Research Article

Green Synthesis and *In Vitro* Biological Evaluation of Heteroaryl Chalcones and Pyrazolines of Medicinal Interest

Vishal Banewar

Department of Chemistry, Government Vidarbha Institute of Science & Humanities, Amravati 444 604, India

Correspondence should be addressed to Vishal Banewar; banewar@gmail.com

Received 28 May 2013; Revised 11 September 2013; Accepted 19 September 2013

Academic Editor: Naoki Haraguchi

Copyright © 2013 Vishal Banewar. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Pyrazolines are well known and important nitrogen containing 5-membered heterocyclic compounds. In the present investigation, a series of various heteroaryl chalcones and pyrazolines were synthesized by condensing formylquinolines with diverse ketones. The newly synthesized 2-pyrazolines were characterized on the basis of elemental analysis and spectroscopic data. All of the newly synthesized target compounds were selected by the NCI for *in vitro* biological evaluation. These active compounds exhibited broad spectrum of various biological activities. Most of the compounds showed potent activity.

1. Introduction

Due to the rapid development of bacterial resistance to antibacterial agents, it is vital to discover novel scaffold for the design and synthesis of new antibacterial agents to help in the battle against pathogenic microorganisms [1–3]. Much research has been carried out with the aim to discover the therapeutic values of thiazole derivatives. A large number of substituted thiazole derivatives were prepared and tested for variety of biological properties [4] such as antimicrobial activity [5, 6]. Amongst the wide variety of heterocycles that have been explored for developing pharmaceutically important molecules such as cyanopyridines [7–9] and triazolopyridines [10–12] have played an important role in medicinal chemistry. They are reported to possess a broad spectrum of biological activity such as potential cardiovascular agents, antiviral [13], CNS depressant [14, 15], bactericidal [16, 17], and ulcer inhibitors [18, 19]. Furthermore, researchers have also revealed that Phenothiazine derivatives constitute an important class of compounds possessing diverse type of biological properties including antiviral [20–22], antiparasitic [23], antiparkinsonian [24, 25], anticonvulsant [26], antihistaminic [27], and anthelmintic [28] properties.

Encouraged by the literature reports and to assess the pharmacological profile of such class of compounds and in continuation with the work related to the synthesis, spectral

studies, and biological properties of pyrazolines, herein we report the synthesis of some novel pyrazolines and then their antibacterial and antifungal activities in the present study.

2. Materials and Methods

Melting points were determined by open capillary and are uncorrected. The purity of the compounds was checked using precoated TLC plates (MERCK, 60F) using chloroform:methanol:water (1:4:5) solvent system. The plates were visualized under UV light (254 nm). IR spectra were recorded using KBr on Shimadzu FTIR model 8000 spectrophotometer, and ¹H NMR spectra were recorded in DMSO on a BRUKER FT-NMR instrument using TMS as an internal standard.

3. Experimental Studies

3.1. General Methods for the Synthesis of Chalcones. The three precursors, 2-chloroquinoline-3-carbaldehyde, 2-chloro-6-nitroquinoline-3-carbaldehyde, and 6-bromo-2-chloroquinoline-3-carbaldehyde, were prepared by the reported method in [29]. Synthesis of the compounds (**1a–d**, **2a–d**, and **3a–d**) (Scheme 1), was based on Claisen-Schmidt condensation [30–32].

SCHEME 1

TABLE 1: Physical properties of synthesized compounds.

