



J. Serb. Chem. Soc. 77 (11) 1561–1570 (2012)
JSCS–4371

Journal of
the Serbian
Chemical Society

JSCS-info@shd.org.rs • www.shd.org.rs/JSCS

UDC 546.654+547.831.7:542.913+
544.478:615.28

Original scientific paper

Lanthanum triflate-triggered synthesis of tetrahydroquinazolinone derivatives of *N*-allylquinolone and their biological assessment

HARDIK H. JARDOSH and MANISH P. PATEL*

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

(Received 21 January, revised 27 March 2012)

Abstract: A series of 24 derivatives of tetrahydroquinazolinone has been synthesized by the one-pot cyclocondensation reaction of *N*-allyl quinolones, cyclic β -diketones and (thio)urea/*N*-phenylthiourea in the presence of lanthanum triflate catalyst. This methodology allowed the products to be achieved in excellent yield by stirring at room temperature. All the synthesized compounds were investigated against a representative panel of pathogenic strains using the broth microdilution MIC (minimum inhibitory concentration) method for their *in vitro* antimicrobial activity. Amongst these sets of heterocyclic compounds **5h**, **6b**, **6h**, **5f**, **5l**, **5n** and **6g** were found to have admirable activity.

Keywords: quinolone; Biginelli reaction; one-pot synthesis; catalyst; antimicrobial activity.

INTRODUCTION

Quinazolinones possess diverse pharmacological and biological activities associated with the pyrimidine core, such as hypotensive,¹ analgesic and anti-inflammatory,² calcium antagonist³ and central nervous system (CNS) depressant.⁴ Furthermore, quinazolinones were found to exhibit antimicrobial activity against *Staphylococcus aureus*, *Escherichia coli* and *Candida albicans*.⁵ Therefore, the synthesis of quinazolinone derivatives still attract much attention of modern-day medicinal chemistry research. On other hand, quinolones have maintained their pharmacological importance since their discovery based on nalidixic acid in the early 1960s.⁶ Quinolones possess various biological activities, such as anti-HIV,⁷ antitumor,⁸ anti-anaerobe⁹ and antimicrobial.¹⁰ It is well established that hydrophobicity is one of the factors that directly correlates to antimicrobial activity and intensifies the potency of a molecule.^{11,12} In view of this, an allyl group was in-

* Corresponding author. E-mail: patelmanish1069@yahoo.com
doi: 10.2298/JSC120121039J



serted at the *N* of quinolone ring to increase the hydrophobicity of the compounds. Thus, based on the above reports, an attempt was undertaken to synthesize *N*-allylquinolone-incorporated quinazolinone derivatives based on the premise that allylic compounds have an additive effect to antimicrobial potency and the amalgamation of two bioactive moieties into a single scaffold may produce novel heterocycles with appealing antimicrobial activities.

Tetrahydroquinazolinone derivatives have been synthesized under Biginelli reaction conditions (protic acid) but these methods suffer from low to moderate yields, lengthy reaction time and harsh reaction conditions.¹³ It was found that not only protic, but also Lewis acids could be used as a catalyst for the synthesis of tetrahydroquinazolinone derivatives.¹⁴ More recently, a number of reports expressing the utility of triflates as a Lewis acid catalyst in Biginelli protocols to give excellent yields, shorter reaction time and mild reaction conditions were published.¹⁵

From the aforementioned facts and as a part of ongoing studies in the development of new antimicrobial agents containing various heterocyclic systems having a quinoline nucleus,¹⁶ *N*-allylquinolone-incorporated tetrahydroquinazolinone derivatives **5a–p** and **6a–h** were prepared *via* a multiple component condensation (MCC) approach using lanthanum triflate (La(OTf)₃) as the catalyst and the results are reported herein. The constitution of all the products was characterized using elemental analysis, and FT-IR, ¹H-NMR, ¹³C-NMR and mass spectrometry. The synthesized compounds were subjected to an *in vitro* antimicrobial study against a representative panel of seven human pathogens using the broth microdilution minimum inhibitory concentration (*MIC*) method.¹⁷

