



## Studies on synthesis and antimicrobial activity of 2-amino-1-cyanobenzopyrano[4,3-d]pyrimidine derivatives.

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### Abstract

The behavior of 2-amino-4[H],5[H]3,4-dihydro[1] benzopyrano [4,3]pyrimidin-4,5-dione-1-carbonitrile(1) towards some nucleophilic and electrophilic reagents has been described with the aim of preparing some poly functionally fused heterocyclic compounds. All these compounds were characterized by means of their IR, HNMR, Mass spectroscopic data and microanalysis, and were evaluated by the Cup plate method.

**Key words:** Amino benzopyranopyrimidine-dione-carbonitrile Synthesis, Studies and Antimicrobial activity

### Introduction

Fused pyran-2-ones are important biologically active compounds and organic synthesis. Recently, a rapid progress has been done in the field of [4H]-1-benzopyran-2-ones and related pyrimidine, due to the interaction of several drugs, receptor binding models, which enabled a systematic and rational design of novel inhibitors of various enzymes, such as HIV protease [1] and DNA gyrase or topoisomerase [2] tetrahydro-2H-benzopyran-2-ones. This possesses a wide variety of activities such as antiarrhythmic, anti-inflammatory, anesthetic, analgesic and platelet anti aggregating [3-5] and pyrimidine derivatives which are known to have wide pharmacological activities [6-8] including antibacterial, antitumor and antihepatic activity. Therefore, an important task of modern organic synthesis is to provide selective transformation convert lead compounds into the desired product in high yields. During this phase of the current research [9-11] a novel synthesis of 2-amino-4[H],5[H]-3,4-dihydro[1]benzopyrano[4,3-d]pyrimidin-4,5-dione-1-carbonitrile 1 has been reported as a target molecule via the interaction between 3-ethoxycarbonyl coumarin and cyanoguanidine in absolute ethanol in the presence of anhydrous potassium carbonate.

### Results and Discussion

The structure of compound 1 was confirmed via its analytical and spectral data. The IR spectrum showed strong absorption bands at 3332.8 and 3186.2  $\text{cm}^{-1}$  due to  $\nu\text{NH}_2$  group, at 2191.0  $\text{cm}^{-1}$  characteristic for  $\nu\text{CN}$  group, at 1728.1  $\text{cm}^{-1}$  equivalent to  $\nu\text{CO}$  of  $\alpha$ -lactone and at 1651.0  $\text{cm}^{-1}$  due to  $\nu\text{CO}$  of cyclic amide. The  $^1\text{HNMR}$  ( $\text{DMSO-d}_6$ ) spectrum showed a multiplet at  $\delta$  7-8.2 ppm due to aromatic protons (4H) and H3, H4 of

pyranone ring, a singlet at 11.2 ppm due to (2H) of NH<sub>2</sub> group. The mass spectrum of compound 1 showed a mass ion peak at  $m/e = 230$  (13.6%) corresponding to  $[M - CN]^+$ . Thus, the compound 1 was condensed with formamide to yield the aminotriazine derivative 212. Confirmatory evidences for the structure assigned to this compound were provided from elemental analysis and spectral data. The IR spectrum revealed strong absorption bands at 3332.3, 3194.5  $\text{cm}^{-1}$  equivalent to  $\nu\text{NH}_2$  group, at 1734.6  $\text{cm}^{-1}$  due to  $\nu\text{CO}$  of  $\delta$ -lactone and at 1650.3  $\text{cm}^{-1}$  due to  $\nu\text{CO}$  of cyclic amide. Further support for this structure was indicated from the mass spectrum which showed a parent peak at  $m/e$  283 (4.4%), corresponding to the molecular formula  $\text{C}_{13}\text{H}_9\text{N}_5\text{O}_3$ .

It was found that the interaction between compound 1 and formic acid resulted in the formation of the hydroxytriazine 3. The chemical structure of this compound was proved based on elemental analysis and spectral data. The IR spectrum displayed strong absorption bands at 3332.8  $\text{cm}^{-1}$  characteristic for  $\nu\text{NH}$  and,  $\nu\text{OH}$ , at 1728.1  $\text{cm}^{-1}$  due to  $\nu\text{CO}$  of  $\alpha$ -lactone and at 1643.2  $\text{cm}^{-1}$  equivalent to  $\nu\text{CO}$  of cyclic amide. The mass spectrum revealed a molecular ion peak at  $m/e$  284 (2.4%) equivalent to molecular formula  $\text{C}_{13}\text{H}_8\text{N}_4\text{O}_4$ .