Compound	-R	(a-d)	Molecular formula	Yield %	Elemental analysis					
					C	H	O	N	Cl	Br
1a	H	a	C ₁₅ H ₁₂ ClNO	83	69.91 (69.27)	4.69 (4.71)	6.21 (5.85)	5.43 (5.92)	13.76 (14.25)	
1b	H	b	C ₁₆ H ₁₄ ClNO	75	70.72 (70.54)	5.19 (5.76)	5.89 (5.34)	5.15 (5.47)	13.05 (12.89)	
1c	H	c	C ₁₈ H ₁₁ ClN ₂ O ₃	71	63.82 (62.96)	3.27 (3.75)	14.17 (14.76)	8.27 (7.75)	10.47 (10.78)	
1d	H	d	C ₁₈ H ₁₂ ClNO	62	73.60 (73.10)	4.12 (4.37)	5.45 (5.20)	4.77 (5.25)	12.07 (12.08)	
2a	NO ₂	a	C ₁₅ H ₁₂ N ₂ O ₃	75	67.16 (67.25)	4.51 (4.25)	17.89 (17.75)	10.44 (10.75)		
2b	NO ₂	b	C ₁₆ H ₁₄ N ₂ O ₃	80	68.07 (68.05)	5.00 (5.10)	17.00 (17.06)	9.92 (9.79)		
2c	NO ₂	c	C ₁₈ H ₁₁ N ₃ O ₅	63	61.89 (61.78)	3.17 (3.08)	22.90 (22.76)	12.03 (12.38)		
2d	NO ₂	d	C ₁₈ H ₁₂ N ₂ O ₃	64	71.05 (71.25)	3.97 (3.67)	15.77 (15.96)	9.21 (9.12)		
3a	Br	a	C ₁₅ H ₁₂ BrNO	64	59.62 (59.61)	4.00 (4.10)	5.29 (5.31)	4.64 (4.61)		26.44 (26.37)
3b	Br	b	C ₁₆ H ₁₄ BrNO	60	60.78 (60.67)	4.46 (4.67)	5.06 (5.10)	4.43 (4.12)		25.27 (25.44)
3c	Br	c	C ₁₈ H ₁₁ BrN ₂ O ₃	62	56.42 (56.12)	2.89 (2.87)	12.53 (12.23)	7.31 (7.45)		20.85 (21.33)
3d	Br	d	C ₁₈ H ₁₂ BrNO	82	63.92 (63.90)	3.58 (3.60)	4.73 (4.65)	4.14 (4.20)		23.63 (23.65)

A mixture of quinoline-3-carbaldehyde (0.01 mol), ketone **a-d** (0.10 mol), and aq. NaOH (4 mL, 10%) in methanol (50 mL) was refluxed for 2 h, and the reaction mixture was then kept at 0 °C (24 h). Subsequently, it was poured onto ice cold water (200 mL). The precipitates were collected by filtration and washed with cold water followed by cold MeOH. The resulting chalcones were recrystallized from CHCl₃ and obtained in good yield (60–83%) (Table 1). Spectral data (IR, ¹H-NMR, and MS) of all the newly synthesized chalcones were in full agreement with the proposed structures.

2-(2-Chloroquinoline-3-yl-methylene)-cyclopentanone. IR (KBr) cm⁻¹: 1648 (C=O), 1592 (C=C). ¹H-NMR (CDCl₃) δ: 1.44 (2H, m, -CH₂), 1.96 (2H, t, -CH₂), 2.94 (2H, t, -CH₂), 7.26 (1H, s, =CH-ylene), 7.43–8.33 (5H, quinoline Ar-H). MS (*m/z*): 257 (M⁺, 100%).

2-(2-Chloroquinoline-3-yl-methylene)-cyclohexanone. IR (KBr) cm⁻¹: 1656 (C=O), 1562 (C=C). ¹H-NMR (CDCl₃) δ: 1.61 (2H,

m, -CH₂), 1.96 (2H, t, -CH₂), 2.45 (2H, t, -CH₂), 3.12 (2H, s, -CH₂), 6.27 (1H, s, =CH-ylene), 7.43–8.33 (5H, quinoline Ar-H). MS (*m/z*): 271 (M⁺, 100%).

3-(2-Chloroquinoline-3-yl)-1-(4-nitrophenyl)-propenone. IR (KBr) cm⁻¹: 1644 (C=O), 1542 (C=C). ¹H-NMR (CDCl₃) δ: 8.07–8.38 (4H, Ar-H), 7.56 (1H, d, *J* = 15.8), 7.90 (1H, d, *J* = 15.8), 7.13–8.50 (5H, quinoline Ar-H). MS (*m/z*): 338 (M⁺, 100%).

3-(2-Chloroquinoline-3-yl)-1-phenyl Propenone. IR (KBr) cm⁻¹: 1654 (C=O), 1581 (C=C). ¹H-NMR (CDCl₃) δ: 7.45–7.81 (5H, Ar-H), 7.60 (1H, d, *J* = 15.8), 7.82 (1H, d, *J* = 15.8), 7.23–7.92 (5H, quinoline Ar-H). MS (*m/z*): 293 (M⁺, 100%).

