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Synthesis and antibacterial activity of pyrimido[5, 4-*c*]quinolin-2,5-dione and their derivatives

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ABSTRACT

*Novel pyrimido[5,4-c]quinolin-2,5-dione (**5a-f**) were obtained from the precursor 2, 4-dichloro-3-formylquinolines (**2a-f**) which in turn were synthesized by using Vilsmeir adduct with 4-hydroxyquinolin-2(1H)-ones (**1a-f**) [18]. Most of the compounds were screened for in vitro growth inhibitory activity against Escherichia coli, Shigella dysenteriae and Klebsiella pneumoniae.*

Keywords: Pyrimido[5,4-*c*]quinolin-2,5-dione; 2, 4-dichloro-3-formylquinolines; Vilsmeir Reagent; 2, 4-dichloro quinoline.

INTRODUCTION

Heterocyclic chemistry is one of the most essential branches in organic chemistry. It is a vast and expanding area of chemistry because of the obvious applications of compounds derived from heterocyclic rings in pharmacy, medicine, agriculture and other fields. Heterocyclic compounds are widely distributed in nature [1] and drugs [2 - 4] and are essential to life, in various ways. A large number of compounds such as antibiotics, alkaloids, nucleic acids, vitamins, hemoglobin, hormones, enzymes, chlorophyll, plant pigments, dyes and many synthetic drugs contain heterocyclic ring systems. They have high pharmacological potential as antimicrobial, anti cancer agents [5 - 8] and active against normal and multi drug resistant tumor cell lines [9]. Nitrogen heterocyclic compounds from one such group of extraordinary variety and are of great interest. Among them, quinolines, acridines, carbazoles, naphthyridines and pyrimidines found valuable applications. Pyrimidines have been studied extensively for their broad spectrum of pharmacological activities such as analeptics, sedatives, hypnotics [10 - 12], anticonvulsants [13], anti-inflammatory [14], anti-malarial [10], as central nervous system stimulant, bronchilators and diuretics, antibacterial [14, 15], anti-tumor [16] agents, anti-allergic [17], etc. A great deal of research is being carried out to synthesize new heterocyclic compounds having biological importance. The increasing interest in this field promoted us to synthesize some pyrimido quinoline compounds.

Based on the above fact, our present work was undertaken with an aim to evolve the general route to synthesize pyrimido[5,4-*c*]quinolin-2,5-diones (**5**) from the precursor 4-hydroxyquinolin-2(1*H*)-ones (**1**).

MATERIALS AND METHODS

Experimental

TLC was performed using glass plates coated with silica gel–G containing 13% calcium sulphate as binder. Petroleum ether, benzene, ethyl acetate, methanol, chloroform were used as developing solvents. A chamber containing iodine vapour was used to locate the spots. Separation and purification of the crude products were carried out using chromatographic columns packed with activated silica gel. Melting points were determined on Raaga melting point apparatus and were uncorrected. They are expressed in degree centigrade. IR spectrum was recorded on Shimadzu FTIR 8201 (PC) spectrometer using KBr pellets, and the absorption frequencies are expressed in

reciprocal centimeters (cm^{-1}). ^1H NMR spectra were recorded on JEOL GSX 400 (MHz) spectrometer using tetramethylsilane (TMS) as an internal standard. The chemical shifts are expressed in parts per million (PPM).

Preparation of 4-chloro-3-formylquinolin-2-(1*H*)-one: (4)
General procedure
2,4-dichloro-3-formylquinoline (5 mmol) and aqueous hydrochloric acid (15 mL,6M) were heated under reflux for 4 hours in an oil bath at 120-130 ºC and then allowed to cool to room temperature. After 1 hour the reaction mixture was poured into crushed ice, when the product was separated as a yellow solid. It was filtered, washed with water, dried and recrystallised from aqueous acetic acid.

4-chloro-3-formylquinolin-2(1*H*)-one: (4a)
Yield 85.8%. M.p. 290 ºC (dec); IR (KBr, cm^{-1}) 1669, 2877, 3250; ^1H NMR 11.8 (s, 1H, -NH), 10.6 (s, 1H, -CHO), 8.17 (d, 1H, C_5-H, *J* = 7.2 Hz), 7.7 (d, 1H, C_8-H, *J* = 7.5 Hz), 7.3-7.4 (m, 2H, C_6-H& C_7-H); CHN analysis (%): Calcd. C 57.85, H 2.91, N 6.74; $C_{10}H_6ClNO_2$ (207.59) Found: C 57.82, H 2.88, N 6.70.