A new route for synthesise of 2-amino-3-cyano-1[H],4[H],7[H],8[H]-3,4-dihydro [1]benzo[4,3-d]pyrimidino 5 was formed by the interaction between compound 1 and malononitrile when it was refluxed in DMF in the presence of piperidine as catalyst to yield pyrrole not isolated pyrimidine structure 4.

Attempts are made to synthesize the ethoxymethyleneamino derivative 8 via reacting compound 1 with triethylorthoformate either in a refluxing dimethylsulfoxide or in the presence of acetic anhydride under reflux. However, these attempts resulted in formation of compounds 9 and 10 respectively (scheme 1). The structure 8 was excluded on the bases of elemental analysis and spectral data. Thus, the IR spectrum of compound 9 revealed absorption bands at 3258.9  $\text{cm}^{-1}$  equivalent to  $\nu\text{NH}$ , at 2922.5  $\text{cm}^{-1}$  which indicated the absorption frequency of the aliphatic C-H bonds, at 1743.6 characteristic for  $\nu\text{CO}$  of  $\alpha$ -lactone. The band at 1655.0  $\text{cm}^{-1}$  is diagnostic for  $\nu\text{CO}$  of cyclic amide. Further confirmation for structure 9 was based on its formation chemically when the target compound 1 was refluxed alone in dimethylsulfoxide to yield the product assigned structure 9. Supporting evidences for the structure of compound 10 were provided from the IR spectrum which showed strong absorption bands at 3169.9  $\text{cm}^{-1}$  characteristic for  $\nu\text{NH}$ , at 2982.0, 2930.2  $\text{cm}^{-1}$  due to  $\nu\text{CH}$  aliphatic, a band at 1750.0  $\text{cm}^{-1}$  related to  $\nu\text{CO}$  of saturated  $\alpha$ -lactone. Additional absorption bands appeared at 1716.6  $\text{cm}^{-1}$  equivalent to  $\nu\text{CO}$  of the acetyl function and a band at 1666.6  $\text{cm}^{-1}$  due to  $\nu\text{CO}$  of cyclic amide. The <sup>1</sup>HNMR (DMSO-*d*<sub>6</sub>) spectrum of compound 10 showed two singlets at  $\delta$  2.21 and 2.26 which are characterizing for the presence of the two methyl groups. It showed a multiplet at 7.3-8.2 equivalent to six protons due to aromatic (4H) and (2H), at C3, C4 (of pyranone) protons. Finally, a singlet at 11.01 ppm indicates the presence of NH proton. An additional proof for the structure 10 was gained from direct comparison with the product obtained when compound 1 was heated in acetic anhydride only.

Moreover<sup>17</sup>, treatment of compound 1 with hydroxylamine hydrochloride in glacial acetic acid in the presence of fused sodium acetate under reflux, afforded the benzopyranopyrimidinopyrazole derivative 11. The structure assigned to the reaction product was proved based on analytical and spectral data. The IR spectrum showed strong absorption bands at 3330.4, 3192.4  $\text{cm}^{-1}$  corresponding to  $\nu\text{NH}_2$ , at 1733.1  $\text{cm}^{-1}$  equivalent to  $\nu\text{CO}$  of  $\delta$ -lactone, at 1645.4  $\text{cm}^{-1}$  due to  $\nu\text{CO}$  of amide ring and the absorption band at 1616.4  $\text{cm}^{-1}$  is diagnostic for  $\nu\text{C}=\text{N}$ .

The behavior of compound 1 towards dehydrohalogenation was studied. Thus the reaction between compound 1 and phenacyl bromide in alcoholic potassium hydroxide gave imidazopyrimidine carboxylic acid derivative 12. The constitution of this compound was based on analytical and spectral data. The IR spectrum showed a broad absorption band at 3448.5-3266.0  $\text{cm}^{-1}$  related to absorption frequency of COOH and OH groups, a strong absorption band at 2203.0  $\text{cm}^{-1}$  which characterized the presence of the cyano group. It showed no absorption band in the region corresponding to  $\nu\text{CO}$  of  $\delta$ -lactone which confirm the coumarin ring opening, the carboxylic carbonyl function absorbs at 1662.0  $\text{cm}^{-1}$ . Finally the band at 1643.0  $\text{cm}^{-1}$  is equivalent to the cyclic amide. The mass spectrum revealed a parent peak at  $m/e$  372 (2.5%) equivalent to molecular formula  $\text{C}_{20}\text{H}_{12}\text{N}_4\text{O}_4$ .

