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Research Article

SYNTHESIS OF 4-QUINOLONES DERIVATIVES FOR THEIR ANTIHISTAMINIC ACTIVITY

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ABSTRACT

It is revealed from the literature that 1,4-dihydro-4-oxo-quinolin-3-carboxylic acid have been found to be a potent antiallergic agent. In view of this, it was thought worthwhile to synthesize 1,4-dihydro-4-oxo-quinolin-3-carboxamide derivatives having p-chlorobenzyl substitution at 1-position and basic moieties i.e. 2-aminopyridyl, 3-aminopyridyl and 4-aminopyridyl at 3-position. We have synthesized twelve compounds of 6-substituted-1,4-dihydro-4-oxo-quinolin-3-carboxamides by following appropriate synthetic route. 1,4-Dihydro-4-oxo-quinolin-3-carboxylic acid were condensed with different amines in presence of phase transfer catalyst (PTC) to give final compounds. All the synthesized compounds were characterized and subjected to antihistaminic activity by measuring the ability of test compounds to inhibit the histamine induced contractions on guinea pig ileum using azelastine as standard comparator. It was found that all the compounds possess antihistaminic activity. The compound 1-(4-chlorobenzyl)-6-methyl-4-oxo-1,4-dihydro-quinolin-3-carboxylic acid pyridin-2-ylamide exhibited maximum potency of 92.5 % inhibition whereas compound 1-(4-chlorobenzyl)-4-oxo-1,4-dihydro-quinolin-3-carboxylic acid pyridin-4-ylamide exhibited weak activity with only 76.8% inhibition when compared with azelastine which showed 83.6% inhibition. The dose of test compounds and standard drug was 50 µM. The order of activity was as follows: at 6th position CH_3 >F >Cl >H and at 3rd position. The compounds exhibited the potency in the following order: 2-aminopyridine > 3-aminopyridine > 4-aminopyridine.

Keyword: Anti-histaminic, Quinolnoes, Aminopyridine, Azelastine.

INTRODUCTION

The present era of chemotherapy belongs to the quinolone antibiotics, more particularly that of fluoroquinolone antibiotics [1]. Apart from being used as antibacterial [2] agent it possesses various pharmacological activities like gastroprotective [3], anti-inflammatory [4], antitumour [5], hypoglycaemic [6], anti-HIV [7], antiallergy [8,9], bronchodilatory and antiasthmatic [10], PDE 4 inhibitory [11,12], platelet aggregation inhibition [13] etc. It could be noted from the literature that a variety of quinolone derivatives are known to exhibit potent antiasthmatic activity and related activities such as PDE 4 inhibitory and platelet aggregation inhibitory activities which also indirectly help in the treatment of asthma. It is also evident that azelastine [10], an asthma prophylactic, contains three pharmacophoric groups: (i) phthalazinone (ii) p-chlorobenzyl (iii) a basic moiety, N-methylazepine which are responsible for its potential antiallergic properties. 1,4-Dihydro-4-oxo-quinioline-3- carboxylic acids have also been found to be potent antiallergic agents. In view of this and the fact that quinolone moiety is isosteric with phthalazinone nucleus of azelastine it has been thought worthwhile to synthesize 4(1H)-oxo-quinoline derivatives having 4-chlorobenzyl substitution at 1-position and basic moieties attached to quinolone nucleus at 3-position

The basic moieties selected include biologically active secondary amines, viz. 2-aminopyridine, 3-aminopyridine and 4-aminopyridine, which are also present in several potent antihistaminic agents. The final compounds were characterized by spectral data (NMR). These compounds were screened for their antihistaminic activity. Some of the final compounds exhibited significant activity comparable to that of azelastine which is the standard comparator.

MATERIAL AND METHODS

Melting points were determined on melting point apparatus.in an open capillary tubes and are uncorrected IR spectras were recorded on Perkin-Elmer spectrum, Bx-I IR spectrometer, ^{1}H NMR on Jeol-300D (300 MHz) using TMS as internal standard.

