Research Article

Synthesis Characterization and Pharmacological Studies on Novel Pyridazino Quinolines

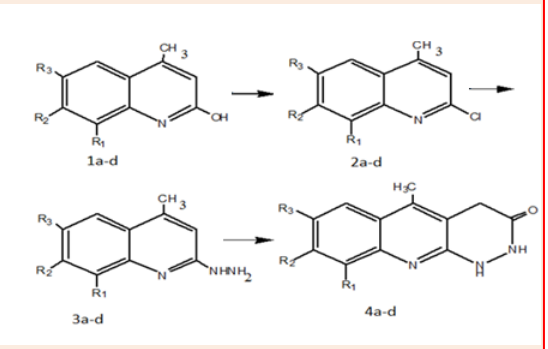
G. Selvi*, G. Sathya Priyadarshini and R. Namitha

Department of Chemistry, PSGR Krishnammal College for Women, peelamedu,Coimbatore,tamilNadu

Abstract

Convenient and efficient synthesise of 5, 7-dimethyl-1, 4-tri hydro-2H- Pyridazino [3,4-*b*] quinolin-3-one 4(a).The precursor 2-chloro 4, 6-dimethyl quinoline2(a) was obtained by the reaction of 2-hydroxy 4, 6-dimethyl- quinoline with phosphrous oxy chloride.The 2-chloro 4,6-dimethyl quinoline refluxed with hydrazine dihydrochloride in 20 mL of ethanol to give 2-hydrazino 4,6-dimethyl quinoline3(a). The antibacterial,antifungal and antioxidant activity of the synthesized compound were also studied and their results were found to be active.

Keywords: Pharmacological Studies, Pyridazino Quinolines, TLC, antioxidant activity



***Correspondence**
G. Selvi,
Email: selvi_gv@rediffmail.com

Introduction

The pyridazinones are also known as **"wonder nucleus"** because it gives out different derivatives with all different types of biological activities [1-8]. Synthetic 3(2H)-pyridazinones are important scaffolds in drug discovery with many of their analogs being used in the treatment of various human pathological states. They were described as nonsteroidal anti-inflammatory drugs (eg :-Emorfazone and related compounds) [9],agents for therapeutic intervention of renal-urologic(eg:-FK838) [10], cardiovascular (eg:-EMD57283) [11], respiratory (eg:-NIP502) [12], dermatologic diseases (eg:-FR-181877) [13]. During recent years on account of their prominent potential as antidepressant, [14] antihypertensive, [15, 17] antithrombotic, [18] anticonvulsant [19] cardiotonic [20], antibacterial [21], diuretic [22], anti-HIV [23] and anti-cancer [24] makes curious interest towards the construction of new pyridazinone compounds. Here we report the highly efficient synthesis of **4(a)** from readily obtainable starting material viz substituted 4-methyl-2-hydroxy quinoline. The structure of the newly synthesized compounds were elucidated on the basis of IR, ^{1}H-NMR, ^{13}C-NMR,MASS spectral data. The antibacterial, antifungal and antioxidant activities of the synthesized compound are also studied.

Experimental

General Procedure

Thin layer chromatography (TLC) was performed using glass plates coated with silica gel. Petroleum ether and ethyl acetate was used as eluant .Spots were visualized with iodine. Purification of crude sample was carried out using chromatographic column packed with silica gel. Melting point were taken in CINTEK melting point apparatus IR spectra were recorded in NICOLET IR 200 FT-IR spectrometer using KBr disc and ATR-IR Affinity instrument and the absorption frequencies quoted in reciprocal centimeters.^{1}H NMR spectra were recorded in AMX-300(300MHz) spectrometer using tetra methyl silane(TMS) as internal reference. The chemical shift were expressed in parts per

million (ppm).^{13}C NMR spectra were recorded in AMX-300(300MHz) spectrometer using tetra methyl silane (TMS) as internal reference. The chemical shifts were expressed in parts per million (ppm).The solvents and reagents used for synthesis were of analar grade and purified by standard methods.

Preparation of Substituted 2-Chloro- 4-Methyl Quinoline 2(a-d)

The substituted 2-hydroxy-4-methyl quinolines**1(a-d)** ,phosphrous oxychloride and 2 drops of N,N- dimethyl aniline were refluxed for 6-20 hours at 100^{o}C.Completion of the reaction was monitored with TLC. After the completion of the reaction, the reaction mixture was poured in to water. The precipitate obtained was filtered, dried and recrystallised.