A new synthetic approach for 1-amino-3[H],5[H],6[H]-3,4-dihydro-[1] benzo pyrano-[4,3-d] pyrimidino[1,2-a] imidazol-5, 6-dione-2-ethylcarboxylate 13 was isolated by the reaction between the target compound 1 and ethyl bromoacetate in a refluxing acetone in the presence of anhydrous potassium carbonate.<sup>18</sup> The structure of such compound was proved based on the fact that its IR spectrum displayed an absorption band at 3455.7, 3332.6  $\text{cm}^{-1}$  indicating the presence of  $\text{NH}_2$  group. A band at 3182.0  $\text{cm}^{-1}$  equivalent to  $\nu\text{NH}$ , the aliphatic CH- was found to be absorbed at 2923.9, 2854.5  $\text{cm}^{-1}$ , an absorption band at 1744.7  $\text{cm}^{-1}$  corresponding to  $\nu\text{CO}$  of  $\delta$ -lactone, at 1682.9  $\text{cm}^{-1}$  related to the absorption frequency of the conjugated ester, at 1648.4  $\text{cm}^{-1}$  due to  $\nu\text{CO}$  of cyclic amide and at 1608.0  $\text{cm}^{-1}$  due to  $\nu\text{C}=\text{N}$ . Moreover compound 13 was correctly micro-analyzed for the molecular formula  $\text{C}_{16}\text{H}_{14}\text{N}_4\text{O}_5$  and the mass spectrum revealed a parent peak at  $m/e$  342 (2.8%) corresponding to the molecular formula  $\text{C}_{16}\text{H}_{14}\text{N}_4\text{O}_5$ .

A convenient route for synthesis of hydrazinotriazole derivative (14) is by refluxing a mixture of compound 1 with N-amino dithiocarbamic acid in DMF. Supporting evidences for this structure assigned to the reaction product were provided from its elemental analysis and spectral data. Its IR spectrum revealed strong absorption bands at 3328.8, 3194.6  $\text{cm}^{-1}$  characteristic for  $\nu\text{NH}_2$  group. It displayed no absorption band for CN group, furthermore, it showed strong absorption band at 1731.9  $\text{cm}^{-1}$  equivalent to  $\nu\text{CO}$  of  $\alpha$ -lactone, at 1651.6  $\text{cm}^{-1}$  due to  $\nu\text{CO}$  of cyclic amide and at 1613.9  $\text{cm}^{-1}$   $\nu\text{C}=\text{N}$ . The mass spectrum showed a molecular ion peak at  $m/e$  368 (2.4%).

When a mixture of acetaldehyde and malononitrile was added to a suspension of compound 1 in absolute ethanol in the presence of pyridine and the mixture was heated under reflux, afforded a quinazoline structure 16 not expected structure 15. The structure of the compound assigned to the reaction product was confirmed via the IR spectrum which revealed strong absorption bands at 3443.2 due to  $\nu\text{OH}$ , at 3361.4, 3250.0  $\text{cm}^{-1}$  characteristic for absorption frequency of  $\text{NH}_2$  group, at 2977.1, 2929.7  $\text{cm}^{-1}$  due to  $\nu\text{CH}$

aliphatic, at  $2200.0\text{ cm}^{-1}$  equivalent to  $\nu\text{CN}$  group. The band at  $1739.4\text{ cm}^{-1}$  is diagnostic for  $\nu\text{CO}$  of  $\delta$ -lactone, an absorption band at  $1703.8\text{ cm}^{-1}$  indicated to  $\nu\text{CO}$  of the cyclic ketone, a band at  $1646.0\text{ cm}^{-1}$  due to  $\nu\text{CO}$  of cyclic amide and at  $1612.2\text{ cm}^{-1}$  related to  $\nu\text{C}=\text{N}$ . The reaction product was correctly micro-analyzed for the molecular formula  $\text{C}_{19}\text{H}_9\text{N}_5\text{O}_4$  and accordingly assigned the structure 16 over 15. Furthermore, the structure 15 was further ruled out based on the mass spectrum, which displayed a parent peak at  $m/e$  371 (5.1%).