Synthesis of anilinomethylenemalonate diethylester (2)

Aniline and substituted anilines (R=H, F, Cl and CH_3) have been condensed with diethyl ethoxymethylenemalonate by heating at 120 – 130° C for two hours as per the procedure described in literature [2]. The malonate **2a** was prepared by condensing aniline (R = H, 2.739 mL, 0.03 mole) and diethylethyoxymethylenemalonate (5.997 mL, 0.03 mole). The residue was recrystallized to give **2a** (R=H) as white crystalline solid. Compounds **2b, 2c** and **2d** were prepared by similar procedure from 4- fluoroaniline, 4-toluidine and 4-chloroaniline respectively. The crude malonate **2** was used in successive reaction without further purification. Physical data of compounds **2a-d** is given in Table 1.

Table 1: Anilinomethylenemalonate diethylester (2)

Comp.	R	M.P. (°C)	Recrystalisation solvent	% yield	IR (cm^{-1})
2a	H	43	n-Hexane	100	878.2 C-H bending, 1336.5(C-N), 1475.0(C=C),1678.2(C=O ester), 3057.2(C-H streching),3272.7(N-H)
2b	F	68	n-Hexane	98	1250.2(C-F), 1559.2(C=C), 1598.4(C-N), 1678.2(C=O ester), 3057.2(C-H streching),3272.7(N-H)
2c	Cl	82-83	n-Hexane	98.8	850.9(C-H), 1145.9 (C-Cl) 1475.0(C=C),1649.1(C=O ester), 3057.2(C-H streching),3272.7(N-H)
2d	CH3	46	n-Hexane	97.5	820.32 (C-H) bending, 1475.0(C=C), 1598.4 (C-N),1678.2(C=O ester), 3057.2(C-H streching),3272.7(N-H)

Synthesis of 1, 4-dihydro-4-oxoquinolin-3-carboxylic acid ethyl esters (3)

The crude malonate **2** (0.0247 mole) was added to diphenylether (73 mL) and refluxed for 3hr. After cooling the solution to room temperature the resulting precipitate of **3** was separated by filtration, washed with benzene and dried. By using this procedure, **2a** (R = H, 6.5 g, 0.0247 mole) was cyclized to give a white solid **3a** (R=H) which was purified by recrystallization. The physical and spectral data of the 4-hydroxyquinolines **(3a-d)** prepared by this method from various diethylesters of anilinomethylenemalonates **(2)** are given in Table 2.

Table 2: 1,4-Dihydro-4-oxoquinolin-3-carboxylic acid ethyl esters (3)