4-chloro-3-formyl-6-methylquinolin-2(1*H*)-one: (4b)
Yield 84.35%. M.p. 302 ºC (dec); IR (KBr cm^{-1}) 1661, 2852, 3200 (-NH); CHN analysis (%): Calcd. C 59.61, H 3.63, N 6.32; $C_{11}H_8ClNO_2$ (221.62) Found: C 59.58, H 3.57, N 6.25.

4-chloro-3-formyl-7-methylquinolin-2(1*H*)-one: (4c)
Yield 82%. M.p 268 ºC (dec); IR (KBr cm^{-1}) 1642, 2962,1610, 3200; CHN analysis (%): Calcd. C 59.61, H 3.63, N 6.32; $C_{11}H_8ClNO_2$ (221.62) Found: C 59.57, H 3.55, N 6.24.

4-chloro-3-formyl-8-methylquinolin-2(1*H*)-one: (4d)
Yield 83%. M.p. 282 ºC (dec); IR (KBr cm^{-1}) 1663, 2924, 3400; CHN analysis (%): Calcd. C 59.61, H 3.63, N 6.32; $C_{11}H_8ClNO_2$ (221.62) Found: C 59.54, H 3.55, N 6.24

4-chloro-3-formyl-6-methoxyquinolin-2(1*H*)-one: (4e)
Yield 77.68%. M.p. 272 ºC (dec); IR (KBr cm^{-1}) 1642, 2923, 3300; ^1H NMR 3.6 (s, 3H, C_6-OCH_3), 7.4 (d, 1H, C_7-H, *J* = 8 Hz), 7.6 (s, 1H, C_5-H); 7.8 (d, 1H, C_8-H, *J* = 7.6 Hz), 11.5 (bs, 1H, -NH), 10.3 (s, 1H, -CHO);CHN analysis (%): Calcd. C 55.60, H 3.39, N 5.89; $C_{11}H_8ClNO_3$ (237.61) Found: C 55.51, H 3.35, N 5.82

4-chloro-3-formyl-8-methoxyquinolin-2(1*H*)-one: (4f)
Yield 75.74%. M.p. 280 ºC (dec); IR (KBr cm^{-1}) 1642, 2928, 3400; CHN analysis (%): Calcd. C 55.60, H 3.39, N 5.89; $C_{11}H_8ClNO_3$ (237.61) Found: C 55.55, H 3.28, N 5.81.

Preparation of pyrimido[5,4-c]quinolin-2,5-dione: (5)
General procedure
4-chloro-3-formylquinolin-2-(1*H*)-one (1 mmol) and urea (1 mmol) were dissolved in 18 mL of glacial acetic acid and refluxed for 14 hrs. The completion of the reaction was monitored by TLC. It was then poured into crushed ice. The solid was washed with water, filtered and dried. It was then purified by eluting over silica gel column using pet. ether : ethyl acetate (65:35).

pyrimido[5,4-*c*]quinolin-2,5-dione: (5a)
Yield 62.19%. M.p. 242 ºC (dec); IR (KBr cm^{-1}) 1681, 1595, 2923, 3180; CHN analysis (%): Calcd. C 61.97, H 3.30, N 19.71; $C_{11}H_7N_3O_2$ (213.17) Found: C 61.94, H 3.28, N 19.62.

9-methyl- pyrimido[5,4-*c*]quinolin-2,5-dione: (5b)
Yield 66%. M.p. 224 ºC (dec); IR (KBr, cm^{-1}) 1666, 1610, 2920, 3162; ^1H NMR 2.47(s,3H, C_9-CH_3), 6.99 (d, 1H, C_8-H, *J*=7.5 Hz), 7.51 (d, 1H, C_7-H, *J*=7.5 Hz), 7.54 (s, 1H, C_{10}-H), 7.9 (s, 1H, C_4-H), 10.2 (s, 1H, C_2-OH), 11.8 (s, 1H, -NH); Mass (IE^+) M^+ =226.81; CHN analysis (%): Calcd. C 63.43, H 3.99, N 18.49; $C_{12}H_9N_3O_2$ (227.20) Found: C 63.39, H 3.91, N 18.46.

8-methyl- pyrimido[5,4-*c*]quinolin-2,5-dione: (5c)
Yield 63%. M.p. 221 ºC (dec); IR (KBr cm^{-1}) 1667, 1610, 2964, 3165, 3380; CHN analysis (%): Calcd. C 63.43, H 3.99, N 18.49; $C_{12}H_9N_3O_2$ (227.20) Found: C 63.39, H 3.90, N 18.32.