The synthesis of the oxadiazine derivatives 18a-c was accomplished via react the target compound 1 with aromatic aldehydes in the presence of catalytic amounts of piperidine under fusion conditions. Supporting evidences for this structure were provided from the elemental analysis and spectral data. The IR spectra displayed strong absorption bands at  $3427.9\text{-}3425.5\text{ cm}^{-1}$  characterizing the presence of NH function and showed no absorption band for the cyano group which confirm the exclusion of structure 17, an absorption band at  $1738.9\text{-}1725.0\text{ cm}^{-1}$  equivalent to  $\nu\text{CO}$  of  $\alpha$ -lactone, the band at  $1671.9\text{-}1669.0\text{ cm}^{-1}$  is diagnostic for  $\nu\text{CO}$  of cyclic amide and at  $1608.8\text{-}1605.4\text{ cm}^{-1}$  due to  $\nu\text{C}=\text{N}$ . Further confirmation was based on the mass spectrum, for example compound 18c showed a parent peak at  $m/e$  403 (2.7%) corresponding to molecular formula  $\text{C}_{19}\text{H}_9\text{N}_5\text{O}_6$ .

## Materials and Methods

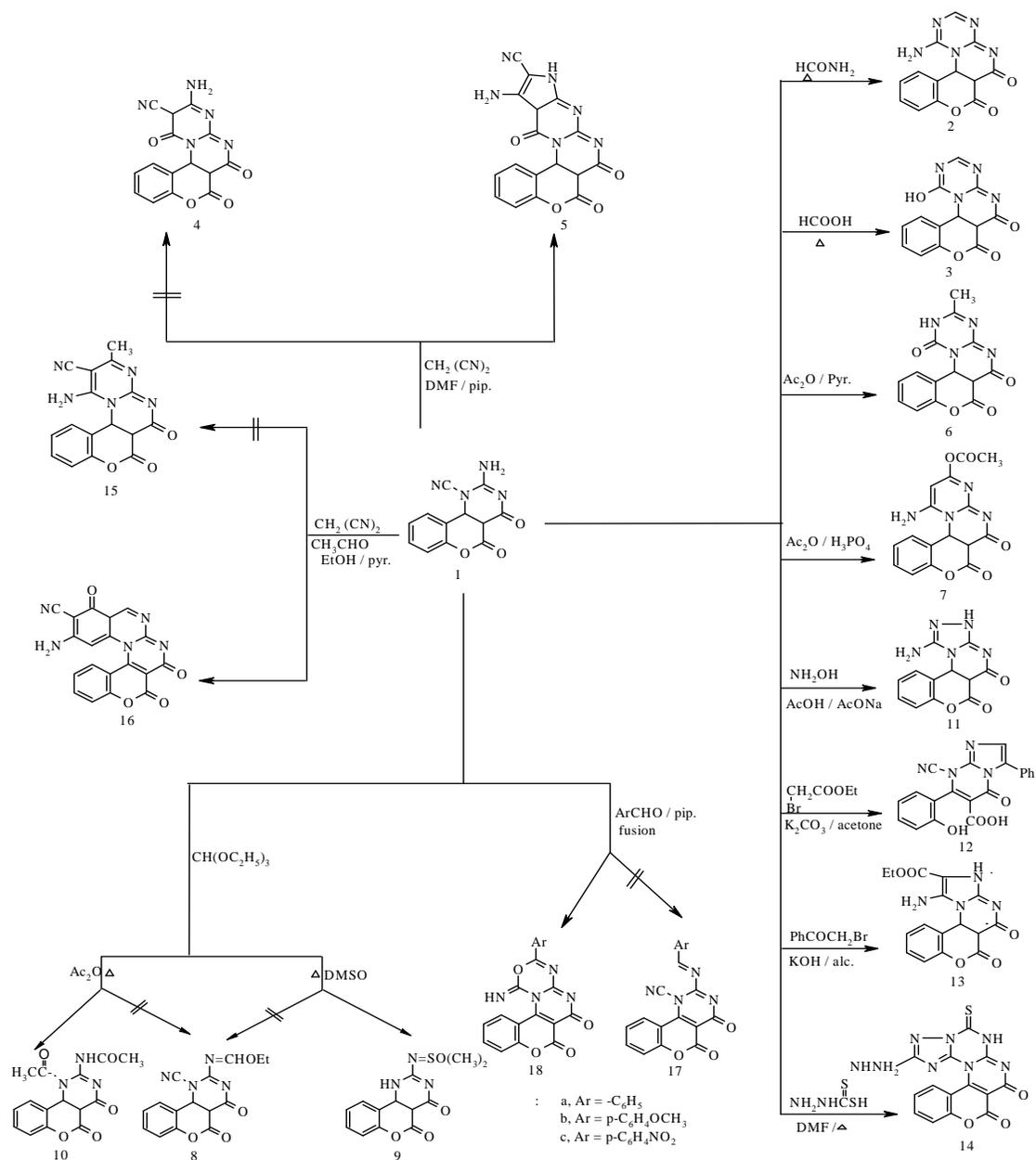
All melting points are uncorrected and were determined on Stuart electric melting point apparatus. Elemental analysis was performed by the Microanalytical center, Faculty of Science, Cairo University. Infrared spectra were recorded on Bruker or Satellite 2000 spectrometer using KBr discs. Mass spectra were determined on GC-MS (QP/000 EX) SHIMADZU spectrometer at an ionizing voltage of 70 eV. Nuclear magnetic resonance spectra were recorded on Varian Mercury 300 MHz spectrometer using TMS as internal standard; chemical shifts are recorded in  $\delta$  units. Characterization data of all the prepared compounds are given in table(1).