Preparation of 2-Chloro-4-Methyl Quinoline 2(b)

2-hydroxy- 4-methyl quinolin : 2g (0.0126moles), Phosphrous oxy chloride:0.9264mL (0.0126 moles), Refluxing time: 8hrs,N, N- dimethyl aniline: 2drops, Yield : 1g (45%), Melting point: 110 ^{O}C.

Preparation of 2, 8-Dichloro-4-Methyl Quinoline 2(c)

8-chloro-2-hydroxy-4-methyl quinoline : 2g (0.0104moles), Phosphorus oxy chloride : 1.5 mL (0.0104 moles), Refluxing time : 6 hrs,N,N-dimethyl aniline:2drops,Yield : 1.5g(68%),Melting point : 106^{O} C.

Preparation of 2-Chloro-4, 5-Dimethyl Quinoline 2(d)

2-hydroxy- 4,5-dimethyl quinoline:5g (0.0289moles),Phosphrous oxy chloride : 3.93mL (0.0289 moles),Refluxing time: 19.5hrs,N,N- dimethyl aniline:2drops,Yield : 1.75g (32%),Melting point : 220^{O} C.

Preparation of Substituted 2-Hydrazino-4-Methyl Quinoline 3(a-d)

The substituted 2-chloro 4-methyl- quinoline (0.0011 moles) **2(a-d)**, hydrazine di hydrochloride (0.0011moles) and 20mL of ethyl alcohol were refluxed for 12-20 hours. Completion of the reaction was monitored with TLC. After the completion of the reaction, the excess solvent was evaporated. The product obtained was washed with petroleum ether and recrystallised.

Preparation of 2-Hydrazino-4-Methyl Quinoline 3(b)

2-chloro 4-methyl quinoline : 0.8000g (0.0044moles),Hydrazine dihydrochloride: 0.4744g (0.0044moles),Ethyl alcohol: 20mL,Refluxing time : 17.5hrs,Yield: 0.650g (86%),Melting point : 120^{O}C

		Elemental analysis (%)		
Mol.Formula:$C_{10}H_{11}N_3$		C	H	N
Mol. Weight: 173.2177	Calculated:	69.33	6.40	24.26
	Found :	69.34	6.41	24.5

Preparation of 2-Hydrazino-8-Chloro-4-Methyl Quinoline 3(c)

2, 8-dichloro 4-methyl quinoline: 1g (0.0048moles),Hydrazine dihydrochloride : 0.4919g (0.0048moles),Ethyl alcohol: 20mL,Refluxing time : 12.5hrs,Yield: 0.700g (62%),Melting point : 280^{O} C

Elemental analysis (%)

Mol.Formula:$C_{10}H_{10}N_3Cl$		C	H	N
Mol. Weight:207.66	Calculated :	57.83	4.85	20.24
	Found :	57.82	4.84	20.25

Preparation of 2-Hydrazino-4, 5-Dimethyl Quinoline 3(d)

2-chloro 4,5-dimethyl quinoline:1.5g(0.0078moles),Hydrazine dihydrochloride : 0.95g (0.0078moles),Ethyl alcohol: 20mL,Refluxing time : 20.5hr,Yield : 1g (64%),Melting point : 190^O C

Elemental analysis (%)

Mol.Formula:$C_{11}H_{13}N_3$		C	H	N
Mol. Weight:187.24361	Calculated :	70.56	7.0	22.45
	Found :	70.54	7.02	22.47

Preparation of Substituted Pyridazino Quinolines 4(a-d)

Equal moles of 2-Hydrazino 4-methyl quinoline **3(a)** and chloro acetyl chloride were refluxed 20 mL of benzene with 2 drops of N N-dimethyl aniline for 9- 17 hours (Scheme 1). Completion of reaction was monitored with TLC plates. After the completion of the reaction ,the excess solvent was evaporated and the product obtained was column chromatographed over silica gel, with petroleum ether and ethyl acetate as eluant.A pale yellow glassy solid was obtained at**(96:4)** petroleum ether : ethyl acetate. The product obtained was recrystallised.

Preparation of 5-Methyl-1, 4-Tri Hydro-2h- Pyridazino [3, 4-*B*] Quinolin-3-One 4(b).

2-hydrazino-4- methyl quinoline: 0.5g (.003moles),Chloro acetyl chloride : 0.5mL (0.003moles),Benzene: 20 mL,N N-dimethyl aniline: 2drops,Refluxing time : 17 hrs,Yield : 0.35g (54%),Melting point : above300^O

Elemental analysis (%)

Mol.Formula:$C_{12}H_{11}N_3O$		C	H	N
Mol. Weight:213.2377	Calculated :	67.59	5.20	19.71
	Found :	67.58	5.21	19.70

Preparation of 5-Methyl-9 Chloro-1, 4-Tri Hydro-2h- Pyridazino [3,4-*B*] Quinolin-3-One (4c)

2-hydrazino- 8-chloro-4- methyl quinoline : 0.55g (.00275moles),Chloroacetyl chloride: 0.401mL (0.00275moles),Benzene: 20 mL,N N-dimethyl aniline: 2drops,Refluxing time: 9.5hrs,Yield: 0.40g(62%),Melting point : above300^O C.

