*-phenylenediamine in acetic acid and dimethylformamide, respectively. Acetylation of **11**, acetamide derivative **12** was obtained. Unexpected product **13** was produced when **11** reacted with 1,2-naphthoquinone-4-sulphonic acid sodium salt . Mixture of **14** and **15** was obtained from reaction of **1** with *o*-aminothiophenol, while the reaction of **1** with *o*-aminophenol compound **16** was achieved alone. Reaction of **1** with ethylenediamine gave **18**, **19** or **20** depending on the used solvent **21** was produced from reaction of **1** with ethanolamine in acetic acid . The structures of the new synthesizied products were established by spectral data. Antibacterial activity of all these products was tested. Compoud **4** show high significance activity.

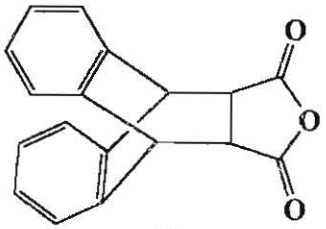
INTRODUCTION

The compounds containing pyridazine ring besides occupying a position of considerable significance in the pesticide activities **[Vaclav *et al.*(1980); Moriya *et al.*(1983) and Mitsubishi(1980)]**, are used as plant-growth regulators **[Toshihiko *et* al.(1983)]** hypertensive materials

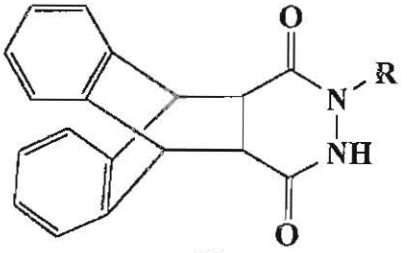
[Shatalov, *et al.*, (1982)], anti-inflammatory agents **[Leonids, et al. (1994)]** and anti-fouling agents **[Ihara (1980)]**. All these biological and physiological activities prompted us to synthesise hithereto unknown compounds containing pyridazine ring incorporated with dibenzobarralene (1) **[Giguere *et al.* (1986); Horyna *et al.* (1983) and Kalindjian *et al.* (1995)]** of expected biological activity.

RESULTS AND DISCUSSION

Thus, refluxing of **1** and appropriate acid hydrazide namely, salicylic acid hydrazide **[Fox *et al.*(1952)]**, *p*-chlorobezoic acid hydrazide **[Laroch (1960)]**, nicotinic acid hydrazide **[Fox *et al.* (1952)]** and benzenesulphonic acid hydrazide in acetic acid or dimethylformamide afforded phthalazinedione derivatives $\mathbf{2}_{a\text{-}d}$ in 72-86% yield. $\mathbf{2}_{d}$ was reacted with acetic anhydride and *p*-toluenesulphonyl chloride in presence of drops of triethylamine to yield phethalazines **3** and **4**, respectively (Scheme 1).

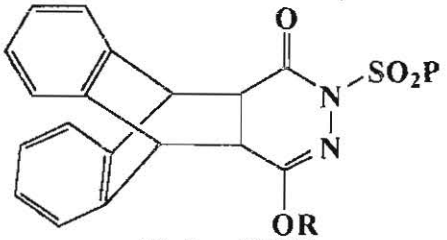


(1)



(2)

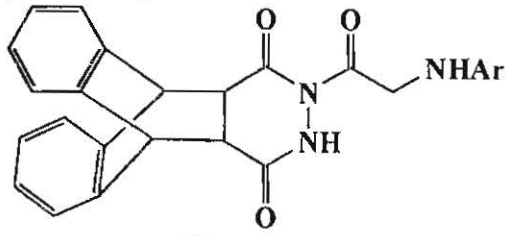
a; R = CO-C_6H_4-2-OH
b; R = CO-C_6H_4-4-Cl
c; R = CO-4-pyridyl
d; R = SO_2-C_6H_4



(3); R = $COCH_3$
(4); R = $SO_2 - C_6H_4 - 4$ - Me

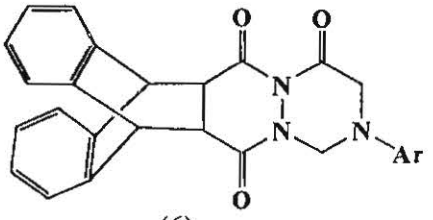
Scheme 1

Further, 2-arylaminoacetic acid hydrazide (namely, 2-anilinoacetic acid hydrazide, *2-p*-toludinoacetic acid hydrazide and 2-*p*-chloroanilinoacetic acid hydrazide) **[Passeron *et al.* (1963)]** were refluxed with **1** in dimethylformamide, phthalazinedione $\mathbf{5}_{a\text{-}c}$ were yielded. Cyclization of $\mathbf{5}_{a\text{-}c}$ to novel heterocyclic compounds $\mathbf{6}_{a\text{-}c}$ were accomplished by reaction of $\mathbf{5}_{a\text{-}c}$ with formaldehyde in acetic acid (Scheme 2).



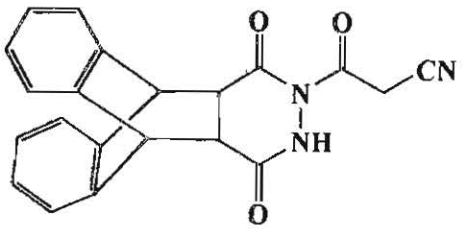
(5)

a; Ar = C_6H_5
b; Ar = 4-MeC_6H_4
c; Ar = 4-ClC_6H_4



(6)

a; Ar = C_6H_5
b; Ar = 4-MeC_6H_4
c; Ar = 4-ClC_6H_4



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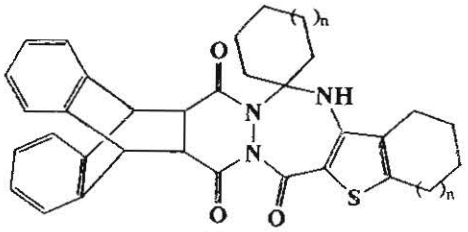
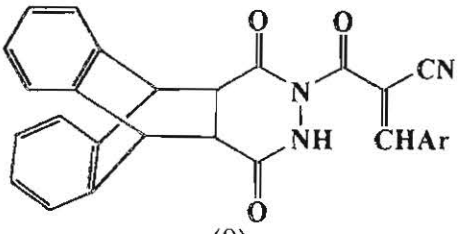


(8)

a; n = 1
b; n = 0



(9)

