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Original Article

AZETIDIN-2-ONE FUSED QUINOLINE ANALOGUES: SYNTHESIS AND BIOLOGICAL EVALUATION OF SOME NOVEL 2-CHLORO-3-FORMYL QUINOLINE DERIVATIVES

GOVIND NAYAK[1]*, BIRENDRA SHRIVASTAVA[1], AKHLESH KUMAR SINGHAI[1]

[1]School of Pharmaceutical Sciences, Jaipur National University, Jaipur- 302025 (India), [2]Lakshmi Narain College of Pharmacy, Bhopal-462021 (India)

Email: nayak.govind@rediffmail.com

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ABSTRACT

Objective: The aim of the present invention is to synthesize and find out the biological significance of the series of the designed azetidin-2-one fused 2-chloro-3-formyl quinoline derivatives.

Methods: A new series of 2-chloro-3-formyl quinolines derivatives 3-chloro-4-(2-chloro-8/7/6-methoxyquinolin-3-yl)-1-phenyl amino)azetidin-2-one, 3-chloro-4-(2-chloro-8/7/6-chloroquinolin-3-yl)-1-(phenylamino) azetidin-2-one, 3-chloro-4-(2-chloro-8/7/6-methylquinolin-3-yl)-1-(phenyl -amino)azetidin-2-one were synthesized by four steps. The cyclization is facilitated by N-aryl acetamides bearing electron donating groups at ortho-position. However yields of quinolines having electron donating groups in all cases. The structures of the synthesized compounds have been established on the basis of physical and spectral data and are screened for diuretic, some of the exhibited significant activity.

Results: The moderate yield of the proposed compounds was obtained. Spectral analysis and physical characteristic showed that the structural confirmation of the quinoline derivatives of the synthesized compounds. Some of the compounds showed lower to moderate level of significant activities.

Conclusion: From the result of spectral data and diuretic activity it has concluded that the compounds were found to exhibited significance activity.

Keywords: 2-chloro-3-formyl-quinoline, Vilsmeier-Haack reagent, N-aryl acetamides, phenyl hydrazine

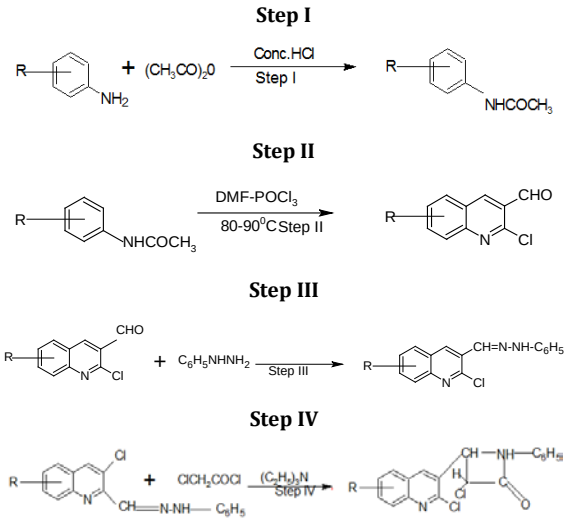
INTRODUCTION

Quinoline ring structure is obtained by *o*-condensation of a benzene ring with pyridine. It is also called l-aza naphthalene or benzo [b] pyridine. In quinoline, the nitrogen atom is one atom away from the position at which the rings are fused. The fused quinolines are known to bind with DNA with high affinity, inhibit DNA topoisomerase and display cytotoxic and antitumor activities [1]. Quinoline derivatives have been reported for antimalarial [2], anti-inflammatory [3], antibacterial [4], antifungal [5], anti-hypertensive [6], and antihistamine [7]. It was found that when one dynamic heterocyclic system was coupled with another heterocyclic system enhanced biological activity was produced.

The present investigation was aimed at synthesizing the various substituted phenylamino-azitidin-2-one quinoline derivatives. Various reports describing the synthesis and activities of quinoline coupled to 3-amino-1H-pyrazolo quinolines, 1, 3, 4-thiadiazopino and 3-cyano-2-chloroquinolines at C-3 position have been reported.

