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Original scientific paper

Design, synthesis and antibacterial activity of new phthalazinedione derivatives

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Abstract: Dibenzobarallene (**1**) was utilized as the key intermediate for the synthesis of some new 2-substituted 1,4-dioxo-3,4,4a,5,10,10a-hexahydro-1*H*--5,10-[1',2']-benzenobenzo[*g*]phthalazine: **2**, **5a**–**d**, **8a**–**c** and **10**. Condensation of **2** with benzaldehyde or anisaldehyde gave the corresponding acrylonitrile derivatives **3a** and **b**, respectively. Thiophene derivatives **4a** and **b** were obtained *via* the Gewald reaction of **2** with cyclohexanone or cyclopentanone, respectively. Treatment of **5d** with acetyl chloride or *p*-toluenesulfonyl chloride afforded the corresponding esters **6** and **7**, respectively. Cyclization of **8a**–**c** with formalin afforded the corresponding triazine derivatives **9a**–**c**. Ring opening of **10** with sodium hydroxide gave the corresponding triazole derivative **11**, which when alkylated with pentyl bromide afforded the pentylthio derivative **12**. Representative compounds of the synthesized products were established and evaluated as antibacterial agents.

Keywords: dibenzobarallene; phthalazine; thiophene; triazine; triazole; antibacterial agents.

INTRODUCTION

In the past decades, the synthesis of heterocyclic compounds was a subject of great interest due to their wide applicability. Heterocyclic compounds occur very widely in nature and are essential to life. Among a large variety of heterocyclic compounds, heterocycles containing the phthalazine moiety are of interest due to their pharmacological and biological activities (Fig. 1).[1–3]

The phthalazine nucleus has pronounced pharmacological applications due to its anticonvulsant,[4] cardiotonic,[5] and vasorelaxant,[6] activities. In continuation of efforts[7,8] to identify new candidates that may be of value in designing new, potent, selective and less toxic antimicrobial agent, herein the syntheses of some new heterocycles incorporating the phthalazine moiety starting from dibenzobarallene are reported.[9]

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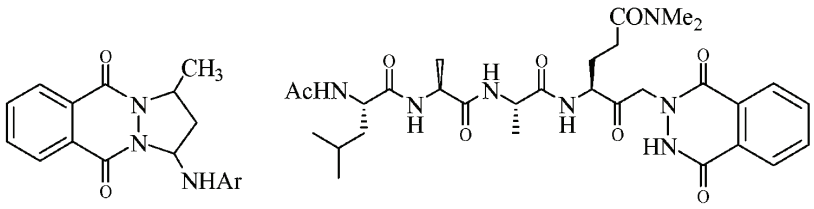


(a) (b)

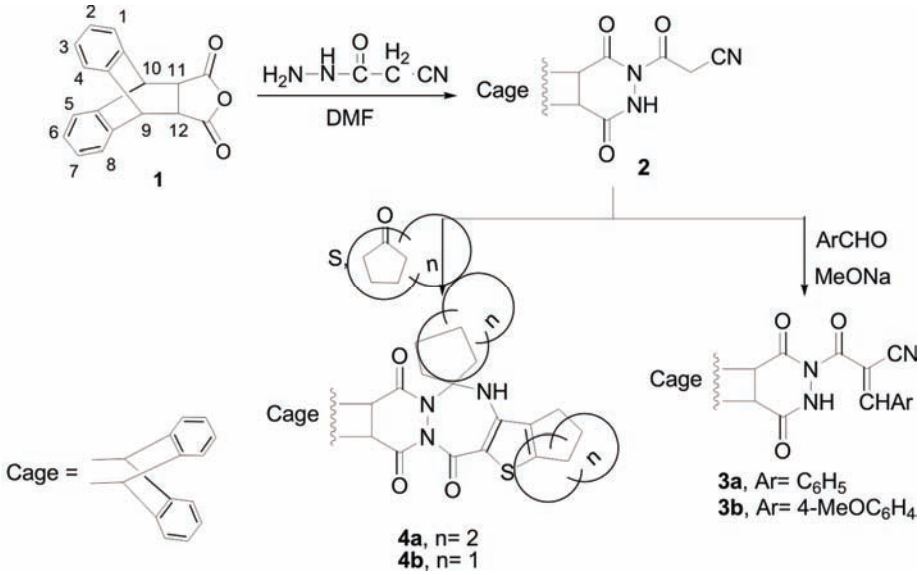
Fig. 1. Antihypoxic, antipyretic agent (a),[1] and HAV 3C inhibitor (b).[2]

RESULTS AND DISCUSSION

Analytical and spectral data of the synthesized compounds are given in the Supplementary material.