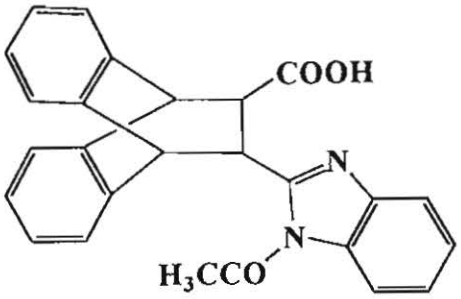
a; Ar = C_6H_5
b; Ar = 4-$MeOC_6H_4$

Scheme 2

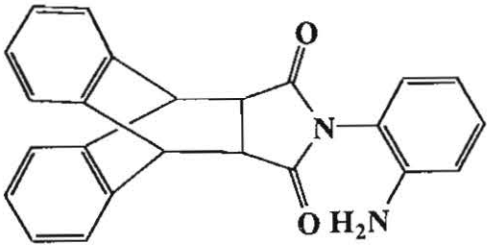
Furthermore, cyanoacetic acid hydrazide **[Fox *et al.* (1952)]** was reacted with **1** in dimethylformamide to produce phthalazinedione **7**. Reaction of **7** with cyclohexanaone or cyclopentanone in 1:2 molar ratio under Gewald reaction conditions **[Arya (1972)]**, polynuclear products $\mathbf{8_{a,b}}$ were achieved in lower yield. Also, reaction of **7** with benzaldehyde or *p*-anisaldehyde in the prescence of sodium methoxide for 15 min. gave acrylonitrile derivatives $\mathbf{9_{a,b}}$,respectively (Scheme 2). ^{13}C-NMR spectrum of $\mathbf{8_a}$ indicated signals at δ 21.8 , 22.1 , 23.1 , 23.8 , 24.5 , 24.9 , 25.3 , 25.7 and 26.9 characteristic for methylene carbons , in addition to signals at δ 78.5 , 139.5 , 128.2 , 126.6 , 125.0 , 177.3 , 177.1 and 174.6 characteristic for spiro , thiophene and carbonyl carbons, respectively.

An extension of our study to synthesis of polynuclear heterocyclic nitrogen compounds **[Berghot *et al.* (2004)]**, **1** was refluxed with equimolar amount of *o*-phenylinediamine in acetic acid to afford N-acetylbenzimidazole derivative **10**, while N-phenylsuccinimide derivative **11** was formed when the same reaction was carried out in dimethylformamide or dioxane/pyridine. The product **11** was next acetylated with acetyl chloride and triethylamine to give acetamide derivative **12** (Scheme 3). Structures of **10**, **11** and **12** were confirmed on the spectral data. It is not worthily that the molecular ion peaks of both **10** and **12** are the same but the fragmentation pattern are different.

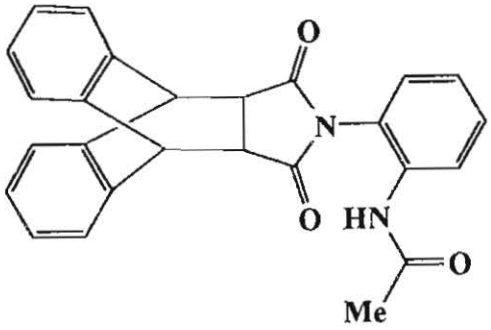
Also, compound **11** was reacted with 1,2-naphthoquinone-4-sulphonic acid sodium salt in water/dimethylformamide (1:1 v) to give unexepected product **13** in good yield. **13** was formed according to plausible mechanism in Scheme 4. Structure of **13** was established on the basis of mass, ^{1}H-NMR and ^{13}C-NMR spectra. Also, **1** was reacted with *o*-aminothiophenol in acetic acid, dimethylformamide or dioxane/pyridine to yield a mixture of **14** and **15**. Whereas, using *o*-aminophenol under the same conditions isoindol derivative **16** was obtained as a single product. **16** was sulphonated with *p*-toluenesulphonyl chloride in dimethylformamide and in the presence of triethylamine to give the corresponding ester derivative **17** in fair yield (Scheme 5). Structures of **14, 15, 16** and **17** were assigned on the basis of their spectroscopic data, especially the mass spectra.



(10)



(11)



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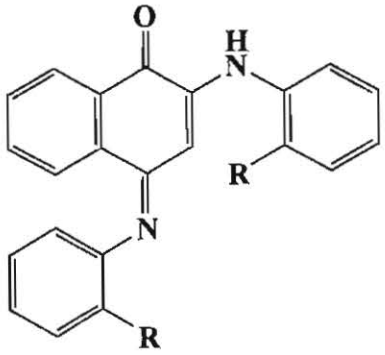

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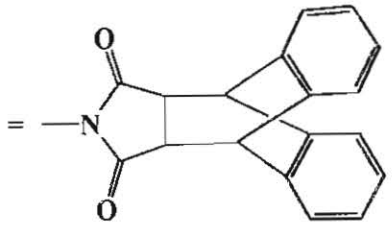
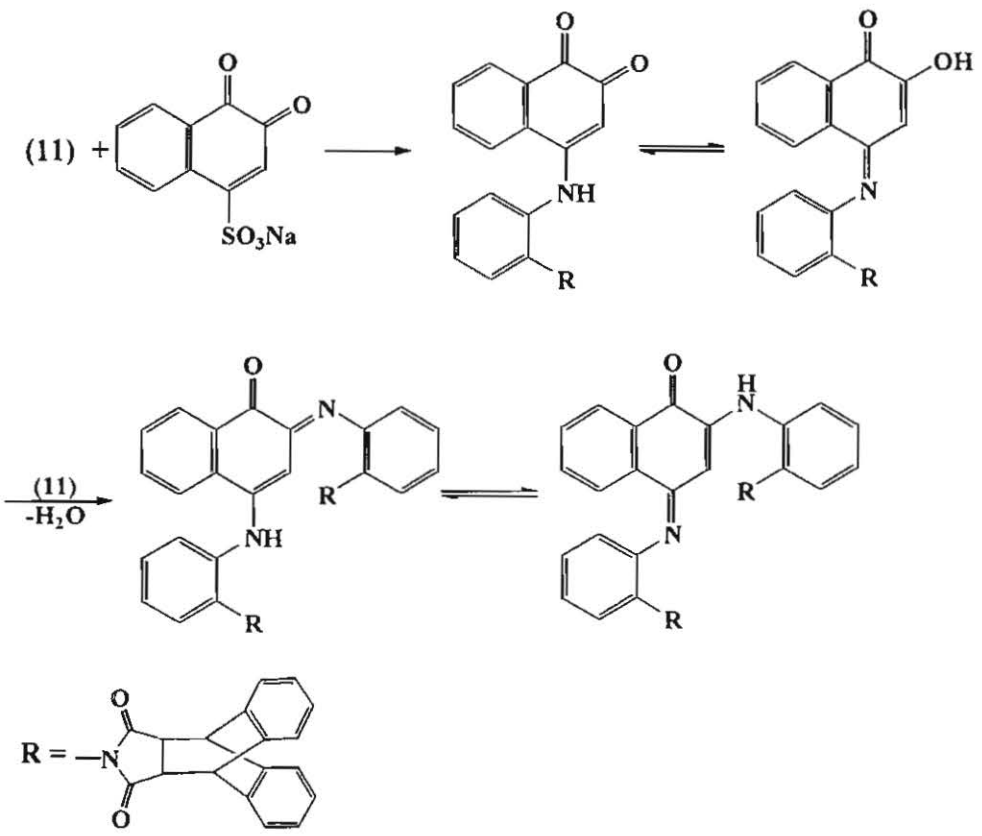
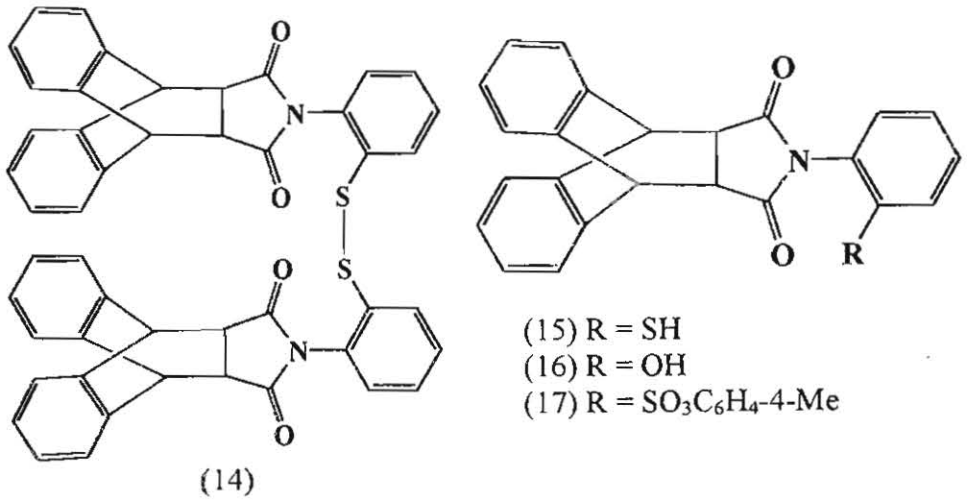