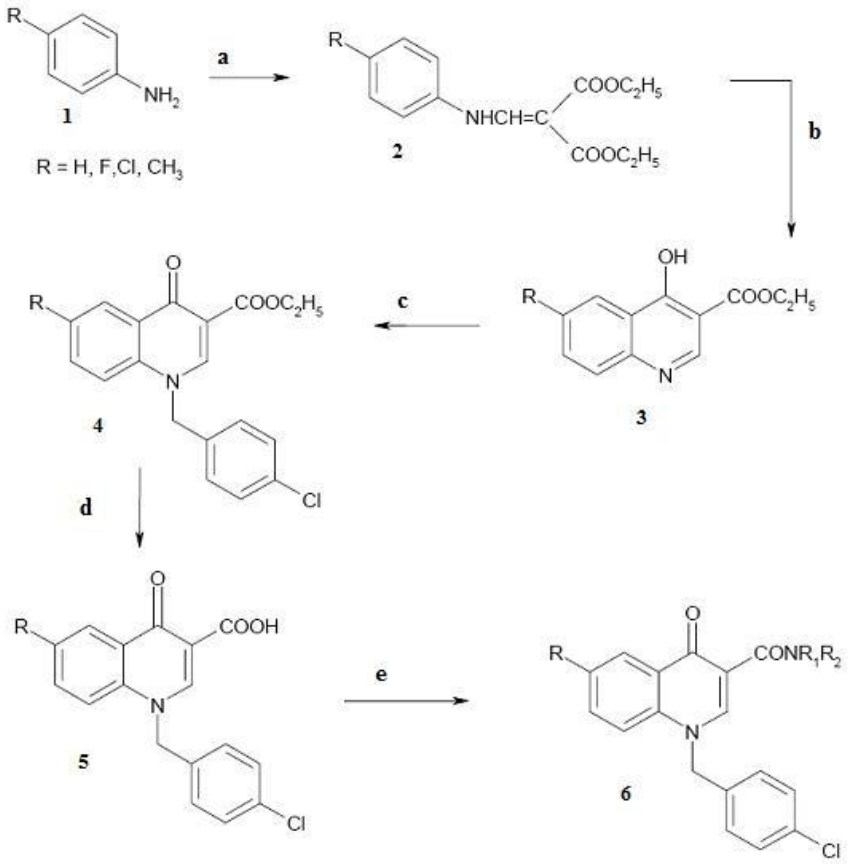
Comp.	R	M.P. (°C)	Recrystalisation solvent	% yield	IR (cm^{-1})
3a	H	242	DMF	67.87	736.0 C-H bending, 1559.2(C=C),1598.4(C=N), 1736.0(C=O ester), 3059.2(C-H streching),3398.2(N-H).
3b	F	269	DMF	51.00	791.6 (C-H) bending(, 1210.1(C-F), 1490.6(C=C), 1571.8(C=N), 1739.5(C=O ester), 3070.8(C-H streching),3398.2 (N-H)
3c	Cl	314 decomp	DMF	67.01	791.6(C-H) bending , 1100.1 (C-Cl) 1490.6 (C=C),1571.8 (C-N) 1739.5 (C=O ester), 3070.8 (C-H streching),3398.2 (N-H)
3d	CH_3	282-283	DMF	77.36	761.6 (C-H) bending, 1490.6(C=C), 1672.8(C=O ester), 3070.8(C-H streching),3398.2 (N-H)

Synthesis of 1-(4-chlorobenzyl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid ethyl esters (4)

1-(4-Chlorobenzyl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid ethyl esters 4 were prepared by heating a mixture of 3 (0.014 mole), potassium carbonate (4.83 g, 0.035 mole), DMF (28 mL) and 4-chlorobenzyl chloride (10.14 g, 0.063 mole) at 80 – 90°C for 10 hrs. The filtrate was evaporated to dryness and extracted with dichloromethane. The dichloromethane layer was washed with water, dried over anhydrous sodium sulphate and evaporated to dryness. The residue was recrystallised from ethanol. By following this procedure from 3a (R=H, 3.0 g, 0.014 mole) 4a was obtained as white solid (R=H), m.p. 195-196°C; yield (3.60 g), 78.9 %.The other 1-(4-chlorobenzyl)-4-oxoquinoline-3-carboxylic acid ethyl esters 4b, 4c and 4d (R=F, CH_3 and Cl) were prepared similarly. Physical and spectral data of 4a-d is given in Table 3.

Table 3: 1-(4-Chlorobenzyl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid ethyl esters (4)

Comp.	R	M.P. (°C)	Recrystalisation solvent	% yield	IR (cm^{-1})
4a	H	195-196	Ethanol	78.94	615.7 C-H bending, 1112.1 (C-Cl) 1490.6(C=C),1571.8(C-N), 1672.8(C=O ring), 1739.5 (C=O ester)3070.8 (C-H streching).
4b	F	201-203	Ethanol	88.00	1189.1(C-Cl), 1205.9(C-F), 1649.1(C=C), 1679.1(C=O ring), 1736.0 (C=O ester), 3100.7 (C-H streching).
4c	Cl	182	Ethanol	83.96	878.2 (C-H) bending, 1167.0 (C-Cl), 1598.4 (C=C), 1679.1 (C=O ring), 1736.0 (C=O ester), 3059.2 (C-H streching).
4d	CH3	148-150	Ethanol	53.95	878.2 (C-H) bending, 1205 (C-Cl), 1559.2 (C=C), 1679.1 (C=O ring), 1736.0 (C=O ester), 3059.2 (C-H streching).



a: diethyl ethoxymethylenemalonate; **b**: diphenylether; **c:** 4-chloro-benzylchloride, K_2CO_3, DMF; **d:** NaOH; **e:** 2-chloro-1-methylpyri-diniumiodide, NHR_1R_2, TEA, DCM.