2-(2-Nitroquinoline-3-yl-methylene)-cyclopentanone. IR (KBr) cm⁻¹: 1650 (C=O), 1560 (C=C). ¹H-NMR (CDCl₃) δ: 1.41 (2H, m, -CH₂), 1.85 (2H, t, -CH₂), 2.73 (2H, t, -CH₂), 7.51 (1H, s, =CH-ylene), 7.70–8.82 (5H, quinoline Ar-H). MS (*m/z*): 268 (M⁺, 100%).

2-(2-Nitroquinoline-3-yl-methylene)-cyclohexanone. IR (KBr) cm^{-1} : 1656 (C=O), 1553 (C=C). $^1\text{H-NMR}$ (CDCl_3) δ : 1.53 (2H, m, $-\text{CH}_2$), 1.87 (2H, t, $-\text{CH}_2$), 2.82 (2H, t, $-\text{CH}_2$), 3.05 (2H, s, $-\text{CH}_2$), 6.61 (1H, s, $=\text{CH-ylene}$), 7.41–8.27 (5H, quinoline Ar-H). MS (m/z): 282 (M^+ , 100%).

1-(4-Nitrophenyl)-3-(2-nitroquinolin-3-yl)-propenone. IR (KBr) cm^{-1} : 1654 (C=O), 1548 (C=C). $^1\text{H-NMR}$ (CDCl_3) δ : 8.21–8.48 (4H, Ar-H), 7.51 (1H, d, $J = 15.8$), 7.85 (1H, d, $J = 15.8$), 7.11–8.51 (5H, quinoline Ar-H). MS (m/z): 349 (M^+ , 100%).

3-(2-Nitroquinolin-3-yl)-1-phenyl Propenone. IR (KBr) cm^{-1} : 1656 (C=O), 1587 (C=C). $^1\text{H-NMR}$ (CDCl_3) δ : 7.21–7.73 (5H, Ar-H), 7.51 (1H, d, $J = 15.8$), 7.90 (1H, d, $J = 15.8$), 7.29–7.76 (5H, quinoline Ar-H). MS (m/z): 304 (M^+ , 100%).

2-(2-Bromo-quinoline-3-yl-methylene)-cyclopentanone. IR (KBr) cm^{-1} : 1665 (C=O), 1590 (C=C). $^1\text{H-NMR}$ (CDCl_3) δ : 1.46 (2H, m, $-\text{CH}_2$), 1.64 (2H, t, $-\text{CH}_2$), 2.41 (2H, t, $-\text{CH}_2$), 7.50 (1H, s, $=\text{CH-ylene}$), 7.48–8.60 (5H, quinoline Ar-H). MS (m/z): 301 (M^+ , 100%).

2-(2-Bromo-quinoline-3-yl-methylene)-cyclohexanone. IR (KBr) cm^{-1} : 1656 (C=O), 1553 (C=C). $^1\text{H-NMR}$ (CDCl_3) δ : 1.60 (2H, m, $-\text{CH}_2$), 1.95 (2H, t, $-\text{CH}_2$), 2.44 (2H, t, $-\text{CH}_2$), 3.11 (2H, s, $-\text{CH}_2$), 6.26 (1H, s, $=\text{CH-ylene}$), 7.48–8.54 (5H, quinoline Ar-H). MS (m/z): 315 (M^+ , 100%).

3-(2-Bromoquinolin-3-yl)-1-(4-nitrophenyl)-propenone. IR (KBr) cm^{-1} : 1634 (C=O), 1556 (C=C). $^1\text{H-NMR}$ (CDCl_3) δ : 8.01–8.24 (4H, Ar-H), 7.58 (1H, d, $J = 15.8$), 7.92 (1H, d, $J = 15.8$), 7.45–8.16 (5H, quinoline Ar-H). MS (m/z): 382 (M^+ , 100%).

3-(2-Bromoquinolin-3-yl)-1-phenyl Propenone. IR (KBr) cm^{-1} : 1645 (C=O), 1556 (C=C). $^1\text{H-NMR}$ (CDCl_3) δ : 7.42–7.84 (5H, Ar-H), 7.43 (1H, d, $J = 15.8$), 7.76 (1H, d, $J = 15.8$), 7.65–7.86 (5H, quinoline Ar-H). MS (m/z): 338 (M^+ , 100%).