Scheme 3



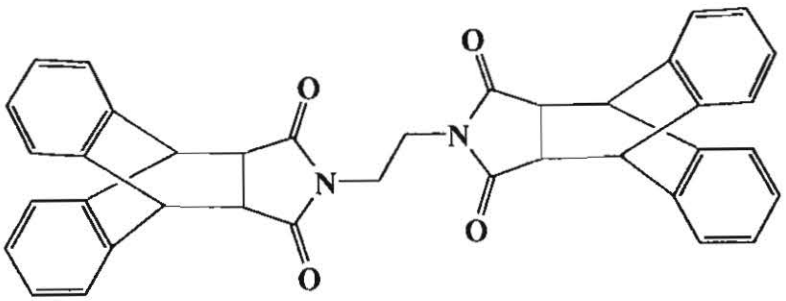
Scheme 4



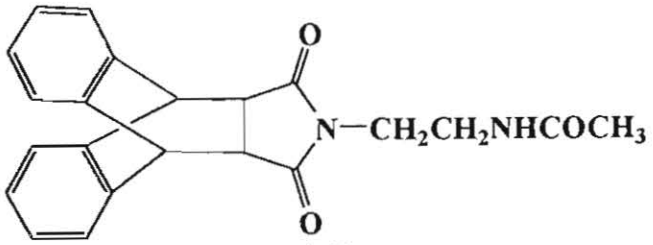
(14)

(15) R = SH
(16) R = OH
(17) R = $SO_3C_6H_4$-4-Me

Scheme 5



(18)



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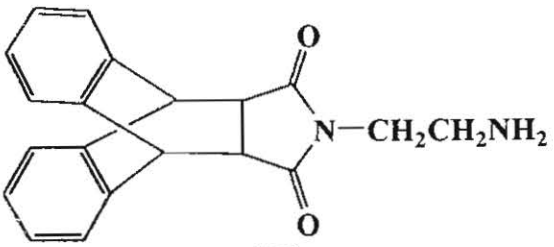

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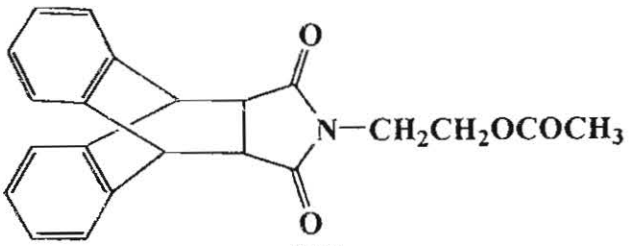

(21)

Scheme 6

Furthermore, treatment of **1** with ethylenediamine in acetic acid afforded a mixture of bis-compound **18** and N-ethylacetamido derivative **19**. While a mixture of **18** and **20** was yielded when the reaction took place in dimethylformamide. **18** was formed alone when the reaction carried out in dioxane/pyridine. Acetylation of **20** with acetic unhydride and pyridine turned to **19** (Scheme 6). Structures **20** and **19** were supported by the spectral data.

Finally, treatment of **1** with ethanolamine in acetic acid gave ethyl ester derivative **21** (Scheme 6) as established by ^{1}H and ^{13}C-NMR spectra.

ANTIBACTERIAL SCREENING

All new synthesized compounds were subject for testing of the potentional antibacterial activity by the Agar diffusion method [**Jain *et al.* (1971)**] *Bacellus theringensis* and *Escherichia coli* were used as test organisms. Septazole solution was used as a standerd material. The resulting inhibition zones against these bacteria are listed in table 1. The present data in table 1 indicate compounds **2b**, **2d** , **3** and **4** show extremely high activities against both *Bacellus theringensis* and *Escherichia coli*. Compounds $\mathbf{5_c}$, 7, and **8** show high activity with selectivity against Bacellus theringensis and moderate activity against *Escherichia coli*. Compound **2a** , **2c** , **5a,b** , **6a,,b,c** and **9-24** show moderate activities against *Bacellus theringensis* and *Escherichia coli*.The obtained results indicated also the phthalazine compounds especially containing sulphonyl or chloro groups caused significant activity against *Bacellus theringensis* and *Escherichia coli*. In general, as concluding remarks it may be stated that these results of the in vitro screening of antibacterial potency of the tested compounds serve merely as a guide to their possible chemotherapeutic evedence from in vivo studies in animal experiment in order to ascertain their margin of safety and freedom from undesirable toxic manifestation on vital functions.

In the host, notably with respect to their lack of interferance with natural and acquried immunological mechanism of the body.

EXPERIMENTAL

2-[2-Aroyl]-2,3,4a,5,10,10a-hexa-hydro-5,10-benzeno-benzo [g]phthalazine-1,4-dione derivatives 2_{a-d}:

General procedure:

A solution of **1** (2.76 g; 0.01 mole) and the corresponding acid hydrazide derivatives (0.01 mole) in dimethylformamide (20 ml) were refluxed for 3-4 hrs. The reaction mixture was diluted with water. The separated product was crystallized from a suitable solvent.

2-[2-Hydroxy-benzoyl]-2,3,4a,5,10,10a-hexahydro-5,10-benzenobenzo[g]phthalaz-ine-1,4-dione 2_a:

Crystallized from dimethylformamide-ethanol as white powder in 75% yield, 3.07g, m.p. = 306°C. IR (KBr): ν 3387 (OH), 3260 (NH), 1724 (2CO) and 1659 cm^{-1} (CO). ^{1}H-NMR (DMSO): δ 3.2 (s, 2H, C_{11}-H and C_{12}-H), 4.9 (s, 2H, C_9-H and C_{10}-H), 7.0-7.8 (m, 12H, Ar-H), 10.8 (s, 1H, OH), and 11.4 (s, 1H, NH). ^{13}C-NMR (DMSO): δ 177.4, 173.8, 159.1, 142.3, 139.4, 135.2, 129.4, 127.2, 126.8, 125.3, 124.7, 119.6, 117.7, 114.3, 44.9 and 44.7.

