Synthesis and Antimicrobial Activity of Some Derivatives of 5-Substituted Indole Dihydropyrimidines

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Abstract: P. Biginelli reported the synthesis of functionalized 3, 4 dihydropyrimidine-2 (1*H*)-ones via three component condensation of an aromatic aldehyde, urea and ethylacetoacetate. This multicomponent reaction is of much importance due to excellent pharmacological properties of dihydropyrimidines. In this account, we synthesized some halo substituted indole dihydropyrimidines and evaluated their antimicrobial activity. The minimum inhibitory concentration (MIC) was determined by micro dilution technique in Mueller-Hinton broth. The MICs were recorded after 24 hours of incubation at 37 °C. These results are promising, showing these compounds are biologically active.

Keywords: Substituted indoles, Dihydropyrimidines, Biginelli Reaction, Multicomponent reaction.

Introduction

In the family of heterocyclic compounds nitrogen containing heterocycles are an important class of compounds in the medicinal chemistry and also contributed to the society from biological and industrial point which helps to understand life processes¹. This seems to be because pyrimidines represents one of the most active class of compounds possessing wide spectrum of biological activity *viz.* significant *in vitro* activity against unrelated DNA and RNA, viruses including polio herpes viruses, diuretic, antitumor, anti HIV, cardiovascular². Biginelli compounds show a diverse range of biological activities. The interest focused on Biginelli compounds leading to the development of nitractin (A)³, that has excellent activity against the virus of trachoma group, the same compounds also exhibit antibacterial activity. 4-Aryl dihydropyrimidines *e.g.* nifedipine (B) are the important and most studied class as

calcium channel modulars. In 1975 their introduction in clinical medicine for the treatment of cardiovascular diseases⁴, some of the analogues were screened as antitumor agents. Pyrimidine -5-carboxamide of type (C) was reported to possess anticarcinogenic activity, anti-inflammatory⁵, analgesic⁶.

The topsentins, as antiviral and antitumor agents from marine sponge represents the emerging class of bis indole alkaloids. During the search of bioactive natural products act as cytotoxic and antifungal compounds belongs to class noprtopsentsins⁷. The presence of highly substituted indole and indolines in a variety of bioactive molecular targets has inspired a number of groups including ours to develop new and improved routes to their synthesis⁸. Recently there is a much interest in the synthesis of small molecules for chemist in accelerating drug discovery⁹.

Experimental

General procedure for synthesis of substituted indole-3-carboxaldehyde (3)

To dimethyl formamide in ice bath, POCl₃ was added drop wise by maintaining temperature below 10 °C. After the addition, the mixture was stirred for 0.5 h. To this formylation complex, solution of indole (**1** or **2**) in DMF was added. During addition temperature was maintained below 10 °C. Then the temperature of the reaction mixture was brought to 35 °C slowly and maintained for 1 h. Then it was cooled to 10 °C and NaOH solution was added till alkaline. The resulting suspension was heated to 60 °C and allowed to cool to room temperature. It was filtered and washed with water.

1-H-Indole -3- carboxaldehyde (3a)

M.p.198 °C; I.R. (KBr pellet): 3460, 3201, 3114, 3083, 2895, 2716, 1627, 1535, 1443, 1235, 787 cm⁻¹; ¹H NMR (DMSO-*d*₆): δ 7.23 (2H, br, H⁵ and H⁶), 7.52 (1H, s, H⁷), 8.17 (1H, s, H⁴), 8.35 (1H, s, H²), 9.95 (1H, s, CHO), 12.20 (H, s, NH). Elemental analysis calc. (%) C 74.47, H 4.86, N 9.65, O 11.02 found C 74.43, H 4.82, N 9.61, O 11.04.

5-Bromo-1H-indole -3-carboxaldehyde (3b)

M.p.202 °C; I.R. (KBr pellet): 3440, 3215, 3103, 3058, 2833, 2773, 1647, 1581, 1535, 1444, 1235, 736 cm⁻¹; ¹H NMR (DMSO-*d*₆): δ 7.40 (1H, s, H⁶), 7.52 (1H, s, H⁷), 8.22 (1H, s, H⁴), 8.35 (1H, s, H²), 9.95 (1H, s, CHO), 12.20 (1H, s, NH). Elemental analysis calc. (%) C 48.25, H 2.70, N 6.25, O 7.14, found C 48.23, H 2.71, N 6.21, O 7.16.

5-Chloro-1H-indole-3-carboxaldehyde (3c)

M.p.200 °C; I.R. (KBr pellet): 3435, 3200, 3102, 2940, 1650, 1560, 1452, 1213, 790, 735cm⁻¹ NMR (DMSO-*d*₆): δ 7.42(1H, s, H⁶), 7.55 1H, s, H⁷), 8.25 1H, s, H⁴), 8.38 1H, s, H²), 9.98 1H, s, CHO), 12.24 1H, s, NH). Elemental analysis calc. (%) C 60.19, H 3.37, N 7.80, O 8.91, found C 60.16, H 3.35, N 7.78, O 8.89.