NHR_1R_2 = 2-aminopyridine, 3- aminopyridine, 4- aminopyridine

Synthesis of 1-(4-Chlorobenzyl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acids (5)

The crude ester 4 (0.0082 mole) was hydrolysed with 2N sodium hydroxide (22.5 mL) by refluxing for 2 hr. The mixture was then acidified with dilute acetic acid and the resulting precipitate of **5** was filtered off, washed with water and dried. Compound **5a** (R=H, 2.7g, 0.0082 mole) was hydrolysed and the resulting solid was recrystallized to give **5a**. The other 1-(4-chlorobenzyl)-4-oxoquinoline-3-carboxylic acids **5b** (R=F), **5c** (R=CH3), **5d** (R=Cl) were prepared by similar procedure. The Physical and spectral data is given in Table 4.

Table 4: 1-(4-Chlorobenzyl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acids (5)

Comp.	R	M.P. (°C)	Recrystalisation solvent	% yield	IR (cm^{-1})
5a	H	246-247	DMF	82.22	797.7 (C-H) bending, 1295.9 (C-Cl) 1492.0(C=C),1616.0 (C-N), 1653 (C=O ring), 1714 (C=O of COOH), 3069.1 (C-H streching).
5b	F	248-249	DMF	76.00	850.7 (C-H) bending,1186.1(C-Cl), 1200.9(C-F), 1492.0 (C=C), 1616.0(C=O ring), 1714.0 (C=O of COOH), 3069.1(C-H streching).
5c	Cl	289	DMF	84.02	797.1 (C-H) bending, 1086.1 (C-Cl), 1616.0 (C=C), 1653.0 (C=O ring), 1714.0 (C=O of COOH), 3069.1 (C-H streching).
5d	CH3	254-256	DMF	70.05	850.4 (C-H) bending, 1295.9 (C-Cl), 1492.0 (C=C), 1653.0 (C=O ring), 1714.0 (C=O of COOH), 3069.1 (C-H streching).

Table 5: 1-(4-chlorobenzyl)-6-substituted 4-oxo-quinolin-3-(N-substituted/N, N-disubstituted) carboxamides

Comp.	R	NR1R2	M.P. (°C)	Recrystal-isation solvent	% yield	IR (cm^{-1})	NMR ppm (DMSO)
6a	H	R1=H, R2=2-pyridyl	202-204	Ethanol	75.5	-	-
6b	H	R1=H, R2=3-pyridyl	285	Ethanol	69.0	-	-
6c	H	R1=H, R2=4-pyridyl	218-220	Ethanol	62.0	1726.0 (C=O), 1679.0 (C=O amide), 3447.0 (N-H)	5.45 (s, 2H, N-CH_2), 7.015-8.53 (m, 13H, aromatic), 12.45 (s, 2H, -NH_2).
6d	F	R1=H, R2=2-pyridyl	90	Ethanol	74.0	1186.1(C-Cl), 1207.0(C-F) 1490.7 (C=C),1661.6(C-N) 1651.6 (C=O ring), 1745.2 (C=O amide), 3075.3 (C-H) stretching, 3398.7(N-H)	4.68 (s, 2H, N-CH_2), 6.99-7.58 (m, 12H, aromatic).
6e	F	R1=H, R2=3-pyridyl	232	Ethanol	70.0	-	-
6f	F	R1=H, R2=4-pyridyl	275	Ethanol	73.0	-	-
6g	Cl	R1=H, R2=2-pyridyl	236	Ethanol	71.2	-	-
6h	Cl	R1=H, R2=3-pyridyl	185	Ethanol	63.0	791.6 (C-H) bending, 1100.1(C-Cl), 1490.6 (C-C), 1571.8 (C-N), 1672.8 (C=O ring), 1739.5 (C=O amide), 3070.8 (C-H) stretching., 3398.2 (N-H).	4.68 (s, 2H, N-CH_2), 7.26-7.58 (m, 12H, aromatic).
6i	Cl	R1=H, R2=4-pyridyl	140	Ethanol	55.0	618.1 (C-H) bending, 1010.1 (C-Cl), 1616.0 (C=C), 1653.9 (C=O ring), 1764.0 (C=O amide), 3069.1 (C-H) stretching, 3398.2 (N-H).	4.59 (s, 2H, N-CH_2), 7.19-7.27 (m, 12H, aromatic).
6j	CH_3	R1=H, R2=2-pyridyl	219	Ethanol	64.9	-	-
6k	CH_3	R1=H, R2=3-pyridyl	135	Ethanol	86.0	797.7 (C-H) bending, 1295.9 (C-Cl), 1492.0 (C=C), 1653.9 (C=O ring), 1714.0 (C=O amide), 3069.1 (C-H) stretching, 3398.7 (N-H).	1.75-1.93 (m, 3H,-CH_3), 5.12 (s, 2H, N-CH_2), 6.87-7.49 (m, 12H, aromatic).
6l	CH_3	R1=H, R2=4-pyridyl	110	Ethanol	74.0	721.5 (C-H) bending, 1232.7 (C-Cl), 1496.3 (C=C), 1585.9 (C=N), 1605.9 (C=O ring), 1762.2 (C=O amide), 3071.3 (C-H) stretching, 3398.7 (N-H).	1.59-2.17 (m, 3H,-CH_3), 4.68 (s, 2H, N-CH_2), 7.19- 7.27 (m, 12H, aromatic).