Chemistry

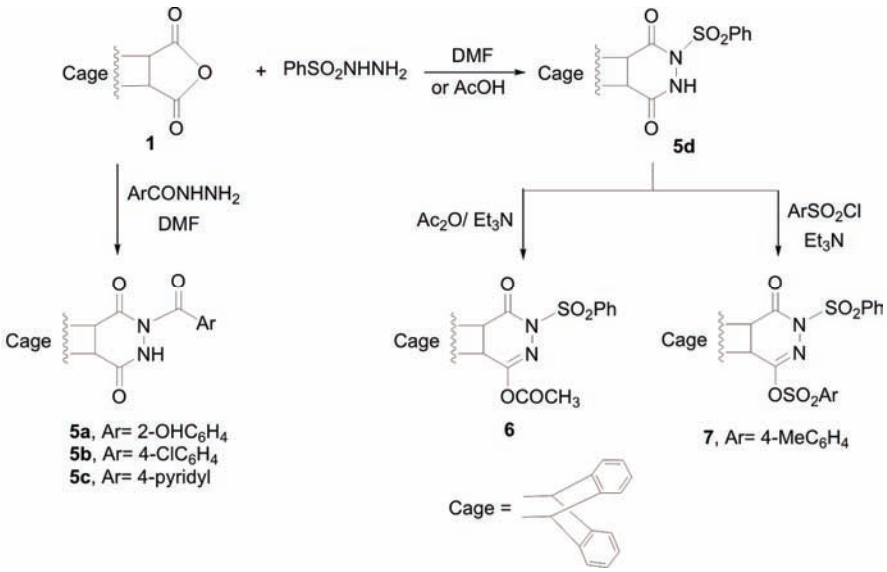
The synthetic procedures adopted to obtain the target compounds are depicted in Schemes 1–3. Dibenzobarallene,[1] and 3-(1,4-dioxo-3,4,4a,5,10,10a-hexahydro-1*H*-5,10-[1',2']-benzenobenzo[*g*]phthalazin-2-yl)-3-oxopropiononitrile (**2**) were prepared according to previously reported methods.[9,10]



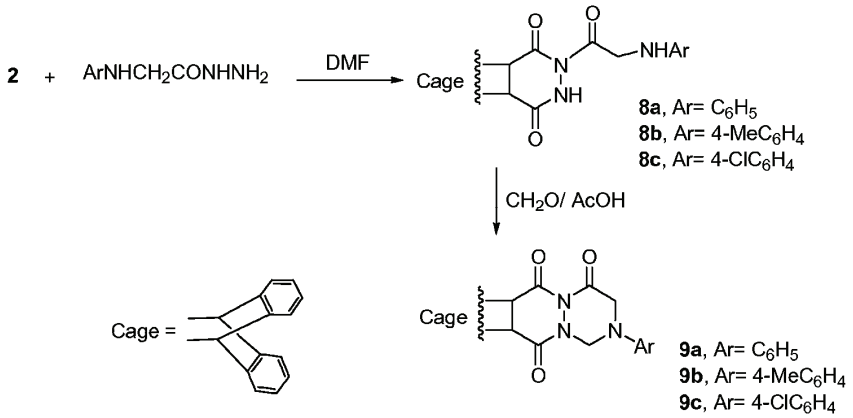
Scheme 1. Gewald and Knoevenagel reactions of propiononitrile derivative **2**.