### *Synthesis of 2-amino-1-cyano-4[H],5[H]-3,4-dihydro[1]benzopyrano[4,3-d]pyrimidine-4,5-dione 1.*

A mixture of 3-ethoxycarbonylcoumarin (21.8 g, 0.1 mole), cyanoguanidine (8.4 g, 0.1 mole) and anhydrous potassium carbonate (13.8 g, 0.1 mole) in absolute ethanol was heated under reflux with stirring for 2 hrs. The reaction mixture was cooled, poured into a mixture of water and glacial acetic acid. The solid product that obtained was filtered off and recrystallized from DMF.

### *Synthesis of 1-amino-6[H],7[H]-3,4-dihydro[1]benzopyrano-[4,3-d]pyrimidino [1,2-a]-[1,3,5]triazin-6,7-dione 2.*

A solution of 1 (2.56 g, 0.01 mole) in formamide (30 ml) was heated under reflux for 3 hrs. The resulting dark red colored solution was cooled, poured into ice cold water and the obtained solid was filtered off and recrystallized.



Scheme 1

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*Synthesis of 1-hydroxy-6[H],7[H]-3,4-dihydro[1]benzopyrano[4,3-d] pyrimidino-[1,2-a][1,3,5]triazin-6,7-dione 3.*

(40 ml) of formic acid was added to (2.56 g, 0.01 mole) of compound 1. The resulting yellow solution was heated under reflux for 24 hrs. Then cooled and the solid product that formed was collected by filtration, dried and recrystallized from DMF.

*Synthesis of 2-amino-3-cyano-1[H,4[H],7[H],8[H]-3,4-dihydro[1] benzopyrano [4,3-d] pyrimidino [1,2-a]- pyrimidino[2,3-b]pyrrol-1,7,8-trione 5.*

A mixture of 1 (1.28 g, 0.005 mole), malononitrile (0.66 g, 0.01 mole) and piperidine (few drops) in DMF (40 ml) was heated under reflux. The reaction mixture acquires a yellow, faint brown then dark brown color. The reflux was continued for 11 hrs, the cooled and poured into ice cold water and the solid that separated was filtered off and recrystallized from ethanol.

*Synthesis of 3-methyl-1[H],2[H],6[H],7[H]-3,4-dihydro[1]benzopyrano[4,3-d]pyrimidino[1,2-a][1,3,5]triazin-1,6,7-trione 6.*

A solution of 1 (2.56 g, 0.01 mole) in a mixture of acetic anhydride (30 ml) and pyridine (15 ml) was refluxed for 5 hrs. The reaction mixture was cooled, poured into crushed ice and left to stand at room temperature for 24 hrs and the solid product formed was collected by filtration and recrystallized from acetic acid.