2-[4-Chloro-benzoyl]-2,3,4a,5,10,10a-hexahydro-5,10-benzeno-benzo[g]phthalazine-1,4-dione (2_b):

Crystallized from dimethylformamide and separated as colorless needless crystal in 77% yield, 3.3 g, m.p. = 328 °C. IR (KBr): ν 3374 (NH), 2964, 2927 (aliphatic C-H), 1727 (2CO) and 1661 cm^{-1} (CO). MS [m/z] (abundance %): 430 [M^++2] (3.5), 428 [M^+] (8.7), 383 (0.9), 319 (2.2), 277 (1.7), 253 (0.8), 204 (1.0), 202 (7.0), 178 (100), 139 (39), 105 (17.4), 77 (7.8) and 55 (18.2).

2-[Pyridine-4-carbonyl]-2,3,4a,5,10,10a-hexahydro-5,10-benzenobenzo[g]phthalaz-ine-1,4-dione (2_c):

Crystallized from benzene-ethanol and separated as colorless needless crystal in 86% yield, 3.4 g, m.p. = 322 °C. IR (KBr): ν 3163 (NH), 2996 (aliphatic C-H), 1729 (2CO) and 1660 cm^{-1} (CO). MS [m/z] (abundance %): 395 [M^+] (17.4), 370 (0.2), 316 (0.4), 275 (0.5), 231 (0.45), 202 (3.4), 178 (100.0), 152 (1.7), 106 (4.8), and 78 (2.2).

2-[Benzenesulphonyl]-2,3,4a,5,10,10a-hexahydro-5,10-benzeno-benzo[g]phthalaz-ine-1,4-dione (2_d):

Crystallized from dimethylformamide -methanol in 72% yield, 3.1g, m.p. = 250°C. IR (KBr): ν 3166 (NH), 2959 (aliphatic C-H), 1718, 1662 (2CO) and 1357 cm^{-1} (SO_2N). ^{1}H-NMR (DMSO): δ 3.1 (s, 2H, C_{11}-H, C_{12}-H), 4.8 (s, 2H, C_9-H, C_{10}-H), 7.1-7.8 (m, 13H, Ar-H), and 10.8 (s, 1H, NH).

Acetic acid-3-benzene-sulphonyl-4-oxo-3,4,4a,5,10,10a-hexahydro-5,10-benzeno-benzo[g]phthalazin-1-yl ester (3):

A mixture of **2d** (0.75 g; 0.0017 mole) and few drops of triethylamine in 10 ml acetic anhydride was warmed for 2 hrs. The separated product was crystallized from benzene-ethanol to give **3** in 93 % yield, 0.75 g, m.p. = 282 °C. IR (KBr): ν 2880 (aliphatic C-H), 1707, 1673 (2CO), and 1380 cm^{-1} (SO_2N).

Toluene-4-sulphonic acid-3-benzenesulphonyl-4-oxo-3,4,4a,5,10,10a-hexahydro-5,10-benzeno-benzo[g]phthalazin-1-yl ester (4):

A mixture of **2d** (1.3 g; 0.003 mole) *p*-toluenesulphonyl chloride (0.66 g; 0.0035 mole) and few drops of triethylamine in methylene chloride (20 ml) was heated under reflux for 3 hrs. The solvent was distilled off and the residue was washed with water, and crystallized from methanol-benzene to give **4**, in 82 % yield, 1.4 g, m.p. = 269 °C.
IR (KBr): ν 2910 (aliphatic C-H), 1732 (CO) and 1387 cm^{-1} (SO_2N). ^{1}H-NMR (DMSO): δ 2.4 (s, 3H, CH_3), 3.2 (s, 2H, C_{11}-H, C_{12}-H), 4.7 (s, 2H, C_9-H, C_{10}-H) and 6.8-7.6 (m, 17H, Ar-H).

2-[1-Oxo-2-arylamino-ethyl]-2,3,4a,5,10,10a-hexahydro-5,10-benzenobenzo[g]-phthalazine-1,4-dione (5a-c):

General procedure:

A solution of **1** (2.76 g; 0.01 mole) and appropriate arylamino-acetylhydrazide namely anilinoacetylhydrazide, *p*-toluidino-acetylhdrazide or *p*-chloroanilinoacetylhydrazide (0.01 mole) in dimethylformamide (20 ml) were heated under reflux for 3-4 hrs. The reaction mixture was diluted with water. The separated products were filtered and crystallized from a suitable solvent to give **5a-c.**

2-[1-Oxo-2-phenylamino-ethyl]-2,3,4a,5,10,10a-hexahydro-5,10-benzeno-benzo[g]-phthalazine-1,4-dione (5_a):

Crystallized from methanol-benzene as white powder in 80 % yield 3.48 g, m.p. = 257 °C. IR (KBr): ν 3369, 3200 (2NH), 1727 (2CO) and 1660 cm^{-1} (CO).

2-[1-Oxo-2-*p*-tolylamino-ethyl]-2,3,4a,5,10,10a-hexahydro-5,10-benzeno-benzo[g]-phthalazine-1,4-dione (5_b):

Crystallized from methanol-benzene in 62 % yield, 2.71 g, m.p. = 248 °C. IR (KBr): ν 3386, 3197 (NH), 2939 (aliphatic C-H), 1717 (2CO) and 1658 cm^{-1} (CO). ^{1}H-NMR (DMSO): δ 2.4 (s, 3H, CH_3), 3.2 (s, 2H, C_{11}-H, C_{12}-H), 4.7 (s, 2H, C_9-H, C_{10}-H), 4.8 (s, (1H, NH), 5.4 (s, 2H, CH_2), 6.8-7.4 (m, 12H, Ar–H) and 9.4 (s, 1H, NH). MS [m/z] (abundance %): 437 [M^+] (3.2), 259 (1.1), 202 (11.3), 178 (100), 120 (22.4) and 91 (33).

2-[1-Oxo-2-*p*-chlorophenylamino-ethyl]-2,3,4a,5,10,10a-hexahydro-5,10-benzeno-benzo[g]phthalazine-1,4-dione (5_c):

Crystallized from benzene-ethanol as white powder in 75 % yield, 3.4 g, m.p. = 260 °C. IR (KBr): ν 3365, 3210 (2NH), 1725 (2CO) and 1658 cm^{-1} (CO).

Pyrido phthalazine derivatives (6_{a-c}).

General procedure:

A solution of 5_{a-c} (0.0017 mole), formaline 37% (0.3 ml, 0.0035 mole) and few drops of glacial acetic acid in dimethylformamide (10 ml) were warmed on water bath for 2-3 hrs. The reaction mixture was diluted with water. The separated product was filtered and crystallized from a suitable solvent to give 6_{a-c}.

2-Phenyl-2,3,5a,6,11,11a-hexahydro-6,11-benzeno-benzo[i]-1H-2,4a,,12a-triaza-anthracene-4,5,12-trione (6_a):

Crystallized from benzene to give white powder in 78% yield, 0.6g, m.p.= 274°C. IR (KBr): ν 2963 (aliphatic C-H), 1737 (2CO) and 1732 cm^{-1} (CO). MS [m/z] (abundance %): 435 [M^+] (13.0), 391 (0.9), 347 (1.8), 288 (0.8), 257 (10.0), 243 (2.6), 203 (7.8), 178 (100.0), 161 (52.0), 105 (22.6), 91 (10.4) and 77 (1.7).

