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Synthesis of New Derivatives of Benzo[f]Pyrido[1,2-a]Indole Carboxylic Acid.

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ABSTRACT

A method of obtain of 6,11-dioxo-6,11-dihydrobenzo[f]pyrido[1,2-a]indole-12-carboxylic acid was optimized. New amide derivatives of 6,11-dioxo-6,11-dihydrobenzo[f]pyrido[1,2-a]indole-12-carboxylic acid were synthesized. Using computer system PASS Online opportunity of displaying biological activity of the synthesized compounds was established.

Keywords: 6,11-dihydrobenzo[f]pyrido[1,2-a]indole-12-carboxylic acid, 6,11-dihydrobenzo[f]pyrido[1,2-a]indole-12-carbonyl chloride, 6,11-dihydrobenzo[f]pyrido[1,2-a]indole-12-carboxamide.

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INTRODUCTION

Quinones play an important role in our life, and interest in their biological functions has stimulated basic chemical research in several areas. The use of quinones, in fact, dates to antiquity, and the history of these compounds is perhaps longer than that of any other group of naturally occurring substances. They are important not only as a pigments but also as a drugs [1-4]. 2,3-Dichloro-1,4-naphthoquinone (1) is known as a key synthetic intermediate in organic, medicinal, and industrial chemistry [5, 6].

Cyclization involving the halogen derivatives of 2,3-dihalo-1,4-naphthoquinone have yielded three- to six-membered heterocyclic rings [7-14]. A number of interesting articles which report on the importance of heterocyclic quinones have been published [15-18].

1,4-Naphthoquinone heterocyclic derivatives are found to exhibit an interesting range of pharmacological properties [19] including antibacterial, antiviral, trypanocidal, anticancer, antimalarial and antifungal activities.

On the other hand benzo[f]pyrido[1,2-a]indole-6,11-diones constitute an important class of annulated indolizines derivatives. Until now, three synthetic approaches have been reported [21-23]. These methods suffered from a limited reaction scope and unsatisfactory product yields. Therefore the development of new convenient and versatile synthetic methods for these compounds is demand.

RESULTS AND DISCUSSION

The work presented here focuses upon the synthesis of new amide derivatives of 6,11-dioxo-6,11-dihydrobenzo[f]pyrido[1,2-a]indole-12-carboxylic acid. Ethyl 6,11-dioxo-6,11-dihydrobenzo[f]pyrido[1,2-a]indole-12-carboxylate **2** [21] was used as starting compound (Figure 1).

Obtain of 6,11-dioxo-6,11-dihydrobenzo[f]pyrido[1,2-a]indole-12-carboxylic acid **3** was reported in work [24] by interaction of 2,3-dichloronaphthalene-1,4-dione and 2,2-dimethyl-1,3-dioxane-4,6-dione in ethanol in the presence of pyridine. We have optimized method of synthesis of compound **3** in the following way. Hydrolysis of **2** by aqueous solution of KOH in *i*-propanol was carried out and obtained potassium 6,11-dioxo-6,11-dihydrobenzo[f]pyrido[1,2-a]indole-12-carboxylate **2** was acidified by dilute hydrochloric acid (Figure 1). Data of ^{1}H and ^{13}C NMR spectra of carboxylic acid **3** agree closely with literature [24].

6,11-Dioxo-6,11-dihydrobenzo[f]pyrido[1,2-a]indole-12-carbonyl chloride **4** was obtain by interaction of acid **4** with excess of thionyl chloride in dry benzene in the presence of 2-3 drops of DMF as catalyst (Figure 1). The reaction mixture was left at a temperature of 60^{0} C for 3 h. Yield of product is 99%.