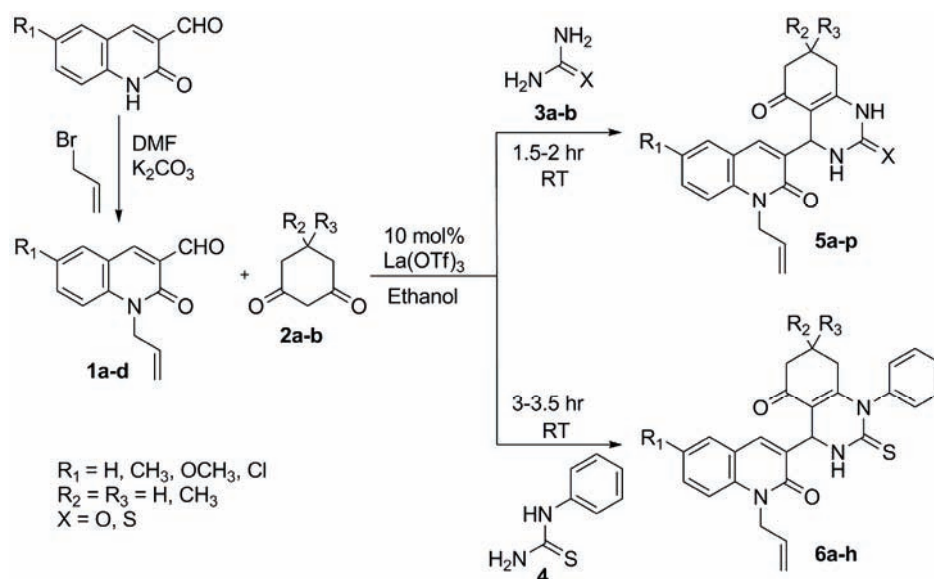
RESULTS AND DISCUSSION

Chemistry

In this protocol, 1-allyl-2-oxo-1,2-dihydroquinoline-3-carbaldehydes **1a–d** were selected as model compounds for the one-pot syntheses to give heterocyclic systems with a quinazolinone core. The key intermediates **1a–d** were prepared by electrophile-favored *N*-alkylation of 2-oxo-1,2-dihydroquinoline-3-carbaldehydes in presence of K₂CO₃ in DMF at room temperature.¹⁸

All the 4-(1-allyl-2-oxo-1,2-dihydroquinolin-3-yl)-4,6,7,8-tetrahydroquinazolinone-2,5(*1H,3H*)-dione derivatives **5a–p** and **6a–h** were obtained by La(OTf)₃ catalyzed reaction^{19–21} of various 1-allyl-2-oxo-1,2-dihydroquinoline-3-carbaldehydes **1a–d**, cyclohexane-1,3-dione or dimedones **2a–b** and (thio)ureas **3a–b** or *N*-phenylthiourea **4** in ethanol at room temperature (Scheme 1). The reaction was examined by taking different mol ratios of catalyst, *i.e.*, 2.5, 5, 7.5, 10 and 12.5 mol %. It was observed that when the amount of La(OTf)₃ was increased to 10 mol %, the reaction rate accelerated within 1.5–2 h for **5a–p** and 3–3.5 h for **6a–h** with high conversion, but the further increase in the amount of La(OTf)₃

had no significant outcome on the reaction. The products were obtained in excellent yield at room temperature in ethanol only by use of 10 mol % catalyst; thus, these conditions were considered as the most optimized conditions for the synthesis of the title quinazolinone derivatives **5a–p** and **6a–h**.