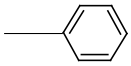
A survey of existing literature revealed that there were no reports describing the synthesis and activity of heterocyclic system in which azetidin-2-one moiety has been linked with substituted quinoline nucleus. Hence it is thought worthwhile to synthesize and explore the activity of these compounds.

Synthesis scheme



AZT a1-AZT i1

S. No.	R	S. No.	R
a	2-OCH_3	**a**	8-OCH_3
b	3-OCH_3	**b**	7-OCH_3
c	4-OCH_3	**c**	6-OCH_3
d	2-Cl	**d**	8-Cl
e	3-Cl	**e**	7-Cl
f	4-Cl	**f**	6-Cl
g	2-CH_3	**g**	8-CH_3
h	3-CH_3	**h**	7-CH_3
i	4-CH_3	**i**	6-CH_3

Step	Ar
III-a1-i1	

Experimental section

Melting points were taken in the open capillary tube and are uncorrected. IR spectra were recorded on a FT-IR (Bruker) spectrophotometer, ^{1}HNMR Bruker Avance II 400 MHz instrument using DMSO as solvent and TMS as an internal reference (Chemical shift in δ, ppm). The following abbreviations were used to indicate the position of functional groups in term of stretching and bending (FT-IR), peak multiplicity s-singlet, d-doublet, t-triplet, q-quartet, m-multiplet, dd-doublet of doublet (^{1}HNMR). Reactions were monitored by TLC, using silica gel $PF_{254,366}$ as an adsorbent and ethyl acetate-hexane in the different ratio as eluent.

Step I Preparation of acetanilide (a1-i1) [8, 9]

Aniline (5 ml) is dissolved in hydrochloric acid (4.6 ml concentrated hydrochloric acid and 12.5 ml water) in a beaker. To the clear solution are added acetic anhydride (6.5 ml). The mixture is stirred until acetic anhydride has completely reacted. The mixture are immediately poured into a solution of sodium acetate (8.3 gm) in water (25 ml). The solution is stirred and cooled in ice. The separated acetanilide is filtered. It is recrystallized from boiling water (100-125 ml) to which ethyl alcohol has been added (table 1).

Step II Preparation of 2-chloro-3-formyl-quinoline CFQ (a1-i1) [8, 9]

To a solution of acetanilide (N-phenylacetamide) (5 mmoles) in dry DMF (15 mmoles) at 0-5 °C $POCl_3$ (60 mmoles) was added dropwise with stirring and the mixture was then stirred at 80–100 °C for a time ranging between 4-16 hr. The mixture was poured on to crush ice, stirred for 5 min and the resulting solid filtered, washed well with water and dried. The compounds were recrystallized from ethyl acetate. Phosphoryl chloride (commonly called phosphorus oxychloride) is a colorless liquid with the formula $POCl_3$. It hydrolyzes in moist air to phosphoric acid to release choking fumes of hydrogen chloride. It is manufactured industrially on a large scale from phosphorus trichloride and oxygen or phosphorus pentoxide. It is mainly used to make phosphate (table 1).

Step III Preparation of 2-chloro-8-methoxy-3-((2-phenyl-hydrazono) methyl) quinoline (3) (a1-i1)

To a DMF solution of 2-chloro-8-methoxyquinoline-3-carbaldehyde 6 mmoles were added aryl hydrazine (phenyl hydrazine 11 mmoles) and refluxed for three hours, and then left to cool to room temperature or the solvent was removed and the separated solid was poured into the water. The precipitated product was filtered, washed well with water and dried (table 1).

Table 1: Characterization data of compounds 2, AZT a1, AZT b1, AZT c1, AZT d1, AZT e1, AZT f1, AZT g1, AZT h1, AZT i1