Synthesis1-(4-chlorobenzyl)-6, -substituted 4-oxo-quinolin-3-(N-substituted/N, N-disubstituted) carboxamides (6)

A mixture of **5** (0.0014 mole,), 2-aminopyridine/ 3-aminopyridine/4-aminopyridine (0.00275 mole), 2-chloro-1-methylpyridiniumiodide (0.70 g, 0.00275 mole) and trimethylamine (0.5 mL) in 16 mL of dichloromethane was refluxed for 12 hr. The reaction mixture was filtered. The filtrate was washed with a little water, dried over anhydrous sodium sulphate and the solvent was removed by distillation in vaccuo. The residue was purified by recrystallization to get compound **6**. From **5c** (R=Cl, 0.0014 mole), **6c** (R=Cl) was obtained as yellow coloured powder on recrystallization. The other N-(aryl)-1,4-dihydro-4-oxo-1-(4-chlorobenzyl) quinoline-3-carboxylic acid derivatives **(6 a-l)** were prepared by using similar procedure. The physical and spectral data of these compounds is given in Table 5.

Pharmacology

All the compounds have been screened for *in vitro* antihistaminic activity on isolated guinea pig ileum. All procedures were conducted as per guidelines of the committee for the purpose of control and supervision of experimental animals. The protocol for the use of animals for this study was approved by the Institutional Animal Ethics committee, Dr. Hari Singh Gour Central University, Sagar, Madhya Pradesh, India. Further, more potent compounds were screened for their toxicity, by standard methods and gross behavioural properties were recorded following the standard procedures [14,15,16,17]. They were safe upto the dose of 300 mg/kg body weight.

Antihistaminic activity

The *in vitro* antihistaminic activity was evaluated using the method of inhibition of the isotonic contractions induced by histamine on isolated guinea pig ileum [15,16,17]. Azelastine was used as a standard comparator.

RESULTS AND DISCUSSION

Antihistaminic activity of all the compounds of series **6** has exhibited percentage inhibition in the range of 76.8% to 92.5%. The compound 1-(4-chlorobenzyl)-6-methyl-4-oxo-1,4-dihydro-quinolin-3-carboxylic acid pyridin-2-ylamide exhibited maximum potency of 92.5 % inhibition whereas compound 1-(4-chlorobenzyl)-4-oxo-1,4-dihydro-quinolin-3-carboxylic acid pyridin-4-ylamide exhibited weak activity with only 76.8% inhibition when compared with azelastine which showed 83.6% inhibition. The result of this study revealed that at 3rd position the compounds with 2-amino pyridyl moiety have better activity than compounds with 3/4- amino pyridyl moiety. The compounds with methyl substitution at 6th position showed better activity then fluoro and chloro substituted compounds which in turn have better activity than unsubstituted compounds. The methyl substitution at 6th position has positively contributed where as the fluoro and chloro substitution at 6th position have slightly contributed towards antihistaminic activity. The order of activity was as follows: at 6th position. CH_3 >F >Cl >H and at 3rd position the compounds exhibited the potency in the following order: 2-aminopyridine > 3-aminopyridine > 4-aminopyridine. The results of antihistaminic activity are shown in Table 6