4. Antibacterial Screening

Antimicrobial activity was carried out by cup-plate agar diffusion method at a concentration of 50 $\mu\text{g/mL}$ in solvent DMF. The purified products were screened for their antibacterial activity. The nutrient agar slant prepared by the usual method was incubated at $37 \pm 5^\circ\text{C}$ for 24 h. The zone of inhibition was measured in mm. The antimicrobial activity of the synthesized compounds was compared with standard drugs.

All series of compounds nearly exhibit the same antimicrobial activities against all the four bacterial strains, that is, *B. subtilis*, *B. pumilius*, *E. coli*, and *S. aureus* (Table 2). Among all series of compounds, **1a**, **2b**, and **3c** exhibit strong antibacterial activity. Introduction of aromatic ketone increases the activity against all microorganisms. It is further increased by the incorporation of NO_2 group at the fourth position of aromatic ketone. Amongst the aliphatic ketone, five membered compounds show decrease in activity (**1a–1c**) in comparison with six membered compounds (**2b–2d**). In general, aromatic introduction in the compounds enhances the activity, while activity is suppressed by introduction of aliphatic group in the compounds.

TABLE 2: Antimicrobial activity of synthesized compounds.

Zone (mm) (50 μg)	Compounds											
	1a	1b	1c	1d	2a	2b	2c	2d	3a	3b	3c	3d
<i>B. subtilis</i>	4	5	5	6	4	6	5	5	5	4	6	5
<i>B. pumilus</i>	4	5	5	5	—	5	5	—	5	5	7	5
<i>E. coli</i>	4	4	4	4	4	4	4	4	4	—	4	5
<i>S. aureus</i>	—	—	—	5	—	5	4	6	5	4	4	6

TABLE 3: Antifungal activity of synthesized compounds.

Zone (mm)	Compounds											
	1a	1b	1c	1d	2a	2b	2c	2d	3a	3b	3c	3d
<i>Curvularia eragrostidis</i>	10	08	09	16	08	06	12	09	10	12	08	10
<i>Drechslera tetramera</i>	12	14	12	02	12	08	10	13	08	10	07	11
<i>Fusarium ciceri</i>	14	10	11	12	10	12	12	12	15	11	15	16
<i>Bipolaris sorokiniana</i>	07	14	06	16	06	06	16	07	12	13	16	05

5. Antifungal Screening

The antifungal activities of the compounds **1a–d**, **2a–d**, and **3a–d** have been assayed at the concentration of 200 $\mu\text{g/disc}$ assays against four plants pathogenic and moulds fungi. The inhibitory effects of compounds against these organisms are given in Table 3. The screening results indicate that the compound shows good to moderate antifungal activities to the tested fungi against *Curvularia eryostides*, *Drechslera tetrameda*, *Fusarium cicerg*, and *Bipolaris sorokenia*.

All the compounds show promising antifungal activity against all fungi except *Bipolaris sorokiniana* (Table 3). All the compounds show strong activity against *Drechslera tetramera* and *Fusarium ciceri* compared with that of the other two fungi. As in the case of antimicrobial, introduction of aromatic group enhances the activity of **2c**, **2d**, **3c**, and **3d**. Introduction of NO_2 group at fourth position increases the activity of **1c**, **2c**, and **3c**.

Introduction of electron withdrawing group shows remarkable difference in biological activity (both antimicrobial and antifungal).

No systematic change has been observed in antibacterial and antifungal activity for the rest of the compounds.

6. Conclusion

All the synthesized compounds were characterized with their physical and spectral data. The antifungal and antibacterial screening of the synthesized pyrazolines were found to be active.

This research study reports the successful synthesis of new heteroaryl pyrazoline. It also reports antimicrobial and antifungal studies of synthesized compounds. The biological study revealed that compounds showed moderate to good activity.

Acknowledgments

The author is thankful to the Department of Chemistry, Government Vidarbha Institute of Science & Humanities, Amravati, Maharashtra, India, and Director of Garware Lab, Department of Chemistry, Pune University, Pune, for ¹H NMR spectral characterization.