2-*p*-Tolyl-2,3,5a,6,11,11a-hexahydro-6,11-benzeno-benzo[i]-1H-2,4a, 12a-triaza-anthracene-4,5,12-trione (6b):

Crystallized from benzene as colorless crystals in 70% yield, 0.52 g, m.p. = 275°C. IR (KBr): ν 2867 (aliphatic C-H), 1727 (2CO) and 1718 cm^{-1} (CO).

2-*p*-Chloro-phenyl-2,3,5a,6,11,11a-hexa-hydro-6,11-benzeno-benzo[i]-1H-2,4a,12a-triaza-anthracene-4,5,12-trione(6c):

Crystallized from benzene-ethanol as white powder in 80% yield, 0.64g, m.p. = 292°C. IR (KBr): ν 2851 (aliphatic C-H), 1742 (2CO) and 1730 cm^{-1} (CO). ^{1}H.NMR (DMSO): δ 3.2 (s, 2H, C_{11}-H, C_{12}-H), 4.7 (s, 2H, C_9-H, C_{10}-H), 5.4 (s, 2H, NCH_2CO), 6.2 (s, 2H, NCH_2N) and 6.8-7.6 (m, 12H, Ar–H). MS [m/z] (abundance %): 471 [M^++2] (0.3), 469 [M^+] (0.4), 291 (0.68), 178 (100), 138 (18.0) and 75 (7.1).

3-[1,4-Dioxo-3,4,4a,5,10,10a-hexahydro-1H-5,10-benzeno-benzo[g]-phthalazin-2-yl]-3-oxo-propionitrile (7):

A solution of **1** (8.28 g; 0.03mole) and cyanoacetic acid hydrazide (3.17 g; 0.032 mole) in dimethylformamide was refluxed for 4.5 hrs. The separated product was recrystallized from benzene-dimethylformamide to give 7; in 65 % yield, 7 g, m.p. = 310 °C IR (KBr): ν 3200 (NH), 2250 (CN), 1727 (2CO) and 1658 cm^{-1} (CO). ^{1}H-NMR (DMSO): δ 3.1 (s, 2H, C_{11}-H, C_{12}-H), 3.7 (s, 2H, CH_2-CN), 4.6 (s, 2H, C_9 -H, C_{10}-H), 7.2-7.6 (m, 8H, Ar–H) and 9.8 (s, 1H, NH). MS [m/z] (abundance %): 357 [M^+] (0.2), 318 (0.3), 290 (7.8), 259 (4.3), 231 (0.9), 202 (5.2), 178 (100), 152 (2.2), 112 (1.8), 82 (0.7), and 55 (1.7)

(4H)-1, 2, 4-Triazepin-7 one derivatives (8a,b):
General procedure:

To a mixture of 7 (1.07 g; 0.003mole), cyclohexanone or cyclopentanone 0.006mole) and sulphur (0.11 g; 0.0035 mole) in ethanol (30 ml), morpholine (0.45 ml) was added. The reaction mixture was heated on a water bath at 80-90 °C with stirring for 1 h. Another portion of morpholine (0.15ml) was added to the reaction mixture and stirred for another 3.5 hrs. The separated product was crystallized from ethanol-benzene to give 8a,b.

Compound 8a separated as colorless crystals in 61 % yield, m.p. = 303 °C. IR (KBr): ν 3270 (NH), 2939 (aliphatic C-H), 1718 (2CO) and 1652 cm^{-1} (CO). ^{1}H-NMR ($CDCl_3$): δ 1.4-2.9 (m, 19H, $9CH_2$, NH), 3.2-

3.3 (s, 2H, C_{11}-H, C_{12}-H), 4.8 (s, 2H, C_9 -H, C_{10}-H), 7.1-7.8 (m, 8H, Ar-H). ^{13}C- NMR ($CDCl_3$): δ 194.8, 174.6, 173.7, 141.3, 139.5, 138.3, 128.2, 127.1, 126.9, 126.6, 125.2, 125.0, 124.2, 78.5, 45.3, 45.0, 41.8, 38.3, 32.0, 26.9, 25.7, 25.3, 24.9, 24.5, 23.8, 23.1, 22.1 and 21.8 MS [m/z] (abundance %): 549 [M^+] (27.0), 506 (10.4), 493 (3.4), 451 (0.15), 371 (8.7), 328 (8.9), 275 (0.8), 259 (8.6), 193 (1.4), 178 (100), 151 (26.0), 123 (2.8), 78 (1.3) and 44 (1.5).

Compound **8b**: separated as a white powder in 62 % yield, 1.05 g, m.p. = 274 °C. IR (KBr): ν 3266 (NH), 2945 (aliphatic C-H), 1725 (2CO) and 1660 cm^{-1} (CO).

^{1}H-NMR ($CDCl_3$): δ 1.4-3.0 (m, 15H, $7CH_2$ and NH), 3.4 (s, 2H, C_{11}-H, C_{12}-H), 4.9 (s, 2H, C_9-H, C_{10}-H) and 7.1-7.7 (m, 8H, Ar-H).

Reaction of 7 with aromatic aldehydes:

General procedure:

A mixture of 7 (3.57 g; 0.01mole) and benzaldehyde or anisaldehyde (0.011mole) was added to a solution of sodium methoxide (0.34 g; 0.015 mole) in methanol (20 ml). The reaction mixture was heated till clear solution. The reaction mixture was left overnight. The product were separated and crystallized from ethanol-benzene to give **9a,b** respectively.

2-[1,4-Dioxo-3,4,4a,5,10,10a-hexahydro-1H-5,10-benzeno-benzo[g]-phthalazine-2-carbonyl]-3-phenyl-acrylonitrile. (9a):

Yellow crystals in 65 % yield, 2.89 g, m.p. = 330 °C IR (KBr): ν 3345 (NH), 2856 (aliphatic C-H), 2214 (CN), 1718 (2CO) and 1662 cm^{-1} (CO). ^{1}H-NMR ($CDCl_3$): δ 3.2 (s, 2H, C_{11}-H, C_{12}-H), 4.7 (s, 2H, C_9 -H, C_{10}-H), 7.5-7.7 (m, 13Ar–H), 7.8 (s, 1H, C=CH-Ar) and 10.5 (s, 1H, NH). ^{13}C-NMR ($CDCl_3$): δ 173.8, 163.6, 145.1, 142.3, 139.4, 133.3, 129.9, 129.0, 128.5, 126.1, 125.8, 124.5, 123.7, 118.3, 112.4, 44.6 and 44.4. MS [m/z] (abundance %): 445 [M^+] (0.86), 378 (0.15), 347 (1.6), 275 (5.2), 204 (0.8), 202 (3.4), 178 (100), 101 (4.3), 89 (11.3), 76 (6.0) and 44 (1.7).