Reaction of the propiononitrile derivative **2** with benzaldehyde or *p*-anisaldehyde, in the presence of sodium methoxide afforded the corresponding acrylonitrile derivatives **3a** and **b**, respectively. The structures of **3a** and **b** were supported by both their analytical and spectral data. The ^{1}H-NMR spectrum of **3a**

displayed a singlet signal at δ 7.8 ppm due to the methine proton of benzylidene. In addition, compound **3b** displayed two singlet signals at δ 3.8 and 7.7 ppm due to OCH_3 and methine protons, respectively. The ^{13}C-NMR spectrum of **3a** exhibited signals at 118.3 and 112.4 ppm due to ethylenic carbons; in addition, **3b** exhibited, among others, signals at δ 114, 109 and 55.3 ppm due to ethylenic and OCH_3 carbons, respectively. Furthermore, the reaction of the propiononitrile derivative **2** with cyclohexanone or cyclopentanone in a 1:2 molar ratio under Gewald reaction condition[11–13] afforded the products **4a** and **b**, respectively, in low yields (Scheme 1).



Scheme 2. Reaction of dibenzobarallene (**1**) with some acid hydrazide derivatives.



Scheme 3. Synthesis of 1,2,4-triazine derivatives **9a**–**c**.

The formulation of **4a** and **b** were based on their mass, IR, ^{1}H- and ^{13}C-NMR spectra. The ^{1}H-NMR spectra of **4a** and **b** displayed multiplet signals at δ 1.4–2.9 ppm and 1.4–3.0 ppm due to methylene and NH protons, respectively. The ^{13}C--NMR spectrum of **4a** displayed signals at δ 21.8, 22.1, 23.1, 23.8, 24.5, 24.9, 25.3, 25.7 and 26.9 ppm due to CH_2 carbons; signals at δ 78.5 due to spiro-, 139.5, 128.2, 126.6 and 125.0 due to thiophene- and 194.8, 177.3 and 174.6 ppm, due to carbonyl carbons. The mass spectrum of **4a** exhibited the molecular ion peak at *m*/*z* 549, which is in agreement with its molecular formula $C_{33}H_{31}N_3O_3S$, in addition to other fragment ion peaks at *m*/*z* 506 and 493, 451, 371, 328, 275 and 259, which are illustrated in the fragmentation pattern shown in Fig. 2.

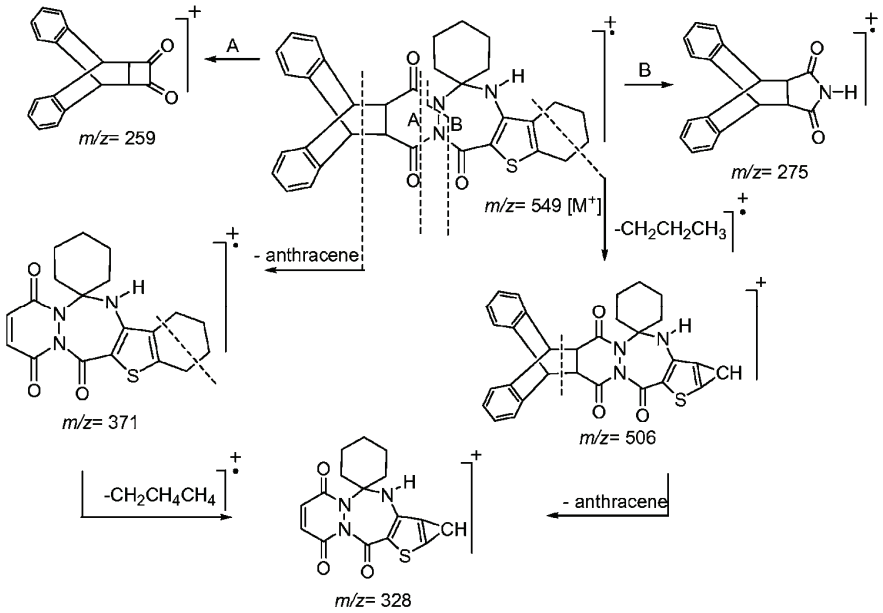


Fig. 2. Fragmentation pattern of compound **4a**.