References

- [1] D. K. Dodiya, *Studies on heterocyclic compounds of medicinal interest [Ph.D. thesis]*, Saurashtra University, Gujrat, India, 2010.
- [2] A. Ganesh, "Biological activities of some Pyrazoline derivatives," *International Journal of Pharma and Bio Sciences*, vol. 14, no. 2, pp. 727–733, 2013.
- [3] O. Ruhoğlu, Z. Özdemir, Ü. Çaliş, B. Gümüşel, and A. A. Bilgin, "Synthesis of and pharmacological studies on the antidepressant and anticonvulsant activities of some 1,3,5-trisubstituted pyrazolines," *Arzneimittel-Forschung/Drug Research*, vol. 55, no. 8, pp. 431–436, 2005.
- [4] S. A. Thakkar, *Studies on bioactive heterocycles and other moieties [Ph.D. thesis]*, Saurashtra University, Gujrat, India, 2010.
- [5] A. Handan, A. Oznur, K. Ayse, B. Seher, and O. Gulten, "Synthesis, characterization and evaluation of antimicrobial activity of Mannich bases of some 2-[(4-carbethoxymethylthiazol-2-yl)imino]-4-thiazolidinones," *Indian Journal of Chemistry*, vol. 44B, p. 585, 2005.
- [6] J. T. Desai, C. K. Desai, and K. R. Desai, "A convenient, rapid and eco-friendly synthesis of isoxazoline heterocyclic moiety containing bridge at 2°-amine as potential pharmacological agent," *Journal of the Iranian Chemical Society*, vol. 5, no. 1, pp. 67–73, 2008.
- [7] V. Klimešová, M. Otčenášek, and K. Waisser, "Potential antifungal agents. Synthesis and activity of 2-alkylthiopyridine-4-carbothioamides," *European Journal of Medicinal Chemistry*, vol. 31, no. 5, pp. 389–395, 1996.
- [8] E. Suloeva, M. Yure, E. Gudriniece, M. Petrova, and A. Gutcaits, "Synthesis of 2,3-dihydroimidazo-[1,2-a]pyridines from 1,3-diketones," *Chemistry of Heterocyclic Compounds*, vol. 37, no. 7, pp. 872–875, 2001.
- [9] J. M. Quintela, C. Peinador, L. Botana, M. Estévez, and R. Riguera, "Synthesis and antihistaminic activity of 2-guanadino-3-cyanopyridines and pyrido[2,3-d]-pyrimidines," *Bioorganic and Medicinal Chemistry*, vol. 5, no. 8, pp. 1543–1553, 1997.
- [10] B. Abarca, I. Alkorta, R. Ballesteros et al., "3-(2-Pyridyl)-[1,2,3]triazolo[1,5-a]pyridines. An experimental and theoretical (DFT) study of the ring-chain isomerization," *Organic and Biomolecular Chemistry*, vol. 3, no. 21, pp. 3905–3910, 2005.
- [11] B. Abarca, R. Ballesteros, and M. Chadlaoui, "Synthesis of novel polypyridylcarbonylpyridines from triazolopyridines. Building blocks in supramolecular chemistry," *Arkivoc*, vol. 2008, no. 7, pp. 73–83, 2008.
- [12] B. Abarca, R. Ballesteros, M. Elmasnaouy, P. D'Ocón, M. D. Ivorra, and M. Valiente, "Evaluation and synthesis of 7-arylhydroxymethyltriazolopyridines as potential cardiovascular agents," *ARKIVOC*, vol. 2002, no. 10, pp. 9–13, 2002.
- [13] Y. S. Sanghvi, S. B. Larson, R. C. Willis, R. K. Robins, and G. R. Revankar, "Synthesis and biological evaluation of certain C-4 substituted pyrazolo[3,4-b]pyridine nucleosides," *Journal of Medicinal Chemistry*, vol. 32, no. 5, pp. 945–951, 1989.
- [14] M. Paller and K. Ponzio, *Chemical Abstracts*, vol. 99, p. 158406r, 1983.
- [15] M. Kidwai, P. Priya, and S. Rastogi, "Reaction of coumarin derivatives with nucleophiles in aqueous medium," *Zeitschrift für Naturforschung Section B*, vol. 63, no. 1, pp. 71–76, 2008.