2-[1,4-Dioxo-3,4,4a,5,10,10a-hexahydro-1H-5,10-benzeno-benzo[g]-phthalazine-2-carbonyl]-3-(4-methoxy-phenyl)-acrylonitrile (9b):

Pale yellow powder in 60 % yield, 2.85 g, m.p. = 324 °C IR (KBr): ν 3330 (NH), 2863 (aliphatic C-H), 2220 (CN), 1721 (2CO) and 1658 cm^{-1} (CO). ^{1}H-NMR ($CDCl_3$): δ 3.2 (s, 2H, C_{11}-H, C_{12}-H), 3.8 (3H,

OCH_3), 4.7 (s, 2H, C_9-H, C_{10}-H), 7.0-7.5 (m, 12Ar–H, Ar-H), 7.7(s, 1H, C=CH-Ar) and 10.5 (s, 1H, NH). ^{13}C-NMR ($CDCl_3$): δ 174.0, 163.8, 160.8, 144.6, 142.2, 139.2, 131.1, 126.3, 126.0, 123.2, 124.7, 124.0, 119.1, 114.3, 109.7, 55.3, 44.6 and 44.5

12-[1-Acetyl-1H-benzimidazol-2-yl)-9,10-dihydro-9,10-ethanoanthracene-11-carboxylic acid. (10):

A mixture of 1 (1.38 g; 0.005 mole), *o*-phenylenediamine (0.54 g; 0.005 mole) and fused sodium acetate (0.41 g; 0.005 mole) in glacial acetic acid (20 ml) was refluxed for 4 hrs. The solvent was concentrated under reducing pressure. The separated product washed with water and crystallized from methanol-benzene to give 10, in 65 % yield, 1.32 g, m.p = 263 °C. IR (KBr): ν 2934 (OH) and 1757, 1714 (2CO). MS [m/z] (abundance %): 408 (0.2), 348 (0.9), 290 (0.15), 227 (0.4), 202 (0.8), 178 (100), 152 (8.7), 114 (1.7) and 63 (1.3).

2-[2-Amino-phenyl]-3a,4,9,9a-tetrahydro-4,9-benzeno-benz[f]isoindole-1,3-dione (11):

A mixture of **1** (1.38 g; 0.005 mole), *o*-phenylenediamine (0.54 g; 0.005 mole) in dioxane/pyridine (20ml; 3.1 V) or dimethylformamide (20 ml) was heated under reflux for 5 hrs. The reaction mixture poured onto ice water. The separated product was crystallized from ethanol-benzene to give **11**, in 92.8 % yield, 1.7 g, m.p. = 277 °C. IR (KBr): ν 3458, 3369 (NH_2) and 1775, 1707 cm^{-1} (2CO). ^{1}H-NMR (DMSO): δ 3.3 (s, 2H, C_{11}-H, C_{12}-H), 4.7 (s, 2H, C_9-H, C_{10}-H), 5.2 (s, 2H, NH_2) and 7.1-7.6 (m, 12H, Ar-H). MS [m/z] (abundance %): 366 [M^+] (27.0), 266 (14.2), 203 (2.6), 188 (4.3), 178 (100), 119 (3.5) and 79 (0.9).

N-[2-(1,3-Dioxo-1,3,3a,4,9,9a-hexahydro-4,9-benzeno-benz[f]isoindol-2-yl)-phenyl]-acetamide (12):

A mixture of **11** (0.5 g; 0.0013 mole), acetyl chloride (5 ml) and triethylamine (0.5 ml) was heated on water bath at 70°C for 15 min. The reaction mixture was allowed to cool. The separated product was crystallized from benzene-ethanol to give **12**, in 94 % yield, 0.5 g, m.p. = 264 °C. IR (KBr): ν 3372, (NH) and 1775, 1706, 1629 cm^{-1} (3CO). MS [m/z] (abundance %): 408 [M^+] (4.3), 366 (3.0), 349 (0.2), 277 (0.3), 203 (1.7), 202 (2.6), 178 (100), 152 (3.5) and 89 (2.5).

2-[2-{4-(2-[1,3-Dioxo-1,3,3a,4,9,9a-hexahydro-4,9-bezeno-benz[f]isoindol-2-yl]-phenylimino)-1-oxo-naphthalen-2-yl-amino}-phenyl]-3a,4,9,9a-tetrahydro-4,9-benzeno-benz[f]isoindole-1,3-dione (13):

A mixture of **11** (1.83 g; 0.005 mole) and 1,2-naphthoquinone-4-sulphonic acid sodium salt (1.56 g; 0.006 mole) in water/dimethyl-formamide (20ml; 1:1 V) was refluxed for 1 hr. The separated product was crystallized from benzene-ethanol to give **13** as red crystals, in 70 % yield, 1.53 g, m.p. = 256 °C. IR (KBr): ν 3256 (NH) and 1766, 1715, 1659 (3CO). ^{1}H-NMR ($CDCl_3$): 3.2-3.6 (m, 4H, C_{11}-H, C_{12}-H), 4.7-4.9 (m, 4H, C_9-H, C_{10}-H), 6.9-7.6 (m, 20H, Ar-H), 8.1 (d, 1H, NH) and 8.4 (s, 1H, C_3 of quinonoid system). ^{13}C-NMR ($CDCl_3$): δ 181, 175.9, 175.3, 156.2, 141.2, 141.0, 138.8, 134.7, 133.6, 130.8, 129.9, 129.4, 128.1, 127.1, 127.0, 126.8, 126.6, 126.4, 125.1, 124.3, 124.1, 122.9, 121.2, 98.0, 47.3, 47.0, 45.8, 45.7 and 45.5 MS [m/z] (abundance %): 870 [M^+] (8.7), 692 [M^+ - anthracene] (98.0), 514 [M^+ - 2 anthracene] (22.6), 418 (2.6), 178 (100) and 89 (7.8).

2,2'-Bis[1,3-dioxo-1,3,3a-,4,9,9a-hexahydro-4,9-benzeno-benz[f]isoindol-2-yl]diphenyl-disulphide (14) and 2-[2-(mercapto-phenyl)]-3a,4,9,9a-tetrahydro-4,9-benzeno-benz[f]-isoindole-1,3-dione (15):

A mixture of **1** (1.38 g; 0.005 mole), *o*-aminothiophenol (0.63 g; 1.005 mole) and fused sodium acetate (0.5 g; 0.006 mole) in glacial acetic acid (20 ml) was refluxed for 5 hrs. The separated product washed with water and crystallized from ethanol to give **14**. The filterate was diluted with water the separated product was crystallized from benzene to give **15**, 1.9 g; m.p. = 319-23 °C.

14: 70 % yield, 0.9 g m. p. = 325 °C. IR (KBr): ν 1775, 1720 (2 CO) and 560, 2552, cm^{-1} (-S-S-). MS [m/z] (abundance %): 764 [M^+] (23.4), 732 (0.05), 586 (1.7), 502 (0.03), 408 (0.07), 383 (9.5), 381 (1.7), 231 (0.4), 204 (7.8), 178 (100), 89 (0.5) and 44 (0.6).

15: 20 % yield, 0.3 g m..p. = 319 cm^{-1}. I.R (KBr): ν 2552, SH, 1775 and 1720 (2CO). MS [m/z] (abundance %): 383 [M^+] (17.4), 351 (0.5), 276 (0.6), 231 (0.7), 202 (6.9), 178 (100), 176 (5.2), 152 (3.8), 96 (0.9) and 54 (0.7).

2-[2-Hydroxy-phenyl]-3a,4,9,9a-tetrahydro-4,9-benzeno-benz[f]isoindole-1,3-dione (16):

A mixture of **1** (1.38 g; 0.005 mole), *o*-aminophenol (0.55 g; 0.005 mole) and fused sodium acetate (0.7 g; 0.007 mole) in glacial acetic acid (20 ml) was heated under reflux for 4 hrs. The separated product washed with water and crystallized from methanol-benzene to give **16**, in 95% yield, 1.75 g; m.p. = 266 °C.