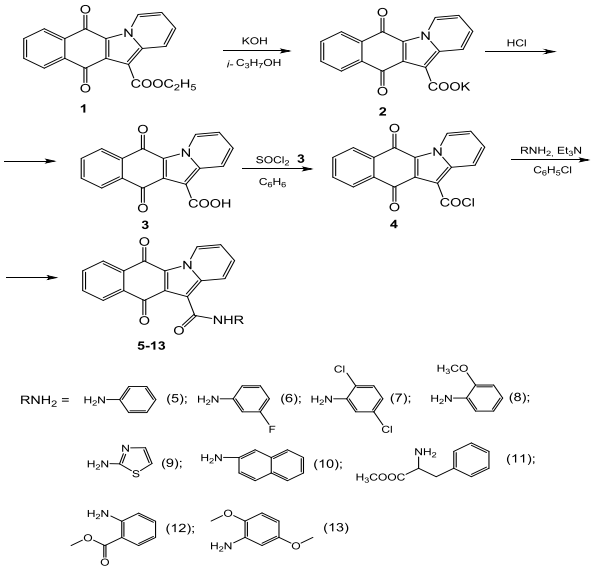

Figure 1

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The reaction of 6,11-dioxo-6,11-dihydrobenzo[f]pyrido[1,2-a]indole-12-carbonyl chloride **4** with amines was carried out at 100°C in chlorobenzene and amides **5-13** were obtained. Triethylamine was used as an acceptor of hydrogen chloride (Figure 1). Singlet signal of proton of NH-group observes at 9.35-9.87 ppm in all ^{1}H NMR spectra of the obtained amide derivatives **5-13**. In the IR spectra the absorption peaks of amide NH-group are present in the region of 3450-3400 cm^{-1}.

Thus, established combinatorial library of 1,4-quinone derivatives enables to select biological targets by ligand-directed virtual screening using PASS (Pa>0.5) [25-28] (Table 1).

Table 1: List of predicted biological activity by program PASS for amides 5-11

Compound	Pa	Activities
5	0,808	Antineoplastic
	0,606	Antineoplastic (non-small cell lung cancer)
	0,600	Kinase inhibitor
	0,601	Membrane integrity agonist
6	0,754	Antineoplastic
	0,696	Antineoplastic (non-small cell lung cancer)
	0,691	Platelet derived growth factor receptor kinase inhibitor
	0,651	Kinase inhibitor
	0,566	DNA intercalator
7	0,633	Antineoplastic
	0,542	Kinase inhibitor
	0,598	Gluconate 2-dehydrogenase (acceptor) inhibitor
	0,543	Antineoplastic (non-small cell lung cancer)
8	0,800	Antineoplastic
	0,687	Gluconate 2-dehydrogenase (acceptor) inhibitor
	0,619	Antineoplastic (non-small cell lung cancer)
	0,628	Kinase inhibitor
9	0,768	Antineoplastic
	0,678	Transcription factor STAT3 inhibitor
	0,645	Transcription factor inhibitor
	0,646	Transcription factor STAT inhibitor
	0,579	Focal adhesion kinase 2 inhibitor
	0,558	Antineoplastic (non-small cell lung cancer)
10	0,797	Antineoplastic
	0,682	Antineoplastic (non-small cell lung cancer)
	0,643	Kinase inhibitor
	0,546	DNA intercalator
11	0,624	CYP2H substrate
	0,549	Antineoplastic
	0,567	Polyporopepsin inhibitor
	0,567	DNA intercalator
12	0,691	Antineoplastic
	0,612	Kinase inhibitor
	0,550	Hexokinase inhibitor
	0,554	Antineoplastic (non-small cell lung cancer)
	0,547	Mediator release inhibitor
	0,515	Membrane integrity agonist
13	0,793	Antineoplastic
	0,708	Gluconate 2-dehydrogenase (acceptor) inhibitor
	0,609	Antineoplastic (non-small cell lung cancer)
	0,604	Kinase inhibitor
	0,512	Transcription factor STAT3 inhibitor

According to the results of the in silico prediction of biological activity by program PASS Online of the number of synthesized compounds we can conclude that general for almost all compounds are an antineoplastic activity, which can be realized by inhibiting the action of several enzymes. Thus, the

determined probability of displaying antineoplastic activity provides an opportunity to study and implement a modification of the synthesized compounds to enhance biological effects.

CONCLUSIONS

Therefore, method of obtain of 6,11-dioxo-6,11-dihydrobenzo[f]pyrido[1,2-a]indole-12-carboxylic acid was optimized by alkali hydrolysis in *i*-propanol of ethyl 6,11-dioxo-6,11-dihydrobenzo[f]pyrido[1,2-a]indole-12-carboxylate **2**. Newly stable crystalline compounds of amides of 6,11-dioxo-6,11-dihydrobenzo[f]pyrido[1,2-a]indole-12-carboxylic acid were obtained. The structures of obtained compounds were confirmed by data of ^{1}H and ^{13}C NMR, IR spectra and elemental analysis. Opportunity for further studies of biological activity of the synthesized compounds was established using computer system PASS Online.

EXPERIMENTAL

All the chemicals used for the synthesis of the compounds were purchased from Aldrich, Merck AG and Acros Chemicals. NMR spectra ^{1}H and ^{13}C are recorded on the device Varian Mercury-400 (400 and 100 MHz respectively) under 25^{o}C in the solution DMSO-d_6 (dimethylsulfoxide), internal standard TMS (tetramethylsilane). Elemental analysis performed on standard equipments for microanalysis. Monitoring the progress of the reaction and the identity of substances TLC was performed on plates "Silufol UV-254" and "Merk Kieselgel 60 F254". IR spectra were recorded on “Specord M80” in tablets of KBr. In determining the melting temperature correction for speaker connections column of mercury was undertaken.