Elemental analysis (%)

Mol.Formula:$C_{12}H_{10}N_3OCl$		C	H	N
Mol. Weight:247.6797	Calculated :	58.10	4.07	16.91
	Found :	58.11	4.06	16.90

Preparation of 5, 7-Dimethyl-1,4-Tri Hydro-2h- Pyridazino [3,4-*B*] Quinolin-3-One 4(d).

2-hydrazino-4,5- dimethyl quinoline :0.9(.0048moles),Chloroacetyl chloride: 0.7713mL (0.0048moles),Ethyl alcohol: 20 mL,N N-dimethyl aniline: 2drops,Stirring time: 16 hrs,Yield : 0.6g(55%),Melting point: above 300^{O} C

Elemental analysis (%)

Mol.Formula: $C_{13}H_{13}N_3O$		C	H	N
Mol. Weight: 227.264	Calculated :	68.70	5.70	18.50
	Found :	68.72	5.72	18.49

Pharmacological Activities

Antibacterial activities of the compounds **4(a)** and **4(b**) against the bacterias *Staphylococcus aureus (S.a), Bacillus cereus (B.c), Micrococcus luteus (M.i), Escherichia coli (E.c), Pseudomonas aeruginosa (P.a)*. found that the compounds were active against *Bacillus cereus (B.c), Micrococcus luteus (M.i), Escherichia coli (E.c),*and is almost equal to the standard gentamicin.The compounds were less active against *Staphylococcus aureus (S.a),*and *Pseudomonas aeruginosa (P.a).*when compared to the standard.

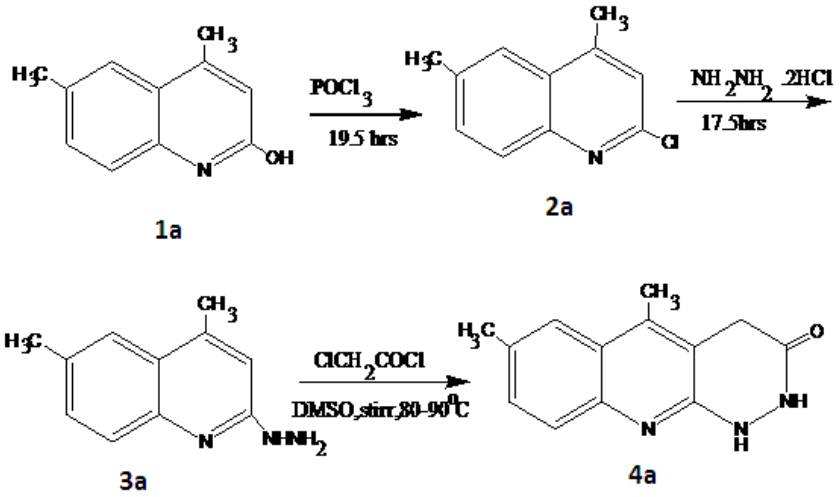
The antifungal activities of the compounds **4(a)** and **4(b)** against the fungals *Candida albicans, Aspergillus flavus and Fusarium sp*. found that the compounds were active against *Candida albicans* and *Aspergillus flavus. Candida albicans* values are almost equal to the standard value. The compounds **4(a), 4(b**) and the standard Clotrimazole were inactive towards *Fusarium sp.* **T**he antioxidant activity of compounds **4(a)** and **4(b)** show good antioxidant activity.It was found from the graph that as the concentration increases the antioxidant activity also increases.

Results and discussion

Pharmacological importance of pyridazinones has indulged us to synthesize the novel pyridazinones via their hydrazine intermediate. The precursor for the synthesis of pyridazinones and their derivatives were prepared by following the reported procedure.