Additionally, reaction of adduct **1** with the appropriate acid hydrazide,[14] in acetic acid or DMF afforded the interesting phthalazinedione derivatives **5a**–**d**; an analogous reaction behavior has already been reported.[15–18] The structures of **5a**–**d** were confirmed based on their spectral data. The IR spectra of **5a**–**d** showed NH bands at 3374–3163 cm^{-1} and three carbonyl bands at around 1729 and 1660 cm^{-1}. Moreover, the IR spectra of **5a** and **d** showed additional bands at 3387 and 1357 cm^{-1}, due to –OH and –SO_2N groups, respectively. Furthermore, the ^{1}H-NMR spectrum of **5a** displayed singlet signals at δ 10.8 and 11.4 ppm due to OH and NH protons, respectively; also, **5d** displayed a singlet signal at δ 10.8 ppm due to the NH proton of the phthalazine ring. The ^{13}C-NMR spectrum of **5a** revealed signals at 173.9 and 177.4 ppm due to three carbonyl carbons. The mass

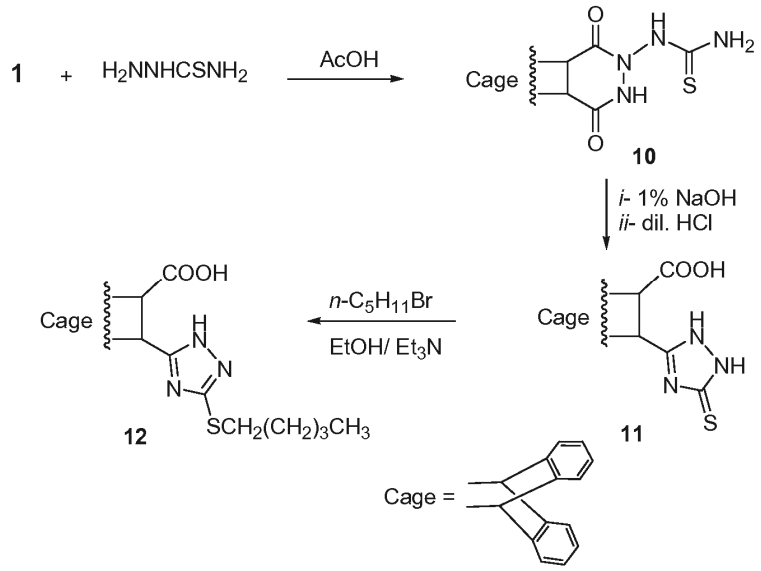
spectrum of **5b** gave the molecular ion peak at *m/z* 428 and 430 corresponding to M^+ and M^++2, which are in agreement with its molecular formula $C_{25}H_{17}ClN_2O_3$. In addition to the base, a peak at *m*/*z* 178 corresponding to anthracene was also observed.

Treatment of **5d** with acetic anhydride and *p*-toluenesulfonyl chloride in the presence of a few drops of TEA yielded the phthalazine derivatives **6** and **7**, respectively. The ^{1}H-NMR spectrum of **7** revealed a singlet signal at δ 2.4 ppm due to the CH_3 group; analogous behaviors were recorded in the literature (Scheme 2).[15,17–20]

Furthermore, condensation of compound **1** with the appropriate 2-(arylamino) acetic acid hydrazide[21] in DMF yielded the corresponding phthalazinedione derivatives **8a**–**c**. The structures of **8a**–**c** were based on spectral data. Thus, the IR spectra of **8a**–**c** showed 2NH bands at 3386–3365 cm^{-1} and 3210–3197 cm^{-1} in addition to carbonyl bands at 1725–1717 cm^{-1} and 1660–1658 cm^{-1}. The mass spectrum of **8b** exhibited a molecular ion peak at *m*/*z* 437, which is in agreement with its molecular formula $C_{27}H_{23}N_3O_3$, the base peak at *m*/*z* 178 corresponding to anthracene and a fragment ion peak at *m*/*z* 259 due to M^+–anthracene. The ^{1}H--NMR spectrum of **8b** displayed singlet signals at δ 2.4, 4.8, 5.4 and 9.4 ppm due to CH_3, NHAr, CH_2 and NHCO protons, respectively.