6,11-Dioxo-6,11-dihydrobenzo[f]pyrido[1,2-a]indole-12-carbonyl chloride (4)

To a suspension of 3.20 g (0.011 mol) of **3** in 100 ml of benzene at constant stirring and at room temperature 1.043 ml (0.0143 mol) of thionyl chloride and 2-3 drops of DMF were added. The reaction mixture was kept at 60^{0}C for 3 h. Then reaction mixture was cooled to room temperature and the solvent was evaporated under vacuum. Yield 3.37 g (99%), mp = 130-131 ^{o}C. ^{1}H NMR (300 MHz, δ, ppm): 10.14 (1H, m, CH); 7.87-8.06 (2H, m, CH_{Ar}); 7.58-7.75 (2H, m, CH_{Ar}); 7.56 (1H, m, CH); 7.24 (1H, m, CH); 6.69 (1H, m, CH). IR (KBr), cm^{-1}: 1765 (COCl); 1680, 1653 (C=O). Found %: C 65.99, H 2.54, Cl 11.39; N, 4.60. $C_{17}H_8ClNO_3$. Calculated %: C 65.93, H 2.60, Cl 11.45, N 4.52.

Synthesis of amide derivatives (5-11)

To a suspension of 5.57 g (0.018 mol) of compound **4** in 100 ml of chlorobenzene at constant stirring and at room temperature a solution of 1.65 ml (0.018 mol) of corresponding amine and 2.76 ml (0.018 mol) of triethylamine were added. The reaction mixture was kept at 80^{o}C for 2 h, then was cooled to room temperature and was evaporated under vacuum. Residue was washed with water and was dried. Amides were crystallized from DMF or chlorobenzene.

6,11-Dioxo-N-phenyl-6,11-dihydrobenzo[f]pyrido[1,2-a]indole-12-carboxamide (5)

Yield 73% (from DMF), mp >300 ^{o}C. ^{1}H NMR (300 MHz, δ, ppm): 10.01 (1H, m, CH); 9.44 (1H, s, NH); 7.89-7.98 (2H, m, CH_{Ar}); 7.58-7.67 (2H, m, CH_{Ar}); 7.45 (1H, m, CH); 7.36-7.29 (5H, m, Ar); 7.23-7.24 (1H, m, CH); 6.65-6.67 (1H, m, CH). ^{13}C NMR (100 MHz, δ, ppm): 114.66, 116.05, 116.59, 120.60, 123.27, 124.36, 124.85, 126.98, 127.52, 128.09, 129.04, 130.24, 132.72, 133.05, 133.10, 134.87, 137.25, 138.46, 164.56, 179.39, 182.77. IR (KBr), cm^{-1}: 3400 (NH), 1675,1655 (C=O). Found %: C 75.48, H 3.77, N 7.71. $C_{23}H_{14}N_2O_3$. Calculated %: C 75.40, H 3.85, N 7.65.

N-(3-Fluorophenyl)-6,11-dioxo-6,11-dihydrobenzo[f]pyrido[1,2-a]indole-12-carboxamide (6)

Yield 67% (from DMF), mp >300 ^{o}C. ^{1}H NMR (300 MHz, δ, ppm): 10.00 (1H, m, CH); 9.76 (1H, s, NH); 7.89-7.98 (2H, m, CH_{Ar}); 7.57-7.67 (2H, m, CH_{Ar}); 7.15-7.21 (3H, m, CH); 6.56-6.65 (2H, m, CH). ^{13}C NMR (100 MHz, δ, ppm): 112.67, 113.14, 114.66, 115.95, 116.59, 118.44, 123.27, 124.85, 126.98, 127.52, 128.09, 130.24, 130.37, 132.72, 133.05, 133.10, 134.87, 137.25, 140.11, 162.63, 164.87, 179.39, 182.77. IR (KBr), cm^{-1}: 3420 (NH); 1670, 1655 (C=O). Found %: C 71.78, H 3.45, F 4.99, N 7.15. $C_{23}H_{13}FN_2O_3$. Calculated %: C 71.87, H 3.41, F 4.94, N 7.29.

