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JSCS–4267 *Original scientific paper*

The design, synthesis and antimicrobial activity of new biquinoline derivatives

NIRAV K. SHAH, NIMESH M. SHAH, MANISH P. PATEL and RANJAN G. PATEL*

Department of Chemistry, Sardar Patel University, Vallabh Vidyanagar-388120, Gujarat, India

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Abstract: A simple and efficient method has been developed for the synthesis of some novel biquinoline derivatives bearing a thiazole moiety through a one-pot three-component condensation of 2-chloro-3-formylquinolines, ethyl cyanoacetate and a *β*-enaminone using a catalytic amount of piperidine in refluxing ethanol. These molecules were evaluated *in vitro* for their antibacterial and antifungal activity. Most of the compounds exhibited moderate antibacterial and antifungal activity against all the tested strains.

Keywords: quinoline; thiazole; antibacterial; antifungal.

INTRODUCTION

The quinoline nucleus is one of the most important and widely exploited heterocyclic rings for the development of bioactive molecules. Recent literature is enriched with progressive findings about the synthesis and pharmacological actions of quinoline and its derivatives. A number of quinoline derivatives are known to possess antimicrobial, antimycobacterial, antidepressant, antimalarial, anticonvulsant, antiviral, anticancer, hypotensive and anti-inflammatory activities.[1]

Compounds containing thiazole rings have remarkable medicinal value due to their potential chemotherapeutic,[2] fungicidal,[3] antiviral[4] and pesticidal[5] properties. In addition, 2-aminothiazole derivatives were reported to exhibit significant biological activities, such as anti-tuberculosis,[6] anti-inflammatory,[7] enzyme inhibition[8] and antitumor activities.[9]

After an extensive literature search, it was observed that quinoline and thiazole are important pharmacophores, but to date, insufficient effort has been made to combine these two moieties as a single molecular scaffold. Hence, the aim of this study was to synthesize and biologically screen a series of new compounds incorporating these moieties.

* Corresponding author. E-mail: patelranjanben@yahoo.com
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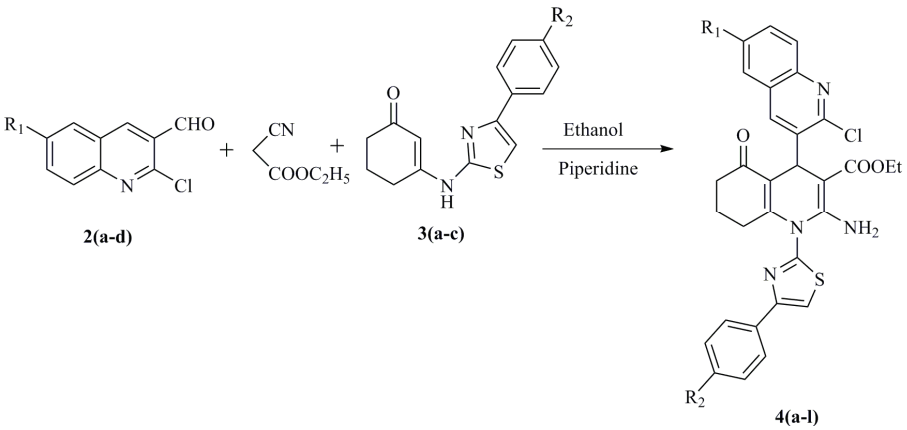
RESULTS AND DISCUSSION

Chemistry

In continuation of the synthesis of biologically potent antimicrobials,[10] a new series of biquinolines synthesized by the one-pot three-component cyclocondensation reaction of 2-chloro-3-formylquinolines **2**(**a**–**d**), ethyl cyanoacetate and 3-[(4-arylthiazol-2-yl)amino]cyclohex-2-en-1-ones (enaminone) **3**(**a**–**c**) is reported herein. The synthetic route depicted in Scheme 1 outlines the chemistry part of the present work. The key intermediates 2-chloro-3-formylquinolines **2**(**a**–**d**) were prepared according to a literature method[11] (Scheme 2). The solid phase reaction of 4-substituted acetophenone, thiourea and iodine for 4 h at 120 °C afforded the respective 2-amino-4-arylthiazole[12] (Scheme 2). The required *β*-enaminones **3**(**a**–**c**) were prepared by the reaction of *β*-diketone with 2-amino-4-arylthiazole in methanol under reflux in the presence of a catalytic amount of acetic acid.