The above procedure was carried out in dioxane/pyridine (20ml; 3.1 V) or dimethylformamide (20 ml) instead of acetic acid-sodium acetate to give **16**, in 98% yield. IR (KBr): ν 3282-3034 (OH) and 1775, 1707 cm^{-1} (2CO). ^{1}H-NMR (DMSO): δ 3.3 (s, 2H, C_{11}-H, C_{12}-H), 4.9(s, 2H, C_9-H, C_{10}-H), 7-7.9 (m, 12H, Ar-H) and 9.9 (s, 1H, OH). ^{13}C-MNR (DMSO): δ 176.4, 162.7, 153.8, 142.1, 139.9, 130.7, 128.8, 127.0, 126.8, 125.3, 124.8, 119.3, 117.0, 47.1 and 45.3.

Toluene-4-sulphonic acid -2-[1,3-dioxo-1,3,3a,4,9,9a-hexahydro-4, 9-benzeno-benz[f]-isoindol-2-yl]-phenylester (17):

A solution of 16 (0.725 g; 0.002 mole), *p*-toluene sulphonyl chloride (0.38 g; 0.002 mole) and few drops of triethylamine in dimethylformamide (10 ml) were heated on water bath at 90 °C for 5 hrs. The separated product was crystallized from ethanol-benzene to give **17**, in 67 % yield, 0.7 g; m.p. = 234 °C. IR (KBr): ν 2958 (aliphatic C-H), 1769, 1713 (2CO) and 1410 cm^{-1} (SO_3). ^{1}H-NMR ($CDCl_3$): δ 2.4 (s, 3H, CH_3), 3.2 (s, 2H, C_{11}-H, C_{12}-H), 4.8 (d, 2H, C_9-H, C_{10}-H) and 7.1-7.8 (m, 16H, Ar-H). ^{13}C-NMR ($CDCl_3$): δ 174.7, 145.6, 145.0, 141.2, 138.9, 132.3, 130.2, 129.8, 129.0, 128.2, 127.4, 126.9, 126.8, 125.1, 124.3, 123.1, 47.1, 45.6 and 21.6.

1,2-Bis[1,3-dioxo-1,3,3a,4,9,9a-hexahydro-4,9-benzeno-benz[f]isoindol-2-yl]-ethane (18) and N-[2-(1,3-dioxo-1,3,3a,4,9,9a-hexahydro-4,9-benzeno-benz[f]isoindol-2-yl)]ethylamine (20):

A solution of 1 (1.27 g; 0.0045 mole), and ethylenediamine (0.3 g; 0.0046 mole) in dimethylformamide (15 ml) were refluxed for 3 hrs. The mixture was left overnight. The separated product was filtered and crystallized from dimethylformamide-methanol to give **18**. The filterate was diluted with water; the separated product was crystallized from ethanol-benzene to give **20**.

18: 30 % yield, .0.81 g, m.p. = 325 °C. IR (KBr): ν 2950, (aliphatic C-H) and 1771, 1713 cm^{-1} (2CO). Elemental analysis Calc. (Found) for the formula $C_{38}H_{28}N_2O_4$: C: 79.16 (79.51 %) and H: 4.86 (4.73 %).
20: 24 % yield, 0.35 g, m.p. = 208 °C. IR (KBr): ν 3404, 3372 (NH_2) and 1771, 1702 cm^{-1} (2CO). ^{1}H-NMR ($CDCl_3$): δ 2.8 (t, 2H, NCH_2)), 3.2 (s, 2H, C_{11}-H, C_{12}-H), 3.4 (t, 2H, $(CO)_2NCH_2$), 4.8 (s, 2H, C_9-H, C_{10}-H), 7.0-7.4 (m, 8H, Ar-H) and 7.9 (s, 2H, NH_2). ^{13}C-NMR ($CDCl_3$): 176.4, 160.9, 141.0, 139.4, 126.9, 126.8, 125.7, 124.3, 46.6, 45.4, 37.9 and 36.1.
The above procedure was carried out in dioxane/pyridine (20 ml; 3.1 V) instead of dimethylformamide. The reaction mixture was refluxed for 3 hrs. The reaction mixture was diluted with water. The separated product was crystallized from methanol-dimethylformamide to give **18**, in 42% yield, 1.1 g, m.p. = 325 °C.

1,2-Bis[1,3-dioxo-1,3,3a,4,9,9a-hexahydro-4,9-benzeno-benz[f]isoindol-2-yl]-ethane (18) and N-[2-(1,3-Dioxo-1,3,3a,4,9,9a-hexahydro-4,9-benzeno-benz[f]isoindol-2-yl)-ethyl]acetamide (19):

A mixture of **1** (0.69 g; 0.0023 mole), ethylenediamine (0.15 g; 0.0023 mole) and fused sodium acetate (0.2 g; 0.0023 mole) in glacial acetic acid (15 ml) was heated under reflux for 3 hrs. The separated product, filtered, washed with water and crystallized from dimethylformamide-methanol to give **18**. The filterate was diluted with water. The separated product was crystallized from ethanol-benzene to give **19. 18**: 14 % yield, 0.2 g, m.p. = 325 °C.
19: 66 % yield, 0.6 g, m.p. = 220 °C. IR: 3271, (NH), 2946 (aliphatic C-H), and 1773, 1707, 1652 cm^{-1} (3CO). ^{1}H-NMR ($CDCl_3$): δ 1.9 (s, 3H, CH_3), 2.9 (t, 2H, CH_2N), 3.2(s, 2H, C_{11}-H, C_{12}-H), 3.4(t, $(CO)_2NCH_2$), and 4.8 (s, 2H, C_9-H, C_{10}-H), 7.1-7.4 (m, 8H, Ar-H) and 10.8 (s, 1H, NH). ^{13}C-NMR ($CDCl_3$): 176.9, 170.0, 141.0, 139.4, 126.9, 126.0, 124.3, 46.7, 45.4, 38.3, 38.1 and 23.0.

Aceticacid-2-[1,3-dioxo-1,3,3a,4,9,9a-hexahydro-4,9-benzeno-benz[f]isoindol-2-yl]-ethyl ester (21):

A mixture of **1** (1.49 g; 0.005 mole), was added to a solution of ethanolamine (0.3g; 0.005 mole) in glacial acetic acid (15 ml). The reaction mixture was heated under reflux for 4 hrs. The reaction was diluted with water. The separated product was crystallized from methanol to give **21**, in 83 % yield, 1.5 g, m.p. = 149 °C. IR (KBr): ν 2961 (aliphatic C-H), and 1773, 1734, 1704 cm^{-1}(3CO). ^{1}H-NMR ($CDCl_3$): δ

1.9 (s, 3H, CH_3), 3.1 (s, 2H, C_{11}-H, C_{12}-H), 3.3 (m, 2H, CH_2N), 3.4 (m, 2H, CH_2O), 4.7 (s, 2H, C_9-H, C_{10}-H) and 7.2-7.4 (m, 8H, Ar-H). ^{13}C-NMR ($CDCl_3$): δ 176.5, 170.5, 141.3, 138.3, 127.0, 126.7, 124.9, 124.2, 60.6, 46.8, 45.4, 37.0 and 20.8.