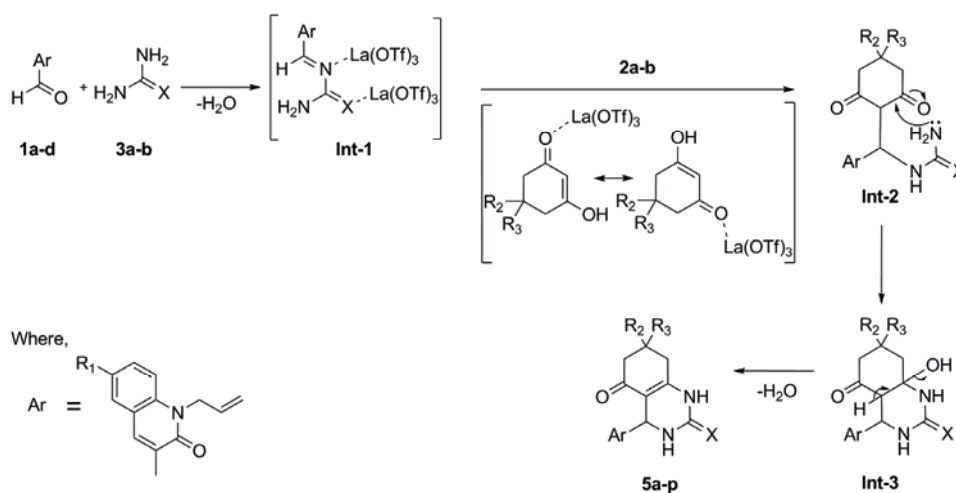


Scheme 1. Synthetic pathway to compounds **1a–d**, **5a–p** and **6a–h**.

The formation of compounds **5a–p** and **6a–h** may proceed *via* two steps (Scheme 2): *i*) the formation of arylidene(thio)urea **Int-1** and *ii*) interception of the acyliminium ion intermediate by an activated cyclic β -diketone to produce an open chain urea **Int-2**, which subsequently undergoes cyclization and dehydration *via* **Int-3** to afford the corresponding quinazolinone. The formation of an acyliminium ion was reported to be the rate-determining step.²⁰ $\text{La}(\text{OTf})_3$ is thought to accelerate the formation of the arylidene(thio)urea **Int-1** and activate the cyclic β -diketone **2a–b** by forming its metal enolate, thus facilitating the addition reaction with a coordinated acyliminium ion.²¹

The identities of all the synthesized compounds **5a–p** and **6a–h** were determined from $^1\text{H-NMR}$, $^{13}\text{C-NMR}$ and FT-IR spectral data and elemental analysis. As an example, $^1\text{H-NMR}$ ($\text{DMSO-}d_6$) spectrum of **5a**, exhibited singlet peaks at δ 9.52 and 7.80 ppm for the ($-\text{NH}-$) protons of the quinazolinone ring. A doublet was observed at around δ 4.90–5.05 ppm for ($\text{N-CH}_2\text{-CH=CH}_2$). Another doublet appeared at δ 5.18 ppm for ($\text{N-CH}_2\text{-CH}$). Multiplets were observed at δ 5.94 and around 7.08–7.60 ppm for (CH=CH_2) and aromatic protons, respectively. The methine proton at C_4 of quinazolinone appeared at δ 5.36 ppm as a singlet. A multiplet appeared at around δ 1.97–2.54 ppm for 3CH_2 . The $^{13}\text{C-NMR}$ spec-

trum is in agreement with the assigned structure. Thus, in the ^{13}C -NMR spectrum of compound **5a**, the signals around δ 105.51–152.04 ppm are attributed to aromatic carbons and the allylic C=C. The signals at around δ 21.28–36.80 ppm and at δ 49.39 ppm arise from aliphatic carbons and the allylic methylene carbon, respectively. In addition, the signal observed at δ 49.31 ppm is due to C₄ of quinazolinone. The signals due to carbonyl carbons appeared at δ 156.69, 160.72 and 193.67. The IR spectrum of **5a** exhibited absorption bands at 3435 and 3352 cm^{-1} for N–H str. and at 1711, 1639, and 1593 cm^{-1} for C=O str. The structure of compound **5a** was also confirmed by mass spectral studies. It gave a molecular ion peak at m/z 350.2 $[\text{M}+1]^+$, corresponding to the molecular formula $\text{C}_{20}\text{H}_{19}\text{N}_3\text{O}_3$. The obtained elemental analysis data are in consonance with the theoretical values.



Scheme 2. Believable mechanistic pathway for the formation of compounds **5a–p** and **6a–h** by $\text{La}(\text{OTf})_3$ catalysis.