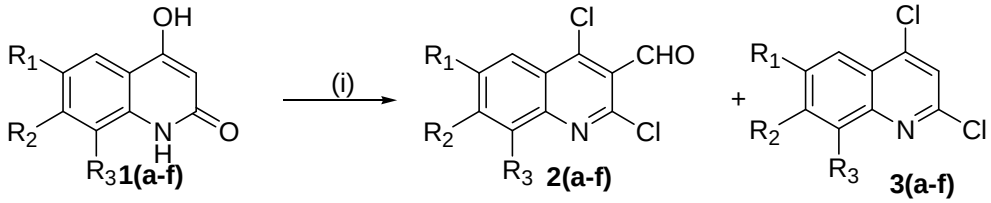
7-methyl- pyrimido[5,4-*c*]quinolin-2,5-dione: (5d)
Yield 64.6%. M.p. 218 ºC (dec). IR (KBr cm^{-1}) 1672, 1636, 2962, 3163, 3359; CHN analysis (%): Calcd. C 63.43, H 3.99, N 18.49; $C_{12}H_9N_3O_2$ (227.20) Found: C 63.41, H 3.93, N 18.42.

9-methoxy-pyrimido[5,4-*c*]quinolin-2,5-dione: (5e)
Yield. 59.3%. M.p. 250 ºC (dec).IR (KBr cm^{-1}) 1678, 1590, 2921, 3180, 3388; CHN analysis (%): Calcd. C 59.26, H 3.72, N 17.28; $C_{12}H_9N_3O_3$ (243.19) Found: C 59.21, H 3.70, N 17.23.

7-methoxy-pyrimido[5,4-*c*]quinolin-2,5-dione: (5f)
Yield 55.78%. M.p 252 ºC (dec). IR (KBr cm^{-1}) 1649, 1592, 2922, 3175, 3390; CHN analysis (%): C 59.26, H 3.72, N 17.28; $C_{12}H_9N_3O_3$ (243.19) Found: C 59.19, H 3.67, N 17.20.

RESULTS AND DISCUSSION

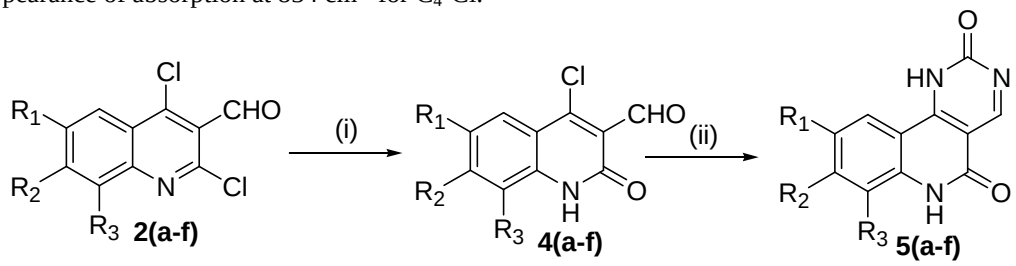
The synthesis of pyrimido[5,4-*c*]quinolin-2,5-dione(**5**) derivatives were carried out using 2,4-dichloro-3-formylquinolines (**2a-f**). The synthesis of the precursor 2, 4-dichloro-3-formyl quinolines (**2a-f**) are described in **Scheme 1**. The later compounds **2a-f** were synthesized from 4-hydroxyquinolin-2(1*H*)-ones (**1a-f**) which in turn were prepared according to reported procedure [18] by using the formylating reagent DMF/$POCl_3$ (Vilsmeir reagent). In this reaction, two products 2, 4-dichloro-3-formylquinolines (**2a-f**) and 2, 4-dichloro quinolines (**3a-f**) were formed in good to moderate yield. The precursor **2** was separated by column chromatography by using the eluent pet.ether : ethyl acetate (85: 15).



a) R_1=H, R_2=H, R_3=H; b) R_1=CH_3, R_2=H, R_3=H; c) R_1=H, R_2=CH_3, R_3=H; d) R_1=H, R_2=H, R_3=CH_3; e) R_1=OCH_3, R_2=H, R_3=H; f) R_1=H, R_2=H, R_3=OCH_3.

Schem 1.Synthesis of 2,4-dichloro-3-formylquinoline derivatives (**2a-f**).
Reagents and conditions: (i) DMF/$POCl_3$

From 2, 4-dichloro-3-formylquinolines (**2a-f**), we synthesized the 4-chloro-3-formylquinolin-2(1*H*)-ones (**4a-f**) by the selective cleavage of 2-chloro to 2-hydroxy with dil. hydrochloric acid (without affecting C_4 chloro). Finally, the compounds **4a-f** were refluxed for 14 hrs with urea in glacial acetic acid to afford pyrimido[5,4-*c*]quinolines (**5a-f**) (**Scheme 2**). The completion of the reaction was monitored by TLC. It was then poured into crushed ice. The solid was washed with water, filtered and dried. It was then purified by eluting over silica gel column using pet. ether: ethyl acetate (65:35). Pure yellow solid with 66% yield was obtained with the melting point 224 ^oC. The IR spectrum of the compound **(5b)**, showed peaks at 1666 cm^{-1} (-C=O), 3162 cm^{-1} (-NH), 2920 cm^{-1} (-CH) and also disappearance of absorption at 834 cm^{-1} for C_4-Cl.