Cyclization of the phthalazinediones **8a**–**c** by reaction with 37 % formaldehyde in glacial acetic acid was studied with the aim of preparing the 1,2,4-triazine derivatives **9a**–**c** with potential biological activities (Scheme 3).[22,23] The structures of **9a**–**c** were based on analytical and spectral data. The IR spectra of **9a**–**c** showed the absence of NH bands. The ^{1}H-NMR spectrum of **9c** revealed, beside the disappearance of NH signal, the appearance of signals at δ 5.4 and 6.2 ppm due to CH_2CO and NCH_2N protons, respectively. The mass spectrum of **9c** exhibited a molecular ion peak at *m*/*z* 469 and 471 corresponding to M^+ and M^++2, which is in agreement with its molecular formula $C_{27}H_{20}ClN_3O_3$. The major fragment ion peaks at *m*/*z* 291 and 178 were attributed to M^+–anthracene and anthracene, respectively (Scheme 3).

The remarkable biological importance of 1,2,4-triazole derivatives,[24–26] prompted an investigation of the synthesis of some new triazole derivatives of expected antimicrobial activity. Thus, the adduct **1** was reacted with thiosemicarbazide in acetic acid or in THF to give **10**. The structure of **10** was ascertained through spectral data. Its mass spectrum exhibited the molecular ion peak M^+ at *m*/*z* 348, which is consistent with the molecular formula $C_{19}H_{15}N_3O_2S$, in addition to other fragment ion peaks at *m*/*z* 275 and 178 due to M^+–$NCSNH_2$ and anthracene, respectively. The derivative **10** was then heated with dilute aqueous sodium hydroxide to yield the corresponding 5-thioxo-2,5-dihydro-1*H*-1,2,4--triazole derivative **11**, the structure of which was confirmed by analytical and spectral data (Scheme 4).



Scheme 4. Synthesis of triazole derivative **12**.

The IR spectrum of **11** showed bands at 3136, 3111 (2NH), 2937–2866 (*br*, OH), 1709 (*br*, 3CO) and 1461, 1256 cm^{-1} (C=S). Moreover, the mass spectrum of **11** exhibited the molecular ion peak at *m*/*z* 203, corresponding to M^+–(CO_2, triazole moiety). Subsequent alkylation of **11** using *n*-pentyl bromide and a few drops of TEA furnished the 5-(pentylthio)-2*H*-1,2,4-triazole derivative **12**. The spectral data of **12** are fully in accordance with the proposed structure, particularly the ^{1}H-NMR spectrum that displayed signals at δ 0.8, 1.2–1.7, 3.6, 11.5 and 12.3 ppm due to CH_3, $3CH_2$, CH_2S, NH and OH protons, respectively. The mass spectrum of **12** added further support to the assigned structure. The molecular ion peak appeared at *m*/*z* 420, the fragmentation pattern proceeded by two different routes. In one pathway, the consecutive expulsion of CO_2 and N_2 from M^+ gave peaks at *m*/*z* 375 and 347, respectively. In the other route, the molecular ion peak underwent fragmentation with the cleavage anthracene (*m*/*z* 178) and another fragment ion at *m*/*z* 241. The synchronous loss of CO_2 from the latter species gave a fragment ion peak at *m*/*z* 197. The characteristic fragment ions are shown in the fragmentation pattern given in Fig. 3.

Pharmacology

Twenty compounds were screened by the agar diffusion technique[27] for their *in vitro* antibacterial activities against two strains of bacteria *Bacillus thuringiensis* and *Escherichia coli*. The bacteria were maintained on nutrient agar. DMSO showed no inhibition zones. The agar media were incubated with different cultures of the tested microorganism. After 24 h of incubation at 30 °C, the

diameter of inhibition zone (mm) was measured (Table I). Ampicillin and chloramphenicol were purchased from the Egyptian market and used in a concentration of 2 mg ml^{-1} as references.