The 2-hydroxy- 4, 6-dimethyl- quinoline **1(a)** was first converted to its chloro compound. Accordingly, 2-hydroxy- 4, 6-dimethyl- quinoline 2g (0.0116moles) **1(a)** was refluxed with phosphrous oxy chloride 1.7085mL (0.0116 moles) for 19.5 hours. The progress of the reaction was monitored by TLC.After the completion of the reaction, the reaction mixture was poured into water. The precipitate obtained was filtered, dried and recrystallised from ethyl acetate. The chloro quinoline **2(a)** thus obtained was treated with hydrazine dihydrochloride to get the corresponding hydrazine derivative. 1.5g (0.0079moles) of 2-chloro-4, 6-dimethyl –quinoline **2(a)** and 0.8181g(0.0079 moles)of hydrazine dihydrochloride in 20 ml of ethanol were refluxed for 17.5 h. The progress of the reaction was monitored by TLC.After the completion of the reaction, the excess solvent was evaporated. The product obtained was washed with petroleum ether and recrystallised from acetone. IR (cm^{-1}) 3(a) spectrum of the compound showed absorption peak at 3338(NH), 3289(NH_2), 1629(C=N). ^{1}H NMR (DMSO) (ppm) spectrum of the compound **3(a)** showed absorption at δ 1.24 (s,3H,CH_3) δ 2.4 (s,3H,CH_3), δ 9 (s,1H,NH), δ 8.1(s,2H,NH_2), δ 7-7.4 (m,4H,Ar-H). The CHNS analysis of the compound 3**(a)** confirmed the molecular formula of the compound to be C_{11} H_{13} N_3. The targeted compound was then obtained by reacting 2-hydrazino- 4, 6-dimethyl- quinoline**3 (a)** and chloro acetyl chloride. Accordingly 0.75g (0.0040 moles) 2-hydrazino -4, 6-dimethyl- quinoline **3(a)** and 0.6425ml (0.0040 moles) chloro acetyl chloride was stirred with 20 mL of DMSO at a temperature of 80-90^{0}C. The progress of the reaction was monitored by TLC. After the completion of the reaction, the excess solvent was evaporated and the product obtained was column chromatographed over silica gel, with petroleum ether and ethyl acetate as eluant.A pale yellow glassy solid was obtained at **(96:4)** petroleum ether : ethyl acetate. The product obtained was recrystallised from ethanol. ^{1}H NMR (DMSO) (ppm) spectrum of the compound **4(a)** showed absorption at δ 2.5(s,3H,CH_3) δ 2.1(s,3H,CH_3), δ 6.8(bs,OH, NHC=O↔N=C-OH), δ 5.1(bs,1H,NH), δ 7-7.7(m,5H,Ar-H,CH_2 of pyridazinone

ring). ^{13}C NMR ($CDCl_3$) (ppm) spectrum of the compound **4(a)** showed absorption at δ 172(C=O), δ13, δ20(C-5, C-7), δ40(C-4), δ60, δ 70, δ 72(C-6, C-8, C-9). Mass spectrum of the compound **4(a)** showed molecular ion peak at 226. (M^+) CHNS analysis of the compound **4(a)** confirmed the molecular formula to be C_{13} H_{13} N_3 O. From the above spectral and analytical data, the compound was confirmed to be 5, 7-dimethyl-1,4-tri hydro-2H- pyridazino [3,4-*b*] quinolin-3-one **4(a).**



Scheme 1

Conclusion

The present work was started with an aim of synthesizing the 5, 7-dimethyl-1, 4-tri hydro-2H- Pyridazino [3,4-*b*] quinolin-3-one **4(a).**The precursor 2-chloro 4, 6-dimethyl quinoline**2(a)** was obtained by the reaction of 2-hydroxy 4, 6-dimethyl- quinoline with phosphrous oxy chloride. The 2-chloro 4,6-dimethyl quinoline refluxed with hydrazine dihydrochloride in 20 mL of ethanol to give 2-hydrazino 4,6-dimethyl quinoline**3(a).** The targeted compound 5,7-dimethyl-1,4-tri hydro-2H-Pyridazino[3,4-*b*] quinolin-3-one 4**(a)** was then obtained by reacting 2-hydrazino 4, 6-dimethyl quinoline and chloro acetyl chloride. The synthesized compound was characterized by both analytical and spectral data. The antibacterial, antifungal and antioxidant activity of the synthesized compound were also studied and their results were found to be active. The reaction scheme was then extended to synthesise**,** 5-methyl-1,4-tri hydro-2H- Pyridazino [3, 4-*b*] quinolin-3-one **4(b),** 5-methyl-9-chloro-1, 4-tri hydro-2H-Pyridazino [3, 4-*b*] quinolin-3-one **4(c),** 5, 8-dimethyl-1, 4-tri hydro-2H- Pyridazino [3,4-*b*] quinolin-3-one **4(d)**.