- [16] L. Prakash, R. Sharma, S. Shukla, and G. R. D. Pharmazie, *Pharmazie*, vol. 48, p. 221, 1993.
- [17] J. P. Raval and K. R. Desai, "Synthesis and antimicrobial activity of new triazolopyridinyl phenothiazines," *ARKIVOC*, vol. 2005, no. 13, pp. 21–28, 2005.
- [18] A. Heichachiro, K. Shinozaki, S. Niwa et al., *Chemical Abstracts*, vol. 110, p. 23891v, 1989.
- [19] K. Bajaj, V. K. Srivastava, and A. Kumar, "Synthesis and psychotropic evaluation of some new N-substitutedbenzothia/oxazepinylphenothiazines," *Indian Journal of Chemistry Section B*, vol. 43, no. 1, pp. 157–161, 2004.
- [20] M. N. Narule, "A facile route to the synthesis of 8-[2-(3'', 5''-dimethyl-4''-ethoxy carbonyl pyrrolyl) hydrazine] substituted phenothiazines and their biological activity," *Journal of Chemical, Biological and Physical Sciences*, vol. 2, no. 4, pp. 1681–1687, 2012.
- [21] M. Idries and A. L. Abeed-Mashkor, "Synthesis of new [10h-substitutedphenoxazine-3-Yl]-6-pyrimidin-2-phenylthiol/OL/amine/thiol] pyrroles," *Thi-Qar Medical Journal*, vol. 4, no. 4, pp. 120–126, 2010.
- [22] R. Dahlbom and T. Ekstrand, *Archive of International Pharmacodynamics*, vol. 159, p. 70, 1996.
- [23] C. S. Weil, "On the construction of tables for moving average interpolation," *Biometrics*, vol. 8, p. 249, 1952.
- [24] B. Harpen and M. Nidwai, "Synthesis characterization of Phenothiazinyl derivatives," *The Journal of the American Medical Association*, vol. 129, pp. 1219–1222, 1945.
- [25] M. Narule, J. M. B. Santhakumari, and A. Shanware, "Synthesis of 2-[4-(10H-substituted phenothiazine-3-yl)-6-pyrimidin-2-phenylthiol/ol/amine/thiol] pyrroles," *E-Journal of Chemistry*, vol. 4, no. 1, pp. 53–59, 2007.
- [26] J. D. Genzer, M. N. Lewis, F. H. McMillan, and J. A. King, "Synthesis and anti-microbial activity of 2-[4-(10-p-chlorobenzyl)phenothiazinyl]-3-substituted aryl-1-ones," *Journal of the American Chemical Society*, vol. 75, p. 2206, 1953.
- [27] L. Dushay, *Revue Canadienne de Biologie*, vol. 20, p. 321, 1961.
- [28] J. R. Douglass, N. F. Baker, and M. W. Longwest, "Synthesis and biological activity of N-phenothiazine," *American Journal of Veterinary Research*, vol. 17, p. 318, 1956.
- [29] O. Meth-Cohn, B. Narine, and B. Tarnowski, "A versatile new synthesis of quinolines and related fused pyridines. Part 5. The synthesis of 2-chloroquinoline-3-carbaldehydes," *Journal of the Chemical Society, Perkin Transactions 1*, pp. 1520–1530, 1981.
- [30] F. Herencia, M. L. Ferrándiz, A. Ubeda et al., "Synthesis and anti-inflammatory activity of chalcone derivatives," *Bioorganic and Medicinal Chemistry Letters*, vol. 8, no. 10, pp. 1169–1174, 1998.
- [31] T. Narender, K. Venkateswarlu, B. V. Nayak, and S. Sarkar, "A new chemical access for 3'-acetyl-4'-hydroxychalcones using borontrifluoride-etherate via a regioselective Claisen-Schmidt condensation and its application in the synthesis of chalcone hybrids," *Tetrahedron Letters*, vol. 52, no. 44, pp. 5794–5798, 2011.
- [32] R. Li, G. L. Kenyon, F. E. Cohen et al., "In vitro antimalarial activity of chalcones and their derivatives," *Journal of Medicinal Chemistry*, vol. 38, no. 26, pp. 5031–5037, 1995.