Compd	R	Molecular formula (mol. Wt.)	m. p. (°C)	Yield (%)	FT-IR(KBr)[10-12]	HNMR (DMSO) (δ, ppm)[10-12]
2	H	$C_{10}H_6NOCl$ (191.61)	144°C	79	1574.14 C=N str 749.25 C–Cl ben	7.3-8.1, m ar H 8.9 Hr, H 4.15CH-Cl, d, 1H 3.35 C=O, d 2.7 CH-N, d
AZT a1	8-OCH_3	$C_{19}H_{15}Cl_2N_3O_2$ (388.672)	285°C	89	2998.81 C–H str 3449.10 N-H str	12.10, s, N-H 9.21, s, 1H, CHO 7.98, s, 1H, CH-4 3.83, s, OCH_3
AZT b1	7-OCH_3	$C_{19}H_{15}Cl_2N_3O_2$ (388.672)	241°C	58	1708.05 C=O str 1518.48 C=N str 989.62 CH_3O str	10.5, s, 1H, CHO, 8.6, s, 1H, H-4 4.0, s, 3H, OCH_3
AZT c1	6-OCH_3	$C_{19}H_{15}Cl_2N_3O_2$ (388.672)	256°C	56	1302.11 C-N str Ar 1108.84 C-N str Al 748.60 C–Cl ben	7.22-8.91,m arH 7.71,d, C=O
AZT d1	8-Cl	$C_{18}H_{12}Cl_3N_3O$ (393.652)	153°C	65	3487.00 C–H str Ar 3306.34 N-H str 1748.36 C=O str	7.23, d,C=O 9.45, s, 1H, CH_3
AZT e1	7-Cl	$C_{18}H_{12}Cl_3N_3O$ (393.652)	254°C	95	3487.00 C–H str Ar 3306.34 N-H str 1748.36 C=O str 1519.21 C = N str	10.2, s,CHO, 1H 7.7, m, 1H, H5 8.5, s, 1H, H-4
AZT f1	6-Cl	$C_{18}H_{12}Cl_3N_3O$ (393.652)	213°C	78	1683.89 C=O str 1582.82 C=N str 1471.97 C-N str 1129.12 CH_3O str 873.49 C-Cl str	10.8, s, 1H, CHO 8.1, m,1H, H-7 7.6, s,1H, H-5
AZT g1	8-CH_3	$C_{19}H_{15}Cl_2N_3O$ (373.453)	267°C	75	1708.05 C=O str 1518.48 C=N str	7.76-8.9, m, arH 11.02, s, 1H, CH, Hr 7.23, d, C=O 3.06, s, 3H, OCH_3
AZT h1	7-CH_3	$C_{19}H_{15}Cl_2N_3O$ (373.453)	289°C	57	1683.89 C=O str 1582.82 C=N str	7.31-8.17,m 10.16, s,1H, CH 8.78, s,1H, H-4 7.28,C=Ogroup (d), 1H 3.17, m, CH-N
AZT i1	6-CH_3	$C_{19}H_{15}Cl_2N_3O$ (373.453)	242°C	78	1748.36 C=O str 1519.21 C = N str	7.40–8.01,m, arH 10.14, s 1H, CH 8.03, s, 1H,H-4 7.50, m, 1H, H-7 6.58, d, C=O

Step IV Preparation of 3-chloro–4-(2-chloro–8-methoxy-quinolin–3-yl)–1-(phenylamino)–azetidin–2-one (AZT a1-AZT i1)

The compound 2-chloro-8-methoxy-3-((2-phenylhydrazono) methyl) quinoline step-III b1 (0.01 mol) was dissolved in DMF (40 ml) and triethylamine (0.02 mol) was added to it. Chloroacetyl chloride (0.02 mol) was added dropwise a period of 30 min. The reaction mixture was refluxed for 5 hr, and filtered to separate the solid formed. The filtrate was poured on to crushed ice; the product was filtered and recrystallized from ethyl acetate (table 1).

Diuretic activity

The compound AZT a1-AZT i1 tested for their diuretic activity by Lipschitz–value [13], normally healthy male albino wistar rats, weighing between 150–200 gms were used for this study. The animals were divided into 8 groups consisting of six animals in each group. These animals were placed in metabolic cages provided with a wire mesh bottom and a funnel to collect the 24 h urine sample. Stainless–steel sieves are placed in the funnel to retain faeces and to allow the urine to pass. The rats were fed with standard diet and water fifteen hours prior to the experiment food and water were withdrawn. The dosage of the drug administered to different groups was as follows.

Group I

A control group received orally 2.5 ml/gm body weight of dimethylformamide solution.

Group II

The standard group received orally 30 mg/kg body weight of furosemide Loop diuretics Lasix.