Table 2 Spectral data of compounds

Compound	IR(cm^{-1})	^1H NMR ($CDCl_3$) (ppm)
(3b)	2973(d,NH_2), 3115(NH),2900(CH),3022(d,NH_2)	δ 8.4(bs,NH), δ8.1(d,NH_2), δ7-7.5(m,Ar-H), δ1.29(s,3H,CH_3)
4(b)	3352(NH),1631(C=N),1671(C=O)	-
3(c)	2925(d,NH_2),3289,(NH),1054(C-Cl),2363(CH stretching)	δ 1.24(s,3H,CH_3) , δ2.4(s,3H,CH_3), δ 9 (s,1H,NH), δ 8.1(s,2H,NH_2), δ 7-7.4(m,4H,Ar-H)
4(c)	1035(C-Cl),1613(C=N)2955,2920(NH),1737(C=O)	δ 6.7-7.7(m,5HAr-H,CH_2-H), δ1.2(CH_3), δ9.6(NH), δ9(NH)
4(d)	1627(C=N)3250,2930(NH),1676(C=O).	–

References

[1] T. Yamasaki, E. Kawaminami, F. Uchimura, Y. Okamoto, T. Okawara, M. J. Furukawa, *Heterocycl. Chem*. **1992,** 29**,** 825.
[2] K. Kaji, H. Nagashima, S. Nagao, K. Tabashi, H. Oda, *Chem. Phurm. Bull*. **1982,** 30, 1030.
[3] T. Yamasaki, Y. Yoshihara, Y. Okamoto, T. Okawara, M. Furukawa, *J. Heterocycl. Chem*. **1992,** 29, 1313.
[4] S. Chen, R. P. Panzica, *J. Org. Chem*. **1981**, 46, 2467.
[5] P. Singh, S. P. Gupta, *Indian J Med. Res*. **1979,** 69, 804.
[6] M. Tisler, B. Stanovnik, *Adv. Heterocycl. Chem*. **1990,** 49, 385.
[7] J. A. Joule, K. Mills, *Heterocyclic Chemistry*; Mir Press, **2004**.
[8] V. D. Piaz, C. Vergelli, M. P. Giovannoni, M. A. Scheideler, G. Petrone, Zaratin, *P. Farmac*o **2003,** 58, 1063.
[9] H.Horino, T.Mimura Kagechika,KOhta,M.Kubo,H.Kitagawa,*M.Chem.Pharm.Bull*. **1998**, 46, 602-609
[10] A. Akahane, , H. Katayama Mitsunaga, T. Kato, et al., *J. Med. Chem.* **1999**,42, 779–783,
[11] A. Yamamoto, T. Iwama, H. Takeda, H. Nagai, *Jpn. J.Pharmacol*. , **1995,** 68, 47–55.
[12] K.Tsubaki, K. Taniguchi, S. Tabuchi, O.Okitsu, K. Hattori, J. Seki, K. Sakane, H. Tanaka, *Bioorg. Med.Chem. Lett*. **2000,** 10**,** 2787.
[13] A. Bakthavatchalam, P. Gilligan, J. *Chem. Abstr*., **2000,** 133, 74025.
[14] M. P. Giovannoni, et al., Viale Pieraccini 6, 50139 Firenze, Italy.
[15] A. Coelho, E. Sotelo, E. Ravina, *Tetrahedron*, **2003,** 59, 2477.
[16] S. Demirayak, A. C. Karaburun, R. Beis, Eur. *J. Med. Chem*. **2004,**39, 1089.
[17] A. A. Siddiqui, S. M .Wani,. *Indian J. Chem*.**, 2004**, 43B, 1574.
[18] S. Archan, W Toller,. Curr. *Opin. Anesthesiol*. **2008,** 21(1), 78.
[19] A. Monge, P. Parrado, M.Font, E. F Alvarez, *J. Med. Chem*. **1987,** 30**,** 1029.
[20] C. Rubat, P.; Coudert, B. Refouvelet, P.; Tronche, P. Bastide, *Chem. Pharm. Bull*. **1990,** 38 (11), 3009.
[21] I. Sircar, R. E. Weishaar, D. Kobylarz, W. H. Moos, J. *A.* Bristol, *J. Med. Chem*.**1987,** 30**,** 1955.
[22] J. G. Longo, I. Verde, M. E. Castro, *J. Pharm. Sci*.**, 1993.** 82, 286
[23] A. Akahane, H. Katayama, T. Mitsunaga, *J. Med. Chem*., **1999,** 42, 779.
[24] D. G. H. Livermone, R. C. Bethell, N .Cammack,. *J. Med. Chem*. **1993,** 36, 3784.

Publication History
Received 18th Mar 2014
Revised 12th Mar 2014
Accepted 13th Mar 2014
Online 26th May 2014