The analytical and spectroscopic characterization data of **5a–p** and **6a–h** are given in the Supplementary material to this paper.

Antimicrobial evaluation

The antibacterial screening data (Table I) revealed that compound **5h** ($\text{MIC} = 20 \mu\text{g mL}^{-1}$) had extraordinary antibacterial activity against *Pseudomonas aeruginosa* when compared with chloramphenicol and ciprofloxacin. Against *Escherichia coli*, compounds **6b** and **6h** ($\text{MIC} = 50 \mu\text{g mL}^{-1}$) were found to have outstanding antibacterial activity when compared with ampicillin and were equipotent to chloramphenicol, while compounds **5l** and **5n** ($\text{MIC} = 62.5 \mu\text{g mL}^{-1}$) were found to have better activity than ampicillin. Against *Staphylococcus aureus*, compounds **5f** and **6g** ($\text{MIC} = 62.5 \mu\text{g mL}^{-1}$) were found to have excellent activity; compounds **5e** and **5p** ($\text{MIC} = 100 \mu\text{g mL}^{-1}$), as well as **5d**, **5g** and **6e**

(MIC = 125 $\mu\text{g mL}^{-1}$) showed remarkable results, while compounds **5i**, **5k**, **5m** and **6h** (MIC = 200 $\mu\text{g mL}^{-1}$) exhibited good activity; compounds **5a**, **5c**, **5h**, **5j** and **6f** (MIC = 250 $\mu\text{g mL}^{-1}$) were found to be equally potent to ampicillin. Against *Streptococcus pyogenes*, compounds **5e**, **5g**, **5m**, **5p** and **6e** (MIC = 100 $\mu\text{g mL}^{-1}$) were found to have comparable activity to that of ampicillin. Against *E. coli*, compounds **5j**, **5k**, **5m** and **6f** (MIC = 100 $\mu\text{g mL}^{-1}$) were equipotent to ampicillin.

TABLE I. Antimicrobial activity (MIC / $\mu\text{g mL}^{-1}$) of compounds **5a–p** and **6a–h**

Compounds	Gram-positive bacteria		Gram-negative bacteria		Fungi		
	<i>S. aureus</i>	<i>S. pyogenes</i>	<i>E. coli</i>	<i>P. aeruginosa</i>	<i>C. albicans</i>	<i>A. niger</i>	<i>A. clavatus</i>
	MTCC 96	MTCC 442	MTCC 443	MTCC 1688	MTCC 227	MTCC 282	MTCC 1323
5a (R ₁ =H, R ₂ =R ₃ =H, X=O)	250	250	125	200	500	1000	1000
5b (R ₁ =H, R ₂ =R ₃ =CH ₃ , X=O)	500	500	200	250	1000	500	500
5c (R ₁ =H, R ₂ =R ₃ =H, X=S)	250	500	250	250	1000	>1000	>1000
5d (R ₁ =H, R ₂ =R ₃ =CH ₃ , X=S)	125	200	200	200	>1000	>1000	>1000
5e (R ₁ =CH ₃ , R ₂ =R ₃ =H, X=O)	100	100	125	125	500	250	500
5f (R ₁ =CH ₃ , R ₂ =R ₃ =CH ₃ , X=O)	62.5	125	500	250	500	1000	1000
5g (R ₁ =CH ₃ , R ₂ =R ₃ =H, X=S)	125	100	250	250	250	500	1000
5h (R ₁ =CH ₃ , R ₂ =R ₃ =CH ₃ , X=S)	250	250	250	20	250	1000	500
5i (R ₁ =OCH ₃ , R ₂ =R ₃ =H, X=O)	200	250	125	200	1000	500	500
5j (R ₁ =OCH ₃ , R ₂ =R ₃ =CH ₃ , X=O)	250	250	100	125	>1000	>1000	>1000
5k (R ₁ =OCH ₃ , R ₂ =R ₃ =H, X=S)	200	200	100	200	>1000	>1000	>1000
5l (R ₁ =OCH ₃ , R ₂ =R ₃ =CH ₃ , X=S)	500	500	62.5	100	500	250	500
5m (R ₁ =Cl, R ₂ =R ₃ =H, X=O)	200	100	100	200	1000	>1000	>1000
5n (R ₁ =Cl, R ₂ =R ₃ =CH ₃ , X=O)	500	200	62.5	125	>1000	>1000	>1000
5o (R ₁ =Cl, R ₂ =R ₃ =H, X=S)	500	250	250	250	>1000	>1000	>1000
5p (R ₁ =Cl, R ₂ =R ₃ =CH ₃ , X=S)	100	100	200	200	500	250	500
6a (R ₁ =H, R ₂ =R ₃ =H)	500	250	125	100	1000	>1000	>1000
6b (R ₁ =H, R ₂ =R ₃ =CH ₃)	500	500	50	125	200	500	500
6c (R ₁ =CH ₃ , R ₂ =R ₃ =H)	500	500	200	250	500	1000	1000