Table 6: In-vitro Antihistaminic activity of compounds

S. No.	Compounds	R	R_1R_2	% Inhibition
1.	6a	H	2-amino pyridine	80.4
2.	6b	H	3-amino pyridine	78.6
3.	6c	H	4-amino pyridine	76.8
4.	6d	F	2-amino pyridine	87.0
5.	6e	F	3-amino pyridine	85.4
6.	6f	F	4-amino pyridine	81.0
7.	6g	Cl	2-amino pyridine	84.2
8.	6h	Cl	3-amino pyridine	78.0
9.	6i	Cl	4-amino pyridine	75.0
10.	6j	CH_3	2-amino pyridine	92.5
11.	6k	CH_3	3-amino pyridine	88.0
12.	6l	CH_3	4-amino pyridine	82.0
13.	Azelastine			83.6

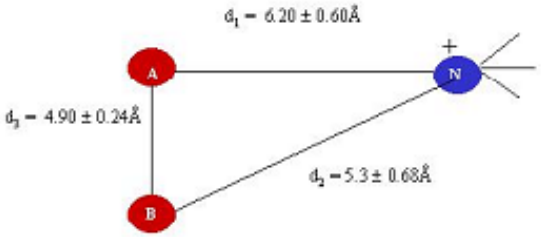


Fig. 1: Geometry of H1 antagonists based on crystal structures

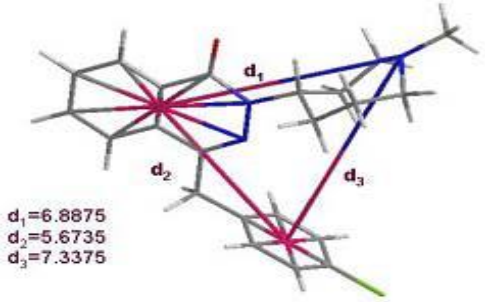


Fig. 2: Azelastine

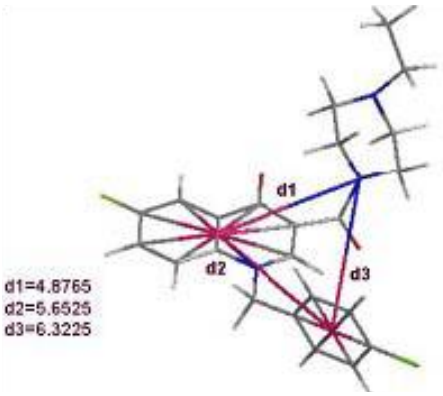


Fig. 3: 1-(4-Chlorobenzyl)-6-substituted-4-oxoquinolin-3-(N,N-disubstituted) carboxamide

X-ray crystallographic studies of several histamine H1–receptor antagonists revealed the significant consistency in distance d1 (d1=6.20±0.60Å) between the protonated nitrogen and the centroid of one of the aromatic rings [18] **(**Fig. 1).

CONCLUSION

In conclusion the results obtained from the limited number of derivatives confirm that the nucleus 1-(4-chlorobenzyl)-1,4-dihydro-4-oxoquinoline if it contains methyl group or other electron-releasing group at 6th position and the basic moiety at 3rd position contains pyridyl amino group, may contribute positively for antihistaminic activity. Our study suggested that distance d1 in azelastine (d1=6.8875Å) is little greater than that found in classical antihistaminics (Fig. 2). Whereas, in quinolone derivatives of 6 series d1 is only 4.8765 Å (Fig. 3). Probably if distance d1 in quinolone derivatives is increased by incorporating additional methylene group between the aromatic nucleus and nitrogen the compounds may have still better activity.

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