Group III–VIII

These groups consist of synthesized compounds AZT a1-AZT i1.

Table 2: Electrolyte excretion and diuretic activity of various synthesized compounds

S. No.	Treatment	Dose ml/kg/mg/kg	Urine volume (ml) 24 h	Electrolyte excretion (ME q/lit)			
				Na^+	K^+	Cl^-	Na^+/K^+
1.	Control	2.5 ml/kg DMF	6.5 ±1.48	106.0 ± 4.56	208.1 ± 8.40	68.43 ± 4.18	0.61
2.	Standard	25 mg/kg	13.8 ± 1.97 *	138.6 ±1.76 **	89.6 ± 7.17 **	97.6 ± 3.96 *	1.45
3.	AZT b1	25 mg/kg	5.0 ± 0.95	108.6 ± 3.96	190. 4 ± 4.08	69.7 ±6.08	0.67
4.	AZT c1	25 mg/kg	8.4 1.21 *	126.6 ± 1.97 **	91.4 ± 2.48 *	93.6 ± 4.96 *	1.54**
5.	AZT d1	25 mg/kg	8.5 ± 1.58 **	120.3 ± 4.06 **	106.18 ±3.08 **	86.5 ± 4.18 *	1.36 *
6.	AZT e1	25 mg/kg	4.4 ± 0.68	107.2 ± 2.18	186.2 ± 7.08	77.46 ± 2.28	0.68
7.	AZT f1	25 mg/kg	8.4 ± 1.42 *	125.6 ± 1.98 **	97.6± 1.65 **	89.7 ± 5.58 *	1.33*
8.	AZT g1	25 mg/kg	6.8 ± 0.87	132.0 ± 0.86	186. ±5.17	62.3 ± 0.86	0.58
9	AZT h1	25 mg/kg	6.0 ± 0.96	118.6 ± 4.96	188.4 ± 4.18	67.6 ± 6.18	0.54
10	AZT i1	25 mg/kg	4.7± 0.93	121.5 ± 0.96	164.3± 5.27	76.4 ± 0.62	0.58

Standard–Lasix (loop diuretic)** P<0.05 Significant, SEM–Standard Error mean * P<0.01 Significant

RESULTS AND DISCUSSION

Although many routes have been developed for functionalized quinoline [14], the Vilsmeier approach is found to be among the most efficient for achieving useful transformations and hetero annulations. Thus, in this communication is reported the synthesis of 2-chloro-3-formyl quinolines from the reaction with N-aryl-acetamide with Vilsmeier reagent and transformation of the 2-chloro-3-formyl groups into different functionalities. The structures of all compounds were confirmed by FT-IR and ^{1}H NMR spectra (table 1). The FT-IR spectra of the azetidine fused 2-chloro-3-formyl quinoline derivatives AZT a1-AZT i1 showed absorption bands at about 1748-1708 cm^{-1}characteristic for C=O stretching vibration, 1528-1519 cm^{-1} for C=N Stretching associated with quinoline, 2927 $cm^{-1}$for C-H aromatic stretching, 759 cm^{-1}absorption for C-Cl stretching, the absorption band at 3306.34 $cm^{-1}$for N-N=C vibration provided confirmatory evidence for ring closure. Further support was obtained from the ^{1}HNMR spectra, resonance assigned 10.6 δ (s, 1H, CHO), 8.5 δ (s,1H, H-4), 2.6 δ (s, 3H, CH_3) for 6-methyl/7-methyl/8-methyl (2.8 δ, s,3H), 4.0 δ (s, 3H, OCH_3) for 6-methoxy/7-methoxy/8-methoxy, 10.7 (s, 1H, CHO), 8.5 (s, 1H, H-4), 7.7 (m, 1H, H-5), 7.5 (s, 1H, H-8), 7.2(m, 1H, H-6), 10.8 (s, 1H, CHO), 8.6 (s, 1H, H-4), 8.1 (m, 1H, H-8), 7.7 (m, 1H, H-7), 7.6 (s, 1H, H-5) for the confirmation of the compounds. Having obtained chloro and formyl group substituted quinolines the possible transformations of these functionalities could afford the new quinolines (AZT a1-AZT i1), which are equally important synthon for the synthesis of fused quinoline systems.