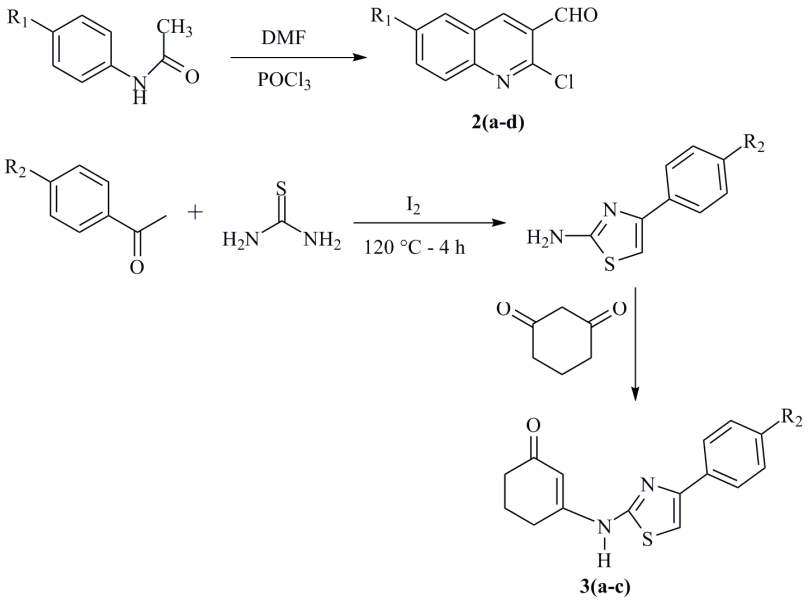


Compd.	4a	4b	4c	4d	4e	4f	4g	4h	4i	4j	4k	4l
R_1	H	CH_3	OCH_3	Cl	H	CH_3	OCH_3	Cl	H	CH_3	OCH_3	Cl
R_2	H	H	H	H	Cl	Cl	Cl	Cl	OH	OH	OH	OH

Scheme 1. Synthetic pathway for the compounds **4**(**a**–**l**).

To choose the most appropriate medium to synthesize compounds **4**(**a**–**l**), several reaction conditions were investigated. Looking for the optimal reaction solvent, the reaction was examined in ethylene glycol, dimethylformamide, acetic acid, tetrahydrofuran and ethanol as solvent under reflux. The reaction in ethanol resulted in higher yields and shorter reaction time than the others, hence, ethanol

was chosen as the appropriate solvent. Moreover, to improve further the reaction yields, different bases, such as NaOH, K_2CO_3, 4-dimethylaminopyridine (DMAP), Et_3N and piperidine were examined in ethanol. Piperidine afforded the target product 4a in 87 % yield. Therefore, it was chosen as the most suitable base for all further reactions.



Scheme 2. Synthetic pathway for the intermediates **2**(**a**–**d**) and **3**(**a**–**c**).

The reaction occurs *via* the initial *in situ* formation of the heteroarylidene-nitriles, containing an electron-poor C=C double bond, by the Knoevenagel condensation of a 2-chloro-3-formylquinoline and ethyl cyanoacetate with the loss of water molecules. Finally, Michael addition of or to the initially formed unsaturated nitrile, *i.e.*, nucleophilic attack of the cyano olefins by an enaminone afforded the cyclized quinoline derivatives **4**(**a**–**l**).