Table (1): Diameter of inhibition zones (I.Z.D.) in m.m. as a criterion of antibacterial activity of the new compounds 2-24 at a concentration level of 0.1 mg/ml.

	Bacteria			Bacteria	
	B. Theringensis	***E. Coli***		***B. Theringensis***	***E. Coli***
2a	1.7	1.5	**10**	1.7	1.3
2b	3.2	2.6	**11**	1.7	1.2
2c	1.6	1.7	**12**	1.8	1.6
2d	2.7	2.3	**13**	1.7	1.7
3	2.6	2.4	**14**	1.5	1.4
4	4.0	2.8	**15**	1.8	1.6
5a	1.8	1.6	**16**	1.7	1.6
5b	1.6	1.8	**17**	1.5	1.8
5c	2.3	2.0	**18**	1.4	1.3
6a	1.7	1.6	**19**	1.3	1.4
6b	1.8	1.6	**20**	1.5	1.1
6c	1.7	1.6	**21**	1.4	1.0
7	2.2	1.6	**22**	1.3	1.5
8	2.0	1.7	**23**	1.1	1.2
9	1.9	1.8	**24**	1.0	1.3
Septazole	4.0	3.8			

Table (2): Physical Data of compounds **2a-21**

	Mol. Formula (Mol. Wt.)	*Analysis (%) Found (Calcd.)*		
		C	*H*	*N*
2a	$C_{25}H_{18}N_2O_4$ (410.42)	72.91 (73.16)	4.63 (4.42)	6.92 (6.83)
2b	$C_{25}H_{17}ClN_2O_3$ (428.87)	70.31 (70.01)	4.21 (3.99)	6.67 (6.53)
2c	$C_{24}H_{17}N_3O_3$ (395.38)	73.11 (72.90)	4.56 (4.32)	10.73 (10.62)
2d	$C_{24}H_{18}N_2O_4S$ (430.49)	67.12 (66.96)	4.32 (4.21)	6.72 (6.51)
3	$C_{26}H_{20}N_2O_5S$ (472.51)	66.31 (66.09)	4.43 (4.26)	5.63 (5.92)
4	$C_{31}H_{24}N_2O_6S_2$ (584.65)	63.89 (63.68)	4.38 (4.13)	4.88 (4.79)
5a	$C_{26}H_{21}N_3O_3$ (423.47)	73.81 (73.74)	5.30 (4.99)	10.21 (9.92)
5b	$C_{27}H_{23}N_3O_3$ (437.49)	74.31 (74.12)	5.32 (5.29)	9.78 (6.60)
5c	$C_{26}H_{20}ClN_3O_3$ (457.91)	68.33 (68.19)	4.56 (4.40)	9.27 (9.17)
6a	$C_{27}H_{21}N_3O_3$ (435.48)	74.59 (74.46)	4.67 (4.86)	9.83 (9.64)
6b	$C_{28}H_{23}N_3O_3$ (449.5)	74.91 (74.81)	5.27 (5.15)	9.42 (9.34)
6c	$C_{27}H_{20}ClN_3O_3$ (469.92)	79.23 (79.01)	4.32 (4.28)	8.68 (8.94)
7	$C_{21}H_{15}N_3O_3$ (357.36)	70.67 (70.58)	4.42 (4.23)	11.81 (11.75)
8a	$C_{33}H_{31}N_3O_3S$ (549.68)	72.31 (72.10)	5.81 (5.68)	7.82 (7.64)
8b	$C_{31}H_{27}N_3O_3S$ (521.63)	71.52 (71.38)	5.49 (5.21)	8.32 (8.05)
9a	$C_{28}H_{19}N_3O_3$ (445.47)	75.31 (75.49)	4.42 (4.29)	8.61 (8.43)
9b	$C_{29}H_{21}N_3O_4$ (475.50)	73.33 (73.25)	4.53 (4.45)	8.61 (8.83)
10	$C_{26}H_{20}N_2O_3$ (408.45)	76.63 (76.45)	4.68 (4.94)	6.71 (6.86)
11	$C_{24}H_{18}N_2O_2$ (366.41)	78.81 (78.67)	4.62 (4.95)	7.49 (7.65)
12	$C_{26}H_{20}N_2O_3$ (408.45)	76.66 (76.45)	4.83 (4.94)	6.68 (6.86)
13	$C_{58}H_{34}N_4O_5$ (866.92)	80.56 (80.35)	4.15 (3.95)	6.61 (6.46)
14	$C_{48}H_{32}N_2O_4S_2$ (464.91)	75.47 (75.37)	4.12 (4.22)	3.51 (3.66)

	Mol. Formula (Mol. Wt.)	*Analysis (%) Found (Calcd.)*		
		C	*H*	*N*
15	$C_{24}H_{17}NO_2S$ (383.46)	75.26 (75.17)	4.59 (4.47)	3.81 (3.65)
16	$C_{24}H_{17}NO_3$ (367.40)	78.50 (78.46)	4.72 (4.66)	3.77 (3.81)
17	$C_{31}H_{23}NO_5S$ (521.58)	71.40 (71.38)	4.68 (4.44)	2.83 (2.69)
18	$C_{38}H_{28}N_2O_4$ (576.64)	79.35 (79.15)	4.77 (4.89)	4.76 (4.86)
19	$C_{22}H_{20}N_2O_3$ (360.41)	73.44 (73.32)	5.68 (5.59)	7.91 (7.77)
20	$C_{20}H_{18}N_2O_2$ (318.37)	75.63 (75.45)	5.86 (5.70)	8.63 (8.80)
21	$C_{22}H_{19}NO_4$ (361.39)	73.16 (73.12)	5.62 (5.30)	3.61 (3.88)

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إستخدام داى بنزوبارالين فى تشيد مركبات حلقية غير متجانسة متعددة الأنوية محتوية على نيتروجين

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أهمية المركبات الإندولية و الفيثاليزية فى التطبيقات الطبية كانت حافزا لهذا البحث ليشمل استخدام داى بنزوبارالين ١ فى تشيد سلسلة من المركبات الحلقية الغير متجانسة والتى تحتوى على حلقة أيزواندول دايون(١١-٢١) وعلى ذلك تم تفاعل المركب١ مع أورثوفينلين ثنائى الأمين ، أورثوامينو فينول ، أورثو أمينو ثيوفينول ، إيثانول أمين و إيثلين ثنائى الأمين. أيضا تم تشيد سلسلة جديدة من المركبات الحلقية الغير متجانسة والتى تحتوى على نواة الفيثاليزين(٢،٥،٧) عن طريق تفاعل المركب١ مع الهيدرازينات و بإجراء تفاعل الأسيلة والسلفنة للمركب٢ نتجت مشتقاتها.

وبتفاعل٥ مع الفورماالديهيد فى وسط حامضى أعطى المركب٦ وعند تفاعل المركب ٧مع الكيتونات الحلقية والألديهيدات نتجت مشتقات الثيوفين والأكليونتريل٨ ،٩ على التوالى .

تم إثبات التركيب الكيميائي لجميع هذه المركبات باستخدام التحاليل الطيفية العديدة والمتنوعة و أختبرت قدرة هذه المركبات كمضادات للبكتيريا والتى أثبتت كفاءة عالية وخاصة المركب٤.