TABLE I. Continued

Compounds	Gram-positive bacteria		Gram-negative bacteria		Fungi		
	S.	S.	E.	P.	C.	A.	A.
	<i>aureus</i>	<i>pyogenes</i>	<i>coli</i>	<i>aeruginosa</i>	<i>albicans</i>	<i>niger</i>	<i>clavatus</i>
	MTCC	MTCC	MTCC	MTCC	MTCC	MTCC	MTCC
	96	442	443	1688	227	282	1323
6d (R ₁ =CH ₃ , R ₂ =R ₃ =CH ₃)	500	500	200	250	1000	500	500
6e (R ₁ =OCH ₃ , R ₂ =R ₃ =H)	125	100	250	250	1000	500	500
6f (R ₁ =OCH ₃ , R ₂ =R ₃ =CH ₃)	250	200	100	100	500	1000	1000
6g (R ₁ =Cl, R ₂ =R ₃ =H)	62.5	200	500	250	500	500	100
6h (R ₁ =Cl, R ₂ =R ₃ =CH ₃)	200	250	50	100	250	100	250
Ampicillin	250	100	100	–	–	–	–
Chloramphenicol	50	50	50	50	–	–	–
Ciprofloxacin	50	50	25	25	–	–	–
Nystatin	–	–	–	–	100	100	100
Griseofulvin	–	–	–	–	500	100	100

The antifungal screening data (Table I) revealed that compounds **6b** ($MIC = 200 \mu\text{g mL}^{-1}$), **5g**, **5h** and **6h** ($MIC = 100 \mu\text{g mL}^{-1}$) were found to have excellent activity against *Candida albicans*, while compounds **5a**, **5e**, **5f**, **5l**, **5p**, **6c**, **6f** and **6g** ($MIC = 500 \mu\text{g mL}^{-1}$) had comparable activity to that of griseofulvin. Compounds **6h** and **6g** ($MIC = 100 \mu\text{g mL}^{-1}$) were found to be equally potent against *Aspergillus niger* and *A. clavatus*, respectively.

The newly synthesized compounds **5a–p** and **6a–h** exerted significant inhibitory activity against the growth of the tested bacterial and fungal strains. The data also revealed that insertion of an allyl chain at the *N* of the quinolone moiety and derivatization at positions R₁, R₂, R₃, X and *N*-1 of tetrahydroquinazolinone produced marked changes in the potency of the synthesized analogues as antimicrobial agents and demonstrated the following assumptions about the structure–activity relationship (SAR):

Compounds having a –CH₃ substituent at the R₂ and R₃ positions have intensified antibacterial effectiveness against Gram negative bacteria, e.g., **5h**, **5l**, **5n**, **6b** and **6h**, but not **5f**. Moreover, an S-atom at the C₂ position and a phenyl group at *N*-1 of tetrahydroquinazolinone may play a significant role in enhancing antifungal activity, e.g., **5h**, **5l**, **6b**, **6h** and **6g**. However, only phenyl substituted compounds displayed similar inhibitory action against the *Aspergillus* family when compared with standard drugs. Compounds with electron withdrawing group –Cl at R₁ of the *N*-allylquinolone ring may have improved activity against *E. coli*, *S. aureus* and all fungal species, e.g., **5m**, **5n**, **6g** and **6h**. On the other hand, the electron donating –OCH₃ group may increase the activity against *E. coli* and *S. aureus*, e.g., **5j**, **5k**, **5l** and **6f**. A lipophilic –CH₃ group at the R₁ position may intensify the potency against *P. aeruginosa*, *S. aureus* and *C. albicans*.