The structures of the compounds were confirmed based on elemental analysis and spectral data (given as supplementary material). As an example, the IR spectrum of compound **4d** (R_1=Cl, R_2=H) showed a band at 3445 cm^{-1} of the asym. N–H stretching, 3345 cm^{-1} of the sym. N–H stretching and at 1660 and 1640 cm^{-1} for the C=O stretching of the carbonyl group. The ^{1}H-NMR spectra of **4d** showed a triplet signal at δ 1.01 ppm for the methyl group, a multiplet signal at δ 1.71–2.25 pmm for the three methylene groups, a quartet signal at δ 3.92 ppm for the OCH_2 group, a singlet at δ 5.30 ppm and at δ 8.45 ppm for the methine group and amino group, respectively, and a multiplet due to the aromatic protons at around δ 7.37–8.24. The ^{13}C-NMR spectrum of **4d** was in good agree-

ment with the assigned structure. The peak at δ 14.74 is attributed to one methyl group, the peaks at δ 21.19, 27.46 and 36.58 ppm are attributed to the three methylene carbons, the peak at δ 35.82 pm is attributed to the methine carbon. The peak at δ 77.93 ppm is assigned to the carbon attached to the carboxylate and the peaks at δ 114.17–156.98 ppm are attributed to aromatic carbons. The peak at δ 168.99 and 195.77 ppm are assigned to the carbonyl carbons. The mass spectra of compounds **4d** and **4j** showed an M^++1 peak in agreement with their exact molar mass.

Biological evaluation

The antibacterial activities of the biquinolines given in Table I indicate that among all the compounds **4a**, **4c**, **4d**, **4e**, **4h**, **4k** and **4l** exhibited good antibacterial activity against the bacterial strain *Escherichia coli*. Similarly, compounds **4a**, **4c**, **4d**, **4g**, **4h**, **4k** and **4l** showed good activity against the Gram-positive bacterial species *Bacillus subtilis* and compounds **4a**, **4c**, **4d**, **4f**, **4h**, **4k** and **4l** against the Gram-positive bacterial species *Staphylococcus aureus*. The remaining compounds showed moderate activity against the tested bacterial strains.

TABLE I. Antimicrobial activity of the compounds **4(a–l)** (Zone of inhibition, in mm). NT = = not tested. Control (DMF) (–) – no activity

Compound	Antibacterial activity			Antifungal activity		
	E. coli	*B. subtilis*	*S. aureus*	*F. oxysporum*	*A. niger*	*R. oryzae*
4a	23	25	22	16	15	18
4b	17	19	18	15	19	16
4c	25	24	23	20	22	25
4d	24	23	25	14	16	21
4e	20	17	18	17	16	18
4f	18	19	20	16	18	17
4g	19	20	18	21	24	22
4h	25	22	24	19	20	21
4i	19	18	15	17	17	14
4j	18	17	16	15	14	18
4k	24	22	23	21	25	24
4l	21	23	25	19	20	17
Ampicillin	28	30	30	NT	NT	NT
Ciprofloxacin	35	34	33	NT	NT	NT
Griseofulvin	NT	NT	NT	26	28	30

The antifungal evaluation of the synthesized compounds revealed that compounds **4c**, **4g** and **4k** displayed excellent antifungal activity towards *Fusarium oxysporum*. Against *Aspergillus niger*, compounds **4c**, **4g**, **4h**, **4k** and **4l** and compounds **4c**, **4d**, **4g**, **4h** and **4k** towards *Rhizopus oryzae* showed good activity. The remaining compounds showed mild to moderate antifungal activity.