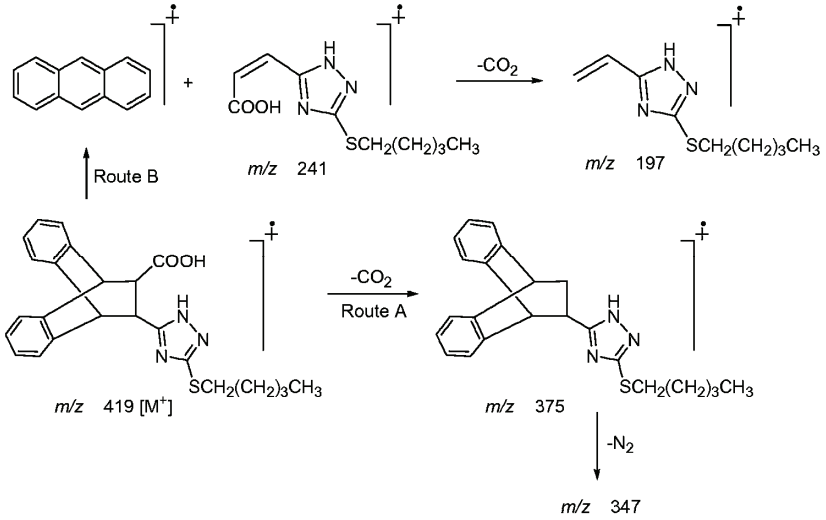


Fig. 3. Fragmentation pattern of triazole derivative **12**.

TABLE I. Inhibition zone (mean diameter of the disc in mm) as a criterion of the antibacterial activities of the newly synthesized compounds

Compound	*B. thuringiensis*	*E. coli*
2	22	16
3a	27	20
3b	28	19
4a	21	20
4b	18	17
5a	17	15
5b	32	25
5c	16	17
5d	27	22
6	26	21
7	40	22
8a	18	16
8b	16	18
8c	20	17
9a	17	16
9b	18	16
9c	17	16
10	15	14
11	16	13
12	24	22
Ampicillin	18	19
Chloramphenicol	23	20

The results depicted in Table I revealed that compounds **3a**, **3b**, **4a**, **5b**, **5d**, **6**, **7** and **12** exhibited interestingly high antibacterial activities against the reference drugs.

Thus, it would appear that the introduction of arylidene, benzothiophene, sulfonyl, sulfonate or triazole moieties enhances the antibacterial properties of 3--(1,4-dioxo-3,4,4a,5,10,10a-hexahydro-1*H*-5,10-[1',2']-benzenobenzo[*g*]phthalazin-2-yl)-3-oxopropiononitrile (**2**) (Fig. 2). By comparing the results obtained for the antibacterial activity of the compounds reported in this study with their structures, the following structure activity relationships (SARs) were postulated: *i*) compounds **3a** and **3b** were more potent than compound **2**, which may be attributed to the introduction of the arylidene moiety; *ii*) compound **4a** was more potent than compound **2** due to presence of the benzothiophenetriazaepine moiety; *iii*) compounds **5d**, **6** and **7** were more potent than compound **2** due to the replacement of the propiononitrile moiety by an arylsulfonyl moiety; *iv*) compound **7** was more potent than **5d** and **6**, which may be due to the presence of two arylsulfonate groups; *v*) compound **12** was more potent than compound **2** which may be attributed to the replacement of the pyridazinedione moiety with a triazole moiety.

EXPERIMENTAL

All melting points are in degree centigrade and were measured on a Gallenkamp electric melting point apparatus. Thin layer chromatography, TLC, analysis was performed on silica gel 60 F254 pre-coated aluminum sheets. The IR spectra were recorded using the KBr wafer technique on a Matson 5000 FTIR spectrometer, at the Faculty of Science, Mansoura University, India. The ^{1}H-NMR spectra were determined on either a Varian XL 200 MHz instrument at the Faculty of Science, Cairo University, Egypt, a Bruker WP 300 instrument at the Georg-August University Göttingen, Germany, or a Brucker AC 300 instrument at the Eberhard-Karls University, Tubingen, Germany, in $CDCl_3$ or DMSO solvent using TMS as the internal standard. The ^{13}C-NMR spectra were determined on a Brucker AC 300 instrument at the Eberhard-Karls University, Tubingen, Germany, in $CDCl_3$ or DMSO solvent using TMS as the internal standard. The mass spectra were recorded on a Finnigan MAT 212 instrument and the elemental analyses (C, H, and N) were performed in the Microanalytical Center of Cairo University, Egypt.