Furthermore, the allyl chain makes the compounds more hydrophobic and may enhance the antimicrobial potency of the title compounds. The study revealed that changes in substitutions have a vast impact on the antimicrobial effectiveness.

Upon comparison with a previous report,^{16b} it could be stated that *i*) insertion of an allyl group at *N* of the quinolone ring increases the antimicrobial properties of the title compounds; *ii*) both electron withdrawing and donating constituents at the R₁ position contribute to enhancement of the antimicrobial effectiveness; *iii*) a phenyl group at *N*-1 of the tetrahydroquinazolinone ring influences the microbial inhibitory action and *iv*) the lipophilic –CH₃ group at the R₁ position has an additive effect on the inhibition of microbial pathogens.

EXPERIMENTAL

Materials, instruments and methods

All the reagents were commercially available and used without further purification. Solvents of analytical grade were used. Melting points were determined by the open tube capillary method (using silicon oil 350 cSt) and are uncorrected. Thin-layer chromatography (TLC, on aluminum plates pre-coated with silica gel, ⁶⁰F₂₅₄, 0.25mm thickness) (Merck, Darmstadt, Germany) was used for monitoring the progress of all reactions, as well as the purity and homogeneity of the synthesized compounds; eluent *n*-hexane:ethyl acetate 1:1. UV radiation and/or iodine were used as the visualizing agents. Elemental analysis (% C, H, N) was realized using a Perkin-Elmer 2400 series-II elemental analyzer (Perkin-Elmer, USA) and the results for all compounds were within ±0.4 % of the theoretical value. The IR spectra were recorded in KBr on a Perkin-Elmer Spectrum GX FT-IR Spectrophotometer (Perkin-Elmer, USA) and only the characteristic peaks are reported in cm⁻¹. ¹H-NMR and ¹³C-NMR spectra were recorded in DMSO-*d*₆ on a Bruker Avance 400F (MHz) spectrometer (Bruker Scientific Corporation Ltd., Switzerland) at 400 and 100 MHz, respectively, using the solvent peak as an internal standard. Chemical shifts are reported in parts per million (ppm). Mass spectra were scanned on a Shimadzu LCMS 2010 spectrometer (Shimadzu, Tokyo, Japan).

General procedure for the synthesis of 4-(1-allyl-2-oxo-1,2-dihydroquinolin-3-yl)-4,6,7,8-tetrahydroquinazolin-2,5(1H,3H)-diones 5a-p and 6a-h

A 100 mL round bottomed flask, was charged with a mixture of 1-allyl-6-(un)substituted-2-oxo-1,2-dihydroquinoline-3-carbaldehydes **1a-d** (3 mmol), cyclohexane-1,3-dione or dimedone **2a-b** (3 mmol) and (thio)urea **3a-b**/*N*-phenylthiourea **4** (3 mmol) in ethanol (15 mL) containing La(OTf)₃ (10 mol %). The mixture was allowed to stir at rt for 1.5–3.5 hr and the progress of the reaction was monitored by TLC. After the completion of reaction (as evidenced by TLC), the solid mass separated was collected by filtration, washed well with ethanol (15 mL) and purified by leaching in equal volume ratio of chloroform and methanol (20 mL) to obtain pure solid sample.