A close examination of the structures of the active compounds in Table I revealed that their antimicrobial activity was strongly bound to the nature of the substituent at the quinoline-C_6, together with the substituent linked to the arylthiazole part of the structure. In general, it could be clearly recognized that compound **4c** without a substituent in the arylthiazole moiety (R_2 = H) and with the quinoline containing a methoxy substituent (R_1 = OCH_3) showed the greatest activity compared to the other studied compounds. Moreover, compound **4k** with the quinoline containing a methoxy substituent (R_1 = OCH_3) and with a hydroxyl substituent in the arylthiazole moiety (R_2 = OH) had a good antimicrobial profile while compound **4g** with the quinoline also containing a methoxy substituent (R_1 = OCH_3) and with a chloro substituent in the arylthiazole moiety (R_2 = Cl) exhibited moderate to good antimicrobial activity. On the other hand, the introduction of a methyl group at position 6 of the quinoline (compounds **4b**, **4j** and **4f**) resulted in a noticeable decrease in the antimicrobial potential of these compounds. Compounds **4a** (R_1 = H, R_2 = H), **4h** (R_1 = Cl, R_2 = Cl) and **4l** (R_1 = Cl, R_2 = OH) showed good antibacterial activity together with a moderate antifungal profile. It is worth mentioning that the biological activity of the target compounds depended not only on the bicyclic heteroaromatic pharmacophore but also on the nature of the substituents and maybe on their spatial relationships. Here, the thiazole moiety was introduced along with a biquinoline ring for activity reinforcement. However, based on the presented observations, it is immature to arrive at any conclusion on the structure–activity aspect of these molecules and further evaluation is required.

EXPERIMENTAL

Chemistry

Solvents used were of analytical grade. All melting points were taken in open capillaries and are uncorrected. Thin-layer chromatography (TLC, on aluminum plates precoated with silica gel, $60F_{254}$, 0.25 mm thickness) (Merck, Darmstadt, Germany) was used for monitoring the progress of all reactions and the purity and homogeneity of the synthesized compounds. The eluent was hexane:ethyl acetate 6:4 and UV radiation and/or iodine were used as the visualizing agents. Elemental analysis (% C, H and N) was performed on a Perkin-Elmer 2400 series-II elemental analyzer (Perkin-Elmer, USA) and all compounds were within ±0.4 % of their calculated composition. The IR spectra were recorded in KBr pellets on a Perkin-Elmer Spectrum GX FT-IR spectrophotometer (Perkin-Elmer, USA), and only the characteristic peaks are reported in cm^{-1}. The ^{1}H-NMR and ^{13}C-NMR spectra were recorded in DMSO-d_6 on a Bruker Avance 400F spectrometer (Bruker, Switzerland) using the solvent peak as an internal standard at 400 and 100 MHz, respectively. The chemical shifts were reported in ppm. The mass spectra were scanned on a Shimadzu LCMS 2010 spectrometer (Shimadzu, Tokyo, Japan). Analytical and spectral data of the synthesized compounds are given in the Supplementary material.

General procedure for the synthesis of 2-amino-4-arylthiazole

The 2-amino-4-arylthiazoles were synthesized, according to a literature procedure[12] by the solid phase reaction of thiourea, a 4-substituted acetophenone and iodine (Scheme 2).

*General procedure for the synthesis of 3-[(4-arylthiazole-2-yl)amino]cyclohex-2-en-1-ones **3(a–c)***

A 1,3-dicarbonyl compound 1,3-cyclohexanedione (30 mmol), 2-amino-4-arylthiazole (30 mmol), methanol (15 mL) and 2 drops of acetic acid were charged into a 100 mL round--bottom flask equipped with reflux condenser. The reaction mixture was slowly heated and refluxed for 1 h. On completion of reaction, monitored by TLC using 30 % EtOAc in toluene as the eluent, the reaction mixture was cooled to room temperature and the solid that separated was filtered and washed with methanol to obtain the pure compounds.

*General procedure for the synthesis of ethyl 2-amino-1-(4-arylthiazol-2-yl)-4-(2-chloro-6--(un)substituted-3-quinolyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylates **4(a–l)***

A mixture of 2-chloro-3-formylquinolines (1.0 mmol), ethyl cyanoacetate (1.0 mmol), and an appropriate *β*-enaminone (1.0 mmol) in ethanol (10 ml) containing a catalytic amount of piperidine was slowly heated and refluxed for 3–4 h. On completion of the reaction, monitored by TLC (ethyl acetate:toluene 3:7), the reaction mixture was cooled to room temperature and the solid that separated was filtered and washed with mixture of chloroform and methanol (1:1) to obtain the pure compounds.