*2-[1,4-Dioxo-3,4,4a,5,10,10a-hexahydro-1*H*-5,10-[1',2']-benzenobenzo[g]-phthalazine-2--carbonyl]-3-(phenyl or* p*-methoxyphenyl)-acrylonitriles **3a**,**b***

General procedure. A mixture of **2** (3.57 g; 0.01 mol) and benzaldehyde or *p*-anisaldehyde (0.011 mol) was added to a solution of sodium methoxide (0.34 g; 0.015 mol) in methanol (20 ml). The reaction mixture was heated until a clear solution was obtained. The reaction mixture was left overnight. The products were separated and crystallized from ethanol–benzene to give **3a** and **3b**, respectively.

*Synthesis of (4*H*)-1,2,4-triazepin-7-one derivatives (**4a**,**b**)*

General procedure. To a mixture of **2** (1.07 g; 0.003 mol), cyclohexanone or cyclopentanone (0.006 mol) and sulfur (0.11 g; 0.0035 mol) in ethanol (30 ml) was added morpholine (0.45 ml). The reaction mixture was heated on a water bath at 80–90 °C with stirring for 1 h. Another portion of morpholine (0.15 ml) was added to the reaction mixture and stirred

for another 3.5 h. The separated products were crystallized from ethanol–benzene to give **4a** and **4b** as colorless crystals and a white powder, respectively.

*Synthesis of 2-[(2-hydroxybenzoyl) or (4-chlorobenzoyl) or (pyridine-4-carbonyl) or (benzenesulfonyl)]-2,3,4a,5,10,10a-hexahydro-5,10[1',2']-benzenobenzo[g]phthalazine-1,4-dione (**5a**–**d**)*

General procedure. A solution of **1** (2.76 g; 0.01 mol) and the corresponding acid hydrazide derivatives (0.01 mol) in DMF (20 ml) were refluxed for 3–4 h. The reaction mixture was poured into a beaker containing ice and then the separated product was crystallized from a suitable solvent to afford the phthalazine-1,4-diones **5a**–**d**. **5a**: white powder, **5b**: crystallization from DMF and separated as colorless needless crystals, **5c**: crystallization from benzene–ethanol and separated as colorless needless crystal, **5d**: crystallization from DMF–methanol.

*Synthesis of acetic acid 3-(benzenesulfonyl)-4-oxo-3,4,4a,5,10,10a-hexahydro-5,10-[1',2']--benzenobenzo[g]phthalazin-1-yl ester (**6**)*

A mixture of **5d** (0.75 g; 0.0017 mol) and a few drops of TEA in (10 ml) acetic anhydride was warmed for 2 h. The separated product was crystallized from benzene–ethanol to give **6**.

*Synthesis of toluene-4-sulfonic acid 3-(benzenesulfonyl)-4-oxo-3,4,4a,5,10,10a-hexahydro-5,10-[1',2']-benzenobenzo[g]phthalazin-1-yl ester (**7**)*

A mixture of **5d** (1.3 g; 0.003 mol) *p*-toluenesulfonyl chloride (0.66 g; 0.0035 mol) and few drops of TEA in dichloromethane (20 ml) was heated under reflux for 3 h. The solvent was distilled off and the residue was washed with water and crystallized from methanol–benzene to give **7**.

*Synthesis of 2-[1-oxo-2-[[(phenyl)/(*p*-tolyl)/(*p*-chlorophenyl)]-amino]-ethyl]-2,3,4a,5,10,10a-hexahydro-5,10-[1',2']-benzenobenzo[g]-phthalazine-1,4-dione (**8a**–**c**)*

General procedure. A solution of **1** (2.76 g; 0.01 mol) and the appropriate arylaminoacetohydrazide, namely anilinoacetohydrazide, *p*-toluidinoacetohydrazide or *p*-chloroanilinoacetohydrazide (0.01 mol) in DMF (20 ml) were heated under reflux for 3–4 h. The reaction mixture was diluted with water. The separated products were filtered and crystallized from a suitable solvent to give **8a**–**c**. **8a**: crystallized from methanol–benzene; white powder, **8b**: crystallized from methanol–benzene; **8c**: crystallized from benzene–ethanol.