Methodology for screening the antimicrobial activity

All the glass apparatus were sterilized before use. The antimicrobial activity of all the synthesized compounds was screened by the broth microdilution method.¹⁷ Mueller–Hinton broth was used as the nutrient medium to grow and dilute the compound suspension for the test bacteria and Sabouraud dextrose broth was used for fungal nutrition. Inoculum size for test strain was adjusted to 10⁸ CFU ml⁻¹ (colony forming unit per milliliter) by comparing the turbidity (turbidimetric method). The strains used for the activity were obtained from Mic-

robial Type Culture Collection (MTCC) of the Institute of Microbial Technology, Chandigarh, India. Each synthesized compound was diluted to a concentration of $2000 \mu\text{g mL}^{-1}$, as a stock solution. DMSO was used as the vehicle to obtain the desired concentrations of the compounds to test upon microbial strains. The results were recorded in the form of primary and secondary screenings. The compounds **5a–p** and **6a–h** were screened for their antibacterial activity against the Gram-positive bacteria: *S. aureus* (MTCC 96) and *S. pyogenes* (MTCC 442), and Gram-negative bacteria: *E. coli* (MTCC 443) and *P. aeruginosa* (MTCC 1688), and antifungal activity against the fungi: *C. albicans* (MTCC 227), *A. niger* (MTCC 282) and *A. clavatus* (MTCC 1323) at concentrations of 1000, 500, and $250 \mu\text{g mL}^{-1}$ as primary screening. Compounds that were found to be active in the primary screening were further screened in a second set of dilution at concentrations of 200, 100, 62.5, 50, 25, 12.5, and $6.25 \mu\text{g mL}^{-1}$. Ten microliters suspension from each well was further inoculated and growth of the bacteria and fungi was noted after 24 and 48 h, respectively. The lowest concentration which resulted in no visible growth (turbidity) after spot subculture was considered as the *MIC* for each compound. The standard drugs used for comparison in this study were ampicillin, chloramphenicol and ciprofloxacin for evaluating the antibacterial activity and griseofulvin and nystatin for the antifungal activity.

CONCLUSIONS

In present protocol, the synthesis and antimicrobial evaluation of 24 new derivatives **5a–p** and **6a–h** of tetrahydroquinazolinone possessing an *N*-allylquinolone nucleus at C_4 of quinazolinone were presented. $\text{La}(\text{OTf})_3$ as catalyst allowed the smooth synthesis of the title derivatives at room temperature in excellent yield. It could be concluded from the antimicrobial screening data that many of the compounds were more or equipotent against a panel of human pathogens when compared with the standard drugs. It is noteworthy that derivatization of the title compounds alter their antimicrobial activity. Further synthetic work to intensify the potency of these derivatives by changing their molecular configuration is in progress. The present study highlights the identification of this new structural class of compounds as antimicrobials, which could be of interest for further detailed pre-clinical investigations.

SUPPLEMENTARY MATERIAL

Analytical and spectroscopic characterization data of the compounds **5a–p** and **6a–h** are available electronically from <http://www.shd.org.rs/JSCS/>, or from the corresponding author on request.

Acknowledgements. The authors are thankful to the Head of the Department of Chemistry, Sardar Patel University, for providing the $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ data and research facilities. We are also thankful to SICART, Vallabh Vidyanagar, for the FT-IR and elemental analysis, Oxygen Health Care Pvt. Ltd., Ahmedabad for the mass spectra and Dhanji P. Rajani, Microcare Laboratory, Surat, for the antimicrobial screening of the compounds reported herein.

ИЗВОД

СИНТЕЗА ТЕТРАГИДРОХИНАЗОЛИНОНСКИХ ДЕРИВАТА N-АЛИЛХИНОЛОНА ПОМОЋУ ЛАНТАН-ТРИФЛАТА И ОДРЕЂИВАЊЕ ЊИХОВЕ БИОЛОШКЕ АКТИВНОСТИ

HARDIK H. JARDOSH и MANISH P. PATEL

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

Синтетисана је серија од 24 деривата тетрахидрохиназолинона циклокондензационом реакцијом N-алилхинолона, цикличног β -дикетона и (тио)урее/N-фенилтиоурее у присуству лантан-трифлата као катализатора. Примењена методологија омогућава добијање производа у високом приносу. Сви добијени производи тестирани су према репрезентативном панелу патогена, а *in vitro* антимикуробне активности одређене су применом метода микроразблаживања и изражене као MIC (минимална инхибиторна концентрација). Утврђено је да седам деривата, **5h**, **6b**, **6h**, **5f**, **5l**, **5n** и **6g**, има запажене активности.