Antimicrobial activity

The *in vitro* antimicrobial activity was realized against 24 h old cultures of three bacteria and three fungi by the disc diffusion method.[13,14] Compounds **4(a–l)** were tested for their antibacterial activity against *E. coli* as Gram-negative bacteria and *B. subtilis* and *Staphylococcus aureus* as Gram-positive bacteria and antifungal activity against *A. niger*, *F. oxysporum* and *R. oryzae*. Nutrient agar and potato dextrose agar were used to culture the bacteria and fungi, respectively. The compounds were tested at 1000 ppm in DMF solution. Ciprofloxacin, ampicillin and griseofulvin were used as standards for comparison of antibacterial and antifungal activities, respectively. Inhibition was recorded by measuring the diameter of the inhibition zone at the end of 24 h for bacteria at 35 °C and 48 h for the fungi at 28 °C. Details of the evaluation of the antimicrobial activity of compounds **4(a–l)** are given in the Supplementary material.

CONCLUSIONS

In conclusion, a simple and efficient method for the synthesis of biquinoline derivatives is developed. The straightforward approach, simplicity and one-step method make it an interesting approach for the synthesis of said compounds. Most of the compounds showed better antibacterial activity. Further optimization and development is needed in designing more potent antibacterial and antifungal agents for therapeutic use.

SUPPLEMENTARY MATERIAL

Analytical and spectral data of synthesized compounds, as well as the details of the evaluation of their antimicrobial activity are available electronically from http://www.shd.org.rs/JSCS/, or from the corresponding author on request.

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И З В О Д

ДИЗАЈН, СИНТЕЗА И АНТИМИКРОБНА АКТИВНОСТ НОВИХ БИХИНОЛИНСКИХ ДЕРИВАТА

NIRAV K. SHAH, NIMESH M. SHAH, MANISH P. PATEL и RANJAN G. PATEL

Department of Chemistry, Sardar Patel University, Vallabh Vidyanagar-388120, Gujarat, India

Развијен је једноставан и ефикасан поступак за синтезу нових бихинолинских деривата који садрже тиазолински структурни фрагмент. Поступак се састоји из трокомпонентне кондензације 2-хлор-3-формилхинолина, етил-цијаноацетата и β-енаминона у једном реакционом кораку, катализоване пиперидином у кључалом етанолу. Испитана је *in vitro* антибактеријска и антифунгална инхибиторна активност добијених једињења. Већина испитаних једињења показује умерену активност према испитиваним сојевима.