*Synthesis of {2-(phenyl)/ (*p*-tolyl)/(*p*-chlorophenyl)}-2,3,5a,6,11,11a-hexahydro-6,11-[1',2']--benzenobenzo[g]-1H-[1,2,4]triazino[1,2-b]phthalayine-4,5,12-trione (**9a**–**c**)*

General procedure. A solution of **8a**–**c** (0.0017 mol), formalin 37 % (0.3 ml, 0.0035 mol) and a few drops of glacial acetic acid in DMF (10 ml) were warmed on a water bath for 2–3 h. The reaction mixture was diluted with water. The separated product was filtered and crystallized from a suitable solvent to give **9a**–**c**. **9a**: crystallized from benzene; **9b**: crystallized from benzene; colorless crystals; **9c**: crystallized from benzene–ethanol; white powder.

Synthesis of N-*[1,4-dioxo-3,4,4a,5,10,10a-hexahydro-1*H-*5,10-[1',2']-benzenobenzo[g]--phthalazin-2-yl]-thiourea (**10**)*

A mixture of **1** (1.38 g; 0.005 mol) and thiosemicarbazide (0.53 g; 0.005 mol) in glacial acetic acid (20 ml) was heated on a water path at 90 °C for 8 h. The separated product was crystallized from benzene–ethanol to give **10**. The above procedure was carried out in THF (20 ml) instead of glacial acetic acid. The reaction mixture was heated under reflux for 2.5 h. The separated product was crystallized to give **10**.

*Synthesis of 12-(5-thioxo-2,5-dihydro-1*H*-1,2,4-triazol-3-yl)-9,10-dihydro-9,10-ethanoanthracene-11-carboxylic acid (**11**)*

A solution of **10** (0.6 g; 0.0017 mol) in 1 % sodium hydroxide (100 ml) was heated on water bath at 95 °C for 2 h. The solution was left to cool and acidified with dilute hydrochloric acid. The separated product was crystallized from benzene–ethanol to give **11**.

*Synthesis of 12-[5-(pentylthio)-2*H*-1,2,4-triazol-3-yl]-9,10-dihydro-9,10-ethanoanthracene--11-carboxylic acid (**12**)*

A solution of **11** (1.0 g; 0.0028 mol), 1-bromopentane (0.5 g; 0.0032 mol) and a few drops of TEA in ethane (25 ml) was heated under reflux for 1 h. The reaction mixture was diluted with water. The separated product was crystallized from ethanol–benzene to give **12**.

In vitro *antimicrobial activity*

The tested compounds were evaluated by the agar diffusion technique,[27] using a 2 mg ml^{-1} solution in DMSO. The test organisms were *B. thuringiensis* as gram-positive bacteria and *E. coli* as gram-negative bacteria. A control using DMSO without the test compound was included for each organism. Ampicillin and chloramphenicol in DMSO were used as the reference drugs.

CONCLUSION

In conclusion, we reported herein a simple and convenient route for the synthesis of some new heterocycles based on the phthalazinedione moiety, which were tested for their antibacterial activity.

SUPPLEMENTARY MATERIAL

Analytical and spectral data of the synthesized compounds are available electronically at http://www.shd.org.rs/JSCS/, or from the corresponding author on request.

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ИЗВОД

СИНТЕЗА И АНТИБАКТЕРИЈСКА АКТИВНОСТ НОВИХ ДЕРИВАТА ФТАЛАЗИНДИОНА

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Дибензобарелен (**1**) је коришћен као главни интермедијер у синтези нових 2-супституисаних (1,4-диоксо-3,4,4a,5,10,10a-хексахидро-1*H*-5,10-бензено-[1',2']-бензо[*g*]фталазина: **2**, **5a**–**d**, **8a**–**c** и **10**. Кондензацијом **2** са бензалдехидом или анизалдехидом добијени су нови деривати акрилонитрила **3a и 3b**. Деривати тиофена **4a** и **4b** добијени су Гевалдовом (*Gewald*) реакцијом **2** са циклохексаноном или циклопентаноном. Реакцијом **5d** са ацетил-хлоридом или *para*-толуенсулфонил-хлоридом добијени су одговарајући деривати триазина **6** и **7**. Циклизацијом деривата **8a**–**c** са формалдехидом добијени су одговарајући деривати триазина **9a**–**c**. Отварањем прстена деривата **10** натријум-хидроксидом добијен је одговарајући дериват **11** који алкиловањем са пентил-бромидом даје пентилтио дериват **12**. Одабрана једињења су испитана као антибактеријски агенси.

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