N-(2,5-Dichlorophenyl)-6,11-dioxo-6,11-dihydrobenzo[f]pyrido[1,2-a]indole-12-carboxamide (7)

Yield 72% (from PhCl), mp =258-259 ^{o}C. ^{1}H NMR (300 MHz, δ, ppm): 10.01 (1H, m, CH_{ar}); 8.15 (1H, m, CH_{ar}); 8.12 (1H, s, NH); 7.98-7.89 (2H, dd, CH_{ar}); 7.69-7.53 (3H, m, CH_{ar}); 7.47-7.44 (1H, m, H_{ar}); 7.25-7.22 (1H, m, CH_{ar}); 6.96-6.93 (1H, m, CH_{ar}); 6.67-6.63 (1H, m, CH_{ar}). ^{13}C NMR (100 MHz, δ, ppm): 114.66, 116.07, 116.59, 122.53, 122.82, 124.82, 124.85, 126.10, 126.98, 127.52, 128.09, 129.70, 130.24, 131.47, 131.98, 133.05, 133.10, 134.59, 134.87, 137.25, 162.15, 179.39, 182.77. IR (KBr), cm^{-1}: 3438 (NH); 1672, 1659 (C=O). Found %: C 63.51; H 2.71; Cl 16.34; N 6.37. $C_{23}H_{12}Cl_2N_2O_3$. Calculated %: C 63.47; H 2.78; Cl 16.29; N 6.44.

N-(2-methoxyphenyl)-6,11-dioxo-6,11-dihydrobenzo[f]pyrido[1,2-a]indole-12-carboxamide (8)

Yield 70% (from DMF), mp = 272-274 ^{o}C. ^{1}H NMR (300 MHz, δ, ppm): 10.01 (1H, m, CH_{ar}); 8.25-8.22 (1H, m, CH_{ar}); 7.98-7.88 (2H, dd, CH_{ar}); 7.70-7.56 (2H, m, CH_{ar}); 7.47-7.44 (1H, m, CH_{ar});
7.26-7.22 (2H, m, CH_{ar}); 7.14 (1H, s, NH); 6.97-6.93 (1H, m, CH_{ar}); 6.76-6.72 (1H, m, CH_{ar}); 6.67-6.63 (1H, m, CH_{ar}); 3.67 (1H, d, CH_3). ^{13}C NMR (100 MHz, δ, ppm): 55.96, 111.47, 114.66, 116.44, 116.59, 120.20, 122.09, 122.87, 123.19, 124.85, 126.63, 126.98, 127.52, 128.09, 130.24, 132.64, 133.05, 133.10, 134.87, 137.25, 153.61, 164.09, 179.39, 182.77. IR (KBr), cm^{-1}: 3453 (NH); 1684, 1669 (C=O). Found %: C 69.91; H 4.53; N 7.69. $C_{24}H_{16}N_2O_4$. Calculated %: C 72.72; H 4.07; N 7.07.

6,11-Dioxo-N-(thiazol-2-yl)-6,11-dihydrobenzo[f]pyrido[1,2-a]indole-12-carboxamide (9)

Yield 73% (from PhCl), mp >300 ^{o}C. ^{1}H NMR (300 MHz, δ, ppm): 10.01-10.04 (1H, m, CH); 8.54 (1H, s, NH); 7.89-7.98 (2H, m, CH); 7.58-7.68 (3H, m, CH); 7.45-7.47 (1H, m, CH); 7.34-7.36 (1H, m, CH); 7.22-7.24 (1H, m, CH); 6.63-6.67 (1H, m, CH). ^{13}C NMR (100 MHz, δ, ppm): 110.50, 115.10, 116.33, 116.59, 121.44, 124.16, 126.98, 127.52, 128.09, 130.24, 130.89, 133.05, 133.10, 134.87, 137.25, 139.84, 161.62, 162.95, 179.39, 180.56. IR (KBr), cm^{-1}: 3400 (NH); 1680, 1657 (C=O). Found %: C 64.41; H 3.04; N 11.11; S 8.64. $C_{20}H_{11}N_3O_3S$. Calculated %: C 64.34; H 2.97; N 11.25; S 8.59.

N-(naphthalen-2-yl)-6,11-dioxo-6,11-dihydrobenzo[f]pyrido[1,2-a]indole-12-carboxamide (10)

Yield 75% (from PhCl), mp >300 ^{o}C. ^{1}H NMR (300 MHz, δ, ppm): 10.01 (1H, m, CH); 9.83 (1H, s, NH); 8.3-8.32 (1H, m, CH); 7.16-7.97 (10H, mm, CH); 6.89-6.91 (1H, m, CH); 6.63-6.67 (1H, m, CH). ^{13}C NMR (100 MHz, δ, ppm): 114.66, 116.51, 116.59, 121.66, 121.80, 123.27, 124.04, 124.85, 125.43, 126.23, 126.50, 126.98, 127.50, 127.52, 128.09, 130.22, 130.24, 132.72, 133.05, 133.10, 133.48, 133.70, 134.87, 137.25, 164.34, 179.39, 182.77. IR (KBr), cm^{-1}: 3410 (NH); 1680, 1653 (C=O). Found %: C 77.96; H 3.81; N 6.79. $C_{27}H_{16}N_2O_3$. Calculated %: C 77.87; H 3.87; N 6.73.