a) R_1=H, R_2=H, R_3=H; b) R_1=CH_3, R_2=H, R_3=H; c) R_1=H, R_2=CH_3, R_3=H; d) R_1=H, R_2=H, R_3=CH_3; e) R_1=OCH_3, R_2=H, R_3=H; f) R_1=H, R_2=H, R_3=OCH_3.

Schem 2.Synthesis of pyrimido[5,4-c]quinoline derivatives (**5a-f**) Reagents and conditions:
(i) DMF/$POCl_3$, 6M HCl, 4 hrs; (ii) Urea, glacial acetic acid, 14 hrs.

The ^{1}H NMR spectrum revealed a three proton singlet at δ2.47, accountable for aliphatic –CH_3 and one proton singlet at δ10.23 for C_2-OH. Two singlets were observed at δ7.9 and δ7.54 for C_4 and C_{10} protons. Two doublets at δ6.99 and δ7.5 correspond to C_8 and C_7 protons. The –NH proton appears at δ11.8. The elemental analysis showed the molecular formula to be $C_{12}H_9N_3O_2$. The compound was confirmed as 9-methyl-pyrimido [5, 4-*c*] quinolin-2, 5-dione **(5b).** Thus the reaction sequence was extended to synthesise the derivatives **5a-f**.

Antibacterial activity

Antibacterial activities of compounds pyrimido[5,4-*c*]quinolin-2,5-dione **(5a)**, 9-methyl-pyrimido[5,4-*c*]quinolin-2,5-dione **(5b)**, 8-methyl-pyrimido[5,4-*c*]quinolin-2,5- dione **(5d)** and 9-methoxy-pyrimido[5,4-*c*]quinolin-2,5-dione **(5e)** were screened for their *in vitro* growth inhibitory activity against *Escherichia coli*, *Shigella dysenteriae* and *Klebsiella pneumoniae.*

The bacteria were grown in nutrient agar medium and used as inoculum for this study. Bacterial cells were swabbed in Petri plates containing nutrient agar medium prepared from sodium chloride (5.0 g), peptone (5.0 g), beef extract powder (3.0 g), yeast extract powder (3.0 g), agar (20.0 g) in one litre of distilled water, pH adjusted to 7.5. The compounds to be tested were dissolved in Dimethyl Sulfoxide (2 mg/ 200 µL). The well was created using gel puncture (diameter 4mm) and a volume of 40 µL was added to the well from stock. Then the plates were incubated at 37 ºC for 24 hrs.

The diameter of zone of inhibition around each well was measured after 24 hrs and the results were tabulated (**Table 1**). Ampicillin was used as standard.

Table 2: Antibacterial activity of the compounds 5a, b, d and e

Compound	Diameter of zone of inhibition in mm		
	E.coli	*Klebsiella sp.*	*Shigella sp.*
5a (10µg/µL)	7	7	7
5b (10µg/µL)	7	6	6
5d (10µg/µL)	6	6	8
5e (10µg/µL)	6	_	7
Std (100µg/µL)	37	_	_

Standard: Ampicillin

The synthesized compounds (**5a, b, d** and **e**) are divided into three classes based on the substitution of parent, methyl and methoxy. Among the above compounds, pyrimido[5,4-*c*]quinolin-2,5-dione **(5a)** and 9-methyl-pyrimido[5,4-*c*]quinolin-2,5-dione **(5b)** showed higher antibacterial activity against *E.coli.* than others. Unsubstituted pyrimidine **5a** exhibited relatively better activity than the compounds **5b** and **5d** against *Klebsiella sp.* However, the methoxy derivative **5e** showed no activity against *Klebsiella sp.* Compound **5d** (8- methyl) was more active against *Shigella sp.* than compounds **5a** (parent) and **5e** (9-methoxy) which were more active than **5b** (9-methyl).

All the four samples **(5a, 5b, 5d and 5e)** showed a marginal activity towards the isolates used when compared to the standard.

CONCLUSION

The compound 4-chloro-3-formylquinolin-2(1*H*)-ones (**4a-f**) were condensed with urea in the medium of acetic acid which resulted in pyrimido[5,4-*c*] quinolin-2,5-diones (**5a-f**) in good yields. Biological screening of selected samples **(5a, 5b, 5d and 5e)** showed promising antibacterial activity.

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