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REFERENCES

1. a) C. Vittorio, B. Guyen, Y. Opoku-Boahen, J. Mann, S. M. Gowan, M. Lloyd, A. R. Martin, N. Stephen, *Bioorg. Med. Chem. Lett.* **10** (2000) 2063; b) P. Senthilkumar, M. Dinakaran, Y. Chandraseakaran, P. Yogeeswari, D. Sriram, *Arch. Pharm.* **342** (2009) 100; c) M. A. Khalil, O. A. El-Sayed, H. A. El-Shamy, *Arch. Pharm.* **326** (1993) 489; d) M. Flipo, I. Florent, P. Grellier, C. Sergheraert, R. Deprez-Poulain, *Bioorg. Med. Chem. Lett*. **13** (2003) 2659; e) L.-P. Guan, Q.-H. Jin, S.-F. Wang, F.-N. Li, Z.-S. Quan, *Arch. Pharm*. **341** (2008) 774; f) X.-Y. Sun, C.-X. Wei, K.-Y. Chai, H.-R. Piao, Z.-S. Quan, *Arch. Pharm*. **341** (2008) 288; g) S. Bawa, S. Kumar, *Indian J. Chem., Sect B* **48** (2009) 142; h) J. M. McCall, R. E. Brink, B. V. Kamdar, L. L. Skaletzky, S. C. Perricone, R. C. Piper, P. J. Delehanty, *J. Med. Chem*. **29** (1986) 133; i) K. K. Luciana, C. H. Pavam, D. Veronese, F. Coelho, J. E. De Carvalho, W. P. Almeida, *Eur. J. Med. Chem*. **41** (2006) 738; j) C. M. Meléndez Gómez, V. V. Kouznetsov, M. A. Sortino, S. L. Álvarez, S. A. Zacchino, *Bioorg. Med. Chem*. **16** (2008) 7908; k) A. A. Bekhita, O. A. El-Sayeda, H. Y. Aboul-Eneinb, Y. M. Siddiquic, M. N. Al-Ahdalc, *J. Enzyme Inhib. Med. Chem.* **19** (2004) 33; l) G. Sathi, V. R. Gujrati, M. Sharma, C. Nath, K. P. Bhargava, K. Shanker, *Arch. Pharm*. **316** (1983) 767
2. H. Liebig, H. Pfetzing, A. Grafe, *Arzneim.-Forsch.* **24** (1974) 887
3. R. B. Pathak, B. Jahan, S. C. Bahel, *Bokin Bobai* **9** (1981) 477
4. F. C. Spector, L. Liang, H. Giordano, M. Sivaraja, M. G. Peterson, *J. Virol.* **72** (1998) 6979
5. Z. Fan, Z. Shi, X. Liu, Z. Fan, Y. Ai, Faming Zhuanli Shenqing Gongkai Shuomingshu, 2006, Chinese patent: CNXXEV CN 1810808 A 20060802
6. K. M. Sytnik, I. Ye. Bylov, S. N. Kovalenko, *Zh. Org. Farm. Khim.* **1** (2003) 71
7. B. Holla, K. Malini, B. Rao, B. Sarojini, N. Kumari, *Eur. J. Med. Chem.* **38** (2003) 313

8. J. Das, J. Furch, C. Liu, R. Moquin, J. Lin, S. Spergel, K. McIntyre, D. Shuster, K. O'Day, B. Penhallow, *Bioorg. Med. Chem. Lett*. **16** (2006) 3706
9. H. I. El-Subbagh, A. H. Abadi, J. Lehmann, *Arch. Pharm*. **332** (1999) 137
10. a) N. M. Shah. M. P. Patel, R. G. Patel, *J. Heterocycl. Chem.* (2011) DOI 10.1002/jhet.918; b) D. C. Mungra, M. P. Patel, D. P. Rajani, R. G. Patel, *Eur. J. Med. Chem*. **46** (2011) 4192; c) N. K. Shah, M. P. Patel, R. G. Patel, *Phosphorus Sulfur Silicon Relat. Elem*. **184** (2009) 2704; d) N. K. Shah, M. P. Patel, R. G. Patel, *Indian J. Chem. Sect. B* **48** (2009) 1170; e) J. A. Makawana, M. P. Patel, R. G. Patel, *Med. Chem. Res*. (2011) DOI 10.1007/s00044-010-9568-6; f) C. B. Sangani, M. P. Patel, R. G. Patel, *Cent. Eur. J. Chem*. **9** (2011) 635; g) N. K. Ladani, M .P. Patel, R .G. Patel, *Arkivoc* **vii** (2009) 292
11. O. Meth-Cohn, N. A. Bramha, *Tetrahedron Lett*. **23** (1978) 2045
12. R. M. Dodson, L. C. King, *J. Am. Chem. Soc*. **67** (1945) 2242
13. C. H. Collins, P. M. Lyne, *Microbial Methods*, University Park Press, Baltimore, USA, 1970
14. T. D. Thangadurai, K. Natarajan, *Indian J. Chem. Sect. A* **40** (2001) 573.