Methyl (6,11-dioxo-6,11-dihydrobenzo[f]pyrido[1,2-a]indole-12-carbonyl)phenyl-alaninate (11)

Yield 71% (from DMF), mp 257-259 ^{o}C. ^{1}H NMR (300 MHz, δ, ppm): 10.01 (1H, s, CH); 7.9-7.98 (2H, m, CH); 7.58-7.68 (2H, m, CH_{Ar}); 7.45-7.47 (1H, m, CH); 6.66-7.42 (7H, m, CH); 6.63-6.67 (1H, m, CH); 5.8 (1H, d, NH); 4.97-5.01 (1H, m, CH); 3.56 (3H, s, CH_3); 3.35-3.38 (2H, m, CH_2). ^{13}C NMR (100 MHz, δ, ppm): 35.86, 51.80, 53.58, 112.98, 114.76, 116.59, 121.99, 125.81, 126.74, 126.98, 127.83, 128.09, 129.18, 130.15, 130.55, 131.02, 133.05, 133.41, 134.87, 137.02, 137.25, 162.74, 171.34, 180.09, 183.26. IR (KBr), cm^{-1}: 3440 (NH); 1675, 1650 (C=O). Found %: C 71.75; H 4.39; N 6.23. $C_{27}H_{20}N_2O_5$. Calculated %: C 71.67; H 4.46; N 6.19.

Methyl 2-(6,11-dioxo-6,11-dihydrobenzo[f]pyrido[1,2-a]indole-12-carboxamido)-benzoate (12)

Yield 71% (from DMF), mp >300 ^{o}C. ^{1}H NMR (300 MHz, δ, ppm): 10.01 (1H, m, CH_{ar}); 9.08 (1H, m, CH_{ar}); 7.99-7.88 (3H, m, CH_{ar}); 6.69-6.56 (2H, m, CH_{ar}); 7.49-7.44 (2H, m, CH_{ar}); 7.25-7.22 (1H, m, CH_{ar}); 6.92-6.88 (1H, m, CH_{ar}); 6.67-6.63 (1H, m, CH_{ar}); 5.88 (1H, c, NH); 3.86 (3H, s, CH_3). ^{13}C NMR (100 MHz, δ, ppm): 52.60, 114.66, 115.73, 116.59, 121.70, 123.08, 123.14, 124.85, 125.12, 126.98, 127.52, 128.09, 130.24, 130.51, 132.59, 133.05, 133.07, 133.10, 134.87, 137.25, 138.58, 164.71, 169.85, 179.39, 182.77. IR (KBr), cm^{-1}: 3330 (NH); 1678, 1662 (C=O). Found %: C 70.81; H 3.73; N 6.69. $C_{25}H_{16}N_2O_5$. Calculated %: C 70.75; H 3.80; N 6.60.

N-(2,5-dimethoxyphenyl)-6,11-dioxo-6,11-dihydrobenzo[f]pyrido[1,2-a]indole-12-carboxamide (13)

Yield 75% (from DMF), mp >300 ^{o}C. ^{1}H NMR (300 MHz, δ, ppm): 10.01 (1H, m, CH_{ar}); 8.30 (1H, s, NH); 7.97-7.87 (2H, dd, CH_{ar}); 7.70-7.56 (3H, m, CH_{ar}); 7.44 (1H, m, CH_{ar}); 7.23 (1H, m, CH_{ar}); 6.84-6.75 (2H, m, CH_{ar}); 6.66 (1H, m, CH_{ar}); 3.78-3.67(2H, d, $2CH_3$). ^{13}C NMR (100 MHz, δ, ppm): 52.60, 114.66,115.73,116.59,121.70, 123.08, 123.14, 124.85, 125.12, 126.98, 127.52, 128.09, 130.24, 130.51, 132.59, 133.05, 133.07, 133.10, 134.87, 137.25, 138.58, 164.71, 169.85, 179.39, 182.77. IR (KBr), cm^{-1}: 3440 (NH); 1680, 1667 (C=O). Found %: C 70.49; H 4.18; N 6.64. $C_{25}H_{18}N_2O_5$. Calculated %: C 70.42; H 4.25; N 6.57.

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