5-Iodo-1H-indole-3-carboxaldehyde (3d)

M.p. 220 °C; I.R. (KBr pellet): 3445, 3201, 3114, 3083, 2895, 2716, 1627, 1535, 1443, 1235, 787 cm⁻¹; ¹H NMR (DMSO-*d*₆): δ 7.40 (1H, s, H⁶), 7.55 (1H, s, H⁷), 8.25 (1H, s, H⁴), 8.42 (1H, s, H²), 9.96 (1H, s, CHO), 12.26 (1H, s, NH). Elemental analysis calc. (%) C 39.88, H 2.23, N 5.17, O 5.90, found C 39.84, H 2.21, N 5.19, O 5.88.

General procedure for the synthesis of indole dihydropyrimidine (6)

A mixture of indole-3-carboxaldehyde **3** (1 eq), urea or thiourea **4** (2 eq), ethylacetoacetate **5** (1 eq) in ethanol was heated under reflux in the presence of acid catalyst. TLC was used to monitor the progress of the reaction. After completion the reaction mixture was poured on crushed ice and filtered under suction, the precipitate was washed with water. The pure product is obtained by recrystallization from ethanol.

4-(5-Bromo-1H-indole-3-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester (6b)

IR (KBr pellet): 3215, 3100, 3060, 1710, 1650, 1525, 1450, 1230, 1095, 750 cm⁻¹; ¹H NMR (DMSO-*d*₆): δ 1.18 (3H, t, OCH₂CH₃), 2.35 (3H, s, CH₃), 4.05 (2H, q, OCH₂CH₃), 6.30 (1H, NHCH), 6.75-7.20 (6H, br, Ar-H) and NH, 7.92 (H, s, NH). Elemental analysis calc. (%) C 50.81, H 4.26, N 11.11, O 12.69, found C 50.80, H 4.23, N 11.09, and O 12.66.

4-(5-Iodo-1H-indole-3-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester (6h)

IR (KBr pellet): 3383, 3276, 3175, 3088, 1617, 1474, 1423, 1199, 1097, 746 cm⁻¹; ¹H NMR (DMSO-*d*₆): δ 1.22 (3H, t, OCH₂CH₃), 2.40 (3H, s, CH₃), 4.15 (2H, q, OCH₂CH₃), 6.6 (1H, NHCH), 6.82-7.25 (6H, br, Ar-H) and NH, 7.9 (1H, s, NH). Elemental analysis (%) calc. C 43.55, H 3.65, N 9.52, O 7.25, found C 43.52, H 3.62, N 9.53, O 7.22, and S 7.26.

Antimicrobial studies***In vitro* antibacterial studies**

Newly synthesized compounds **3a-d** and **6a-h** were screened for their *in vitro* antibacterial activity against *Escherichia coli* (ATCC 10536) and *Pseudomonas aeruginosa* (ATCC 9027) according to the disc diffusion method. The minimum inhibitory concentration (MIC) was determined by the serial dilution technique using dimethylsulphoxide as a solvent. Ciprofloxacin (1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinoline carboxylic acid) was used as standard in these antibacterial screening studies. The MIC calculated were 100 µg/mL for compounds **3a-d**, 50 µg/mL for compounds **6a-d** and 75 µg/mL for compounds **6e-h**.

***In vitro* antifungal studies**

The antifungal screening studies of compounds **3a-d** and **6a-h** were performed by the standard agar disc diffusion method. Seven days old cultures of *Aspergillus niger* (ATCC 16404) and *Fusarium oxysporum* (isolated from rotten fruits) were used as test organisms. They were grown on potato dextrose agar medium. The MIC values were determined by serial dilution technique using dimethylsulphoxide as solvent. The growth of microorganisms was determined visually and the lowest concentration that inhibits the growth of microorganisms for 24 hours at 37 °C was taken as the MIC. The standard used for

comparison in antifungal screening studies was carbendazim (1*H*-benzimidazol-2-yl carbamic acid methyl ester). The MIC calculated were 100 µg/mL for compounds **3a-d**, 75 µg/mL for compounds **6a-d** and 50 µg/mL for compounds **6e-h**.

Results and Discussion

The most obvious approach for carrying out the synthesis of substituted indole dihydropyrimidines is due to potent biological activity of indoles as well as dihydropyrimidines. The synthesis begins from the commercially available indole (**1**), we were able to synthesize 5-substituted indoles (**2**) in three steps using known protocol¹⁰. The further formylation of **2** with DMF/POCl₃ by Wismeyer - Hack method to obtain indole 3-carboxaldehyde (**3**) in good yields¹¹.

In cyclocondensation reaction of indole carboxaldehyde (**3**), urea or thiourea (**4**) and ethylacetoacetate (**5**) in the presence of acid catalyst by refluxing in ethanol to afford indole dihydropyrimidines (**6**)¹². The structural assignments for indole 3-carboxaldehydes (**3**) and indole dihydropyrimidines (**6**) were made by correlating ¹H NMR and IR data with data for corresponding compounds.

In summary, we have synthesized indole dihydropyrimidines via cyclocondensation between indole carboxaldehyde, urea or thiourea and ethylacetoacetate.

Scheme 1. Synthesis of indole-3-carboxaldehydes.

Scheme 2. Synthesis of indole dihydropyrimidines.

Table 1. Derivatives of synthesized compounds.

Entry	Derivative	R	X
1	3a	H	-
2	3b	Br	-
3	3c	Cl	-
4	3d	I	-
5	6a	H	O
6	6b	Br	O
7	6c	Cl	O
8	6d	I	O
9	6e	H	S
10	6f	Br	S
11	6g	Cl	S
12	6h	I	S

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