CONCLUSION

In conclusion, we have described a simple and regioselective synthesis of functionalized quinolines through Vilsmeier cyclisation of N-aryl acetamides. The cyclisation is facilitated by N-aryl acetamides having electron activating groups at ortho-position in the aromatic ring. Increase in urine output a sufficient index for assessing the diuretic effect through estimating the urinary concentration of ions like Na^+, K^+ and Cl^- etc may reveal in specific the ion responsible for the diuretic effect. Tables values reveal that electrolyte excretion and diuretic activity of various synthesized compounds like AZT a1, AZT b1, AZT c1, AZT d1, AZT e1, AZT f1, AZT g1, AZT h1 and AZT i1. Among these compounds significant diuretic activity was observed with compound AZT c1(3-chloro-4-(2-chloro-6-methoxyquinolin-3-yl)-1-(phenyl-amino) azetidin-2-one), AZTd1(3-chloro-4-(2,8-dichloroquinolin-3-yl)-1-(phenyl-amino)azetidin-2-one, and AZT f1(3-chloro-4-(2,6-dichloroquinolin-3-yl)-1-(phenylamino)azetidin-2-one). Also above mentioned potent diuretic compound produced significant fall in K^+excretion compound to control (P<0.001).

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CONFLICT OF INTERESTS

Declare none

REFERENCES

1. Spicer JA, Gamage SA, Finlay GJ, Denny WA. Structure-activity relationships for substituted bis(acridine-4-carboxamides): a new class of anticancer agents. J Med Chem 1997;42:2383-93.
2. Lyon MA, Lawrence S, William DJ, Jackson YA**.** Synthesis and structure verification of an analogue of kuanoniamine A. J Chem Soc: Perkin Trans 1999;1:437-42.
3. Kerry MA, Boyd GW, Mackay SP, Meth-cohn O, Platt L. Pyrazoles in comprehensive heterocyclic chemistry III. J Chem Soc: Perkin Trans; 1999. p. 2315.
4. Vlahov R, Parushev J, Nickel P, Snatzke G. Synthesis of some new quinoline derivatives-potential antimalarial drugs. J Pure Appl Chem Res 1990;7:1303-6.
5. Pramilla S, Garg SP, Nautiyal SR. Some new biologically active quinoline analogues. Indian J Heterocycl Chem 1998;7:201-4.

6. Heinz HP, Milhahn HC, Eckart E. Cycloalkane carboxylic esters derived from Lysergol, Dihydro lysergol-I, and elymoclavine as partial agonists and antagonists at rat 5-HT_{2A}Receptors: pharmacological evidence that the Indolo[4,3-*fg*] quinoline system of the ergolines is responsible for high 5-HT_{2A} receptor affinity. J Med Chem 1999;42:659-68.
7. Srivastava A, Singh MK, Singh RM. Synthesis of 1H-Pyrazolo quinolines and 3-amino-1H–pyrazolo quinoline. Indian J Chem 2005;45B;292:6.
8. Srivastava A, Singh RM. Facile synthesis of 2-chloro-3-formyl quinolines from N-aryl acetamides and transformation into different functionalities. Indian J Chem 2005;44B;1868:75.
9. John RD. Applications of absorption spectroscopy of organic compounds. New Delhi: prentice-Hall of India (P); 1969. p. 33-8.
10. Silverstein RM, Webster FX. Spectrometric Identification of Organic Compounds: John Wiley and Sons Inc; 1998.
11. McLafferty FW. Interpretation of Mass Spectra. New York: WA Benjamin. Inc. publishers; 1974.
12. Lipschitz NL, Hadidian Z, Kerpcsar A. Bioassay of diuretics. J Pharmacol Exp Ther 1943;79:97-110.
13. Tekale AS, Mukhedker SS, Shaikh SAL. A highly efficient synthesis of 2-chloro-3-formyl-8-methyl quinoline: Vilsmeier-haack reagent. Int J Chem Studies 2015;2:42-5.
14. Beniwal M, Jain N. Review article on vilsmeier haack reaction and its applications. Eur J Biomed Pharm Sci 2015;2:1340-74.

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