*Synthesis of 1-amino-3-acetoxy-6[H],7[H]-3,4-dihydro[1]benzopyrano[4,3-d]pyrimidino[1,2-a]pyrimidin-6,7-dione 7.*

(15 ml) of concentrated phosphoric acid was added to a solution of 1 (2.56 g, 0.01 mole) in acetic anhydride (15 ml). The reaction mixture got very hot which on reflux acquire a dark brown color. The reflux was continued for 10 hrs, poured into ice cold water and neutralized with solid sodium carbonate till PH 7 and the solid product that separated out was collected by filtration and recrystallized from DMF.

*Synthesis of 2-N-dimethylsulphoxy 4[H],5[H]-3,4-dihydro[1]benzopyranol[4,3-d]pyrimidin-4,5-dione 9.*

Triethylorthoformate (0.01 mole, 1.6ml) and drops of acetic anhydride was added to a solution of 1(0.01mole, 2.56g) in DMSO (40ml). The reaction mixture was heated under reflux for 7 hrs then cooled and poured into a mix. of ice/HCl. The solid reaction product was collected by filtration, dried and crystallized from methanol.

*Synthesis of 1-acetyl-2-N-acetylamino-4[H],5[H]-3,4-dihydro[1] benzopyrano [4,3-d]pyrimidin-4,5-dione 10.*

0.7 ml (0.005 mole) of triethylorthoformate was added to a solution of compound 1 (1.28 g, 0.005 mole) in acetic anhydride (30 ml) and the reaction mixture was refluxed for 5 hrs. The solvent was left to evaporate. The solid product that separated out was collected by filtration, dried and recrystallized from ethanol.

*Synthesis of 1-amino-3[H],5[H],6[H]-3,4-dihydro[1]benzopyrano[4,3-d]pyrimidino[2,1-c]-[1,2,4]triazol-5,6-dione 11.*

A mixture of compound 1 (2.56 g, 0.01 mole), hydroxylamine hydrochloride (0.69 g, 0.01 mole) and fused sodium acetate (0.2 g) in glacial acetic acid, was heated under reflux for 3 hrs. The solid separated out after concentration and cooling was collected by filtration and recrystallized from acetic acid.

*Synthesis of 1-cyano-4-phenyl-5-oxo-7-(2-hydroxyphenyl)-5[H]-imidazo[1,2-a] pyrimidin-6-carboxylic acid 12.*

A mixture of 1 (2.56 g, 0.01 mole) and phenacyl bromide (1.99 g, 0.01 mole) in alcoholic potassium hydroxide (0.56 g in 40 ml absolute ethanol) was heated under reflux for 5 hrs. Then cooled and poured into ice cold water. The reaction mixture was made acidic by addition of concentrated hydrochloric acid and the formed precipitate was collected by filtration and recrystallized from ethanol.

*Synthesis of 1-amino-2-ethoxycarbonyl-3[H],5[H],6[H]-3,4-dihydro[1]benzopyrano[4,3-d]-pyrimidino[1,2-a]imidazol-5,6-dione 13.*

Ethyl bromoacetate (0.6 ml, 0.005 mole) and anhydrous potassium carbonate (1 g) were added to a solution of compound 1 (1.28 g, 0.005 mole) in a dry acetone (40 ml). The reaction mixture was refluxed with stirring for 12 hrs and allowed to evaporate at room temperature. The residue was treated with a mixture of acetic acid and water, the obtained solid product was filtered off, washed with water and recrystallized from acetic acid.

*Synthesis of 2-hydrazino-5-thiox-6[H],8[H],9[H][1]benzopyrano[4,3-d]pyrimidin[1,2-a]-[1,3,5]triazino[2,1-b][1,2,4]triazol-8,9-dione 14.*

A mixture of compound 1 (2.56 g, 0.01 mole) and N-aminodithiocarbamic acid (1.08 g, 0.01 mole) was dissolved in DMF (40 ml) and then heated under reflux for 6 hrs. The reaction mixture was poured into a crushed ice and the formed solid was collected by filtration, dried and recrystallized from methanol.

*Synthesis of 2-amino-3-cyano-4[H],8[H],9[H][1]benzopyrano[4,3-d]pyrimidino-[1,2-a]quinazolin-4,8,9-trione 16.*

A solution of equimolar amounts of acetaldehyde and malononitrile (0.01 mole) in absolute ethanol (20 ml), was added to a suspension of compound 1 (2.56 g, 0.01 mole) in absolute ethanol and pyridine. The reaction mixture was refluxed for 4 hrs, the solvent was evaporated, the residue was treated with cold water and the formed solid was filtered

off, dried and recrystallized from methanol.