(Примљен 21. јануара, ревидиран 27. марта 2012)

REFERENCES

- O. I. El-Sabbagh, M. A. Shabaan, H. H. Kadry, E. S. Al-Din, *Eur. J. Med. Chem.* **45** (2010) 5390
- a) A. B. A. El-Gazzar, H. N. Hafez, H. S. Abbas, *Eur. J. Med. Chem.* **44** (2009) 4249; b) B. A. Rather, T. Raj, A. Reddy, M. S. Ishar, S. Sivakumar, P. Paneerselvam, *Arch. Pharm. Chem. Life Sci.* **343** (2010) 108
- M. Yarim, S. Sarac, F. S. Kilic, K. Erol, *Farmaco* **58** (2003) 17
- V. Jatav, P. Mishra, S. Kashaw, J. P. Stables, *Eur. J. Med. Chem.* **43** (2008) 135
- M. Minu, A. Thangadurai, S. R. Wakode, S. S. Agrawal, B. Narasimhan, *Arch. Pharm. Chem. Life Sci.* **341** (2008) 231
- G. Y. Leshner, E. J. Froelich, M. D. Gruett, J. H. Bailey, R. P. Brundage, *J. Med. Pharm. Chem.* **5** (1962) 1063
- E. Filippini, G. Cruciani, O. Tabarrini, V. Cecchetti, A. Fravolini, *J. Comput.-Aided Mol. Des.* **15** (2001) 203
- J. Li, J. Tan, L. Chen, J. Zhang, X. Shen, C. Mei, L. Fu, L. Lin, J. Ding, B. Xiong, X. Xiong, H. Liu, X. Luo, H. Jiang, *Acta Pharmacol. Sin.* **27** (2006) 1259
- R. Schaumann, A. C. Rodloff, *Anti-Infect. Agents Med. Chem.* **6** (2007) 49
- F. O'Donnell, T. J. P. Smyth, V. N. Ramachandran, W. F. Smyth, *Int. J. Antimicrob. Agents* **35** (2010) 30
- V. Alptuzun, H. Tasli, E. Erciyas, *J. Fac. Pharm, Ankara* **35** (2006) 177
- C. Praveen, A. Ayyanar, P. T. Perumal, *Bioorg. Med. Chem. Lett.* **21** (2011) 4072
- a) N. N. Tonkikh, A. Strakovs, M. V. Petrova, *Chem. Heterocycl. Compd.* **40** (2004) 43; b) M. M. Candan, E. Kendi, M. Yarim, S. Sarac, M. Ertan, *Anal. Sci.* **17** (2001) 1023
- S. Kantevvari, R. Bantu, L. Nagarapu, *ARKIVOC* **2006** (2006) 136
- M. A. Kolosov, V. D. Orlov, D. A. Beloborodov, V. V. Dotsenko, *Mol. Divers.* **13** (2009) 5
- a) N. K. Shah, N. M. Shah, M. P. Patel, R. G. Patel, *J. Serb. Chem. Soc.* (2011), *J. Serb. Chem. Soc.* **77** (2012) 279; b) P. M. Shah, M. P. Patel, *Med. Chem. Res.* (2011), *Med. Chem. Res.* **21** (2012) 1188; c) D. C. Mungra, M. P. Patel, D. P. Rajani, R. G. Patel, *Eur. J. Med. Chem.* **46** (2011) 4192; d) N. J. Thumar, M. P. Patel, *Arch. Pharm. Chem. Life Sci.* **2** (2011)

- 91; e) H. G. Kathrotiya, R. G. Patel, M. P. Patel, *J. Serb. Chem. Soc.* (2011), *J. Serb. Chem. Soc.* **77** (2012) 983
17. National Committee for Clinical Laboratory Standards (NCCLS), *Performance Standards for Antimicrobial Susceptibility Testing*, Twelfth Informational Supplement (