*Synthesis of 1-imino- 3-aryl-6[H],7[H][1]benzopyrano[4,3-d]pyrimidino[1,2-d]-[1,3,5]oxadiazin-,6,7-dione 18a-c.*

A mixture of compound 1 (2.56 g, 0.01 mole), appropriate aromatic aldehyde (0.01 mole) and few drops of piperidine was fused in mantel. The fusion mixture was dissolved in methanol and the whole mixture was refluxed for 2 hrs and the reaction mixture was cooled. The solid products separated out were collected by filtration and recrystallized from proper solvents to give compounds 18a-c.

#### *Antimicrobial activity*

All the newly synthesized compounds were screened *in-vitro* for their antimicrobial activity using the cup plate method, and agar medium by measuring the zone of inhibition according to a standard procedure against a variety of bacterial strains such as gram +ve bacteria [*Bacillus subtilis* and *Staphylococcus aureus* and gram -ve *Escherichia coli*].

The selected micro organisms were tested to some sensitivity compounds and are presented in Table (2). A concentration of 0.05 and 0.1 ml in dimethylsulfoxide of each compound was used for testing. Standard drugs amoxicillin has screened under similar conditions for comparison. By visualizing the antimicrobial data, it could be observed that some of the compounds posses significant activity. However, the activities of the tested compounds are less than that of standard antibacterial agents, Results are presented in Table (2).

#### **Conclusion**

The screening results revealed that the compounds; 3, 5, 6, 7, 9,10, 11, 12, 13, 14, 16 and 18 have significantly antimicrobial activity, however the compounds; 7, 9 and10 showed moderate to considerable antibacterial activities against all the employed organisms at conc. 0.05 ml, 0.1 ml dose level and are comparable to that of standard drugs (Amoxicillin)

Table(1). Characterization data of the synthesized compounds

Compd.	m.p.(°C) & Colour	Solvent & yield (%)	Formula (M.W)	Analysis		
				Calcd.	Found	
1	> 340 Colorless	DMF 52	C <sub>12</sub> H <sub>8</sub> N <sub>4</sub> O <sub>3</sub> 256.21	C	56.25	56.69
				H	3.14	3.21
				N	21.86	21.65
2	>340 Pale brown	DMF 50	C <sub>13</sub> H <sub>9</sub> N <sub>5</sub> O <sub>3</sub> 283.24	C	55.12	55.43
				H	3.20	3.31
				N	24.72	24.44
3	>340 Pale yellow	DMF 43	C <sub>13</sub> H <sub>8</sub> N <sub>4</sub> O <sub>4</sub> 284.22	C	54.93	55.34
				H	2.83	2.91
				N	19.71	19.66
5	235 Brown	Ethanol 37	C <sub>17</sub> H <sub>10</sub> N <sub>6</sub> O <sub>4</sub> 362.29	C	56.35	56.33
				H	2.78	2.87
				N	23.91	23.66
6	>340 Brown	Acetic acid 42	C <sub>14</sub> H <sub>10</sub> N <sub>4</sub> O <sub>4</sub> 298.25	C	56.37	55.82
				H	3.37	3.45
				N	18.78	18.52
7	>340 Brown	DMF 70	C <sub>16</sub> H <sub>12</sub> N <sub>4</sub> O <sub>5</sub> 340.29	C	56.47	56.27
				H	3.55	3.63
				N	16.46	16.63
9	297-299 Pal yellow	Methanol	C <sub>13</sub> H <sub>11</sub> N <sub>3</sub> SO <sub>4</sub> 425	C	36.7	36.45
				H	2.58	2.41
				N	9.78	9.83
				S	7.52	8.12
10	318 Brown	Ethanol 42	C <sub>15</sub> H <sub>13</sub> N <sub>3</sub> O <sub>5</sub> 315.28	C	57.14	56.77
				H	4.15	4.18
				N	13.32	13.0
11	>340 Yellow	Acetic acid 52	C <sub>12</sub> H <sub>9</sub> N <sub>5</sub> O <sub>3</sub> 271.23	C	53.13	53.40
				H	3.34	3.40
				N	25.82	25.00
12	283-285 Pale yellow	Ethanol 35	C <sub>20</sub> H <sub>12</sub> N <sub>4</sub> O <sub>4</sub> 372.33	C	64.51	64.87
				H	3.24	3.33
				N	15.04	14.79

Table (2) Antimicrobial activity of compounds (3-18)

Compounds	Antibacterial activity					
	Gram +ve				Gram -ve	
	<i>Bacillus subtilis</i>		<i>Staphylococcus</i>		<i>E. coli</i>	
	0.05 ml	0.1 ml	0.05 ml	0.1 ml	0.05 ml	0.1 ml
<b>3</b>	9	10	10	10	11	13
<b>5</b>	11	12	11	13	10	11
<b>6</b>	10	11	11	12	9	12
<b>7</b>	12	12	11	14	10	11
<b>9</b>	13	14	11	13	12	13
<b>10</b>	12	13	11	12	10	10
<b>11</b>	9	10	12	14	10	11
<b>12</b>	8	10	9	9	10	12
<b>13</b>	10	11	9	11	10	11
<b>14</b>	11	13	11	13	9	9
<b>16</b>	10	14	12	14	11	13
<b>18</b>	13	15	10	12	11	13
<b>Amoxicillin</b>	16	18	16	18	14	14

## References

- [1] S. Thaisrivangs, M.N. Jackiraman, K.T. Change, P.K. Tomich, L.A. Dolok, S.R. Turner; J.W. Strohbach, J.C. Lynn, M.M. Harg, R.R. Hinshaw and K.D. water paugh. *J. Med. Chem.*, **1996**, 39, 2400.
- [2] L.L. Shen, L.A. Mitscher, P.N. sharma, T.J.O`Donnell, D.W.T. Chu, C.S. Cooper, T. Rosen and A.G. Pernet, *Biochemistry*, **1988**, 28, 3886.
- [3] M. Longobardi, A. Bargagna, E. Marioni, P.Schenone, M. D`Amico, A. filippelli, C. Palzoramo and E. Tampa. *Farmaco*, **1993**, 48, 112.
- [4] L.Mosti, G. Menizzi, P. Schenone, M. D`Amico, M. Falciani and F. Rossi, *Farmaco*, **1994**, 49, 45.
- [5] P. Trebse, B. Recelj, M. kovevar and S. Polanoe, *J. Heterocyclic Chem*, **1997**, 34, 1247.

- [6] J. Matsumoto, A. Minannidce, Y. Kimura, S. Minami, *Chem. Pharm. Bull.*, **1980**, 28(B) 2531-6.
- [7] A.M. Abdel-Halim, R.M. Abdel-Aziz, G. Abdel-Nasser, A.I. Hashem, *Indian, J. Heterocyclic Chem*, **1995**, 4(3), 195-8.
- [8] E.A. Shokora, L.M. Alimbrova, V.V. Kovaler, *Pharm. Chem.*, **1999**, 33(7),372-376.
- [9] A.Y. Soliman, *Bull. Fac. Sci., Assiut Univ.*, **2000**, 27, 19 [C. A., 132 (2000) 151648].
- [10] H.M. Bakeer. *Chinese J. Chem.*, **2003**, 21, 1219-1223.
- [11] A.Y. Soliman, H. M. Bakeer and I. A. Attia. *Chinese J. Chem.*, **1996**, 14, 532.
- [12] R.M. Shaker, *Pharmazie*, **1996**, 51, 148-151.
- [13] A.S. Aly, N.M.Fathy, S.A. Swelam and F.M.E. Abdel-Megeid. *Egypt. J. Pharm. Sci.*, **1995**, 36, 117.
- [14] J.T. Shaw, W.M. Westeler and B. D. Stefanko. *J. Chem. Soc. Chem. Commun.*, **1972**, 1070.
- [15] J.T.Shaw, M.E. O'Connor, R.C. Allen, W.M. Westeler and B. D. Stefanko, *J. Heterocyclic chem.* **1974**, 11, 627.
- [16] A.R. Kataritzky and A.J. Boulton, *Advances in Heterocyclic Chem.*, **1978**, 22, 345.
- [17] I.S. Abdel Hafiz, A.M. Hussein and V.F.F. Mahmoud, *Z. Naturforsch.*, **1999**, 54b, 1568-1572.
- [18] H.M.F. Madkour, M.R. Mahmoud, A.M. Sakr and M.M. Habashy, *Scientia Pharmaceutica (Sc. Pharm.)*, **2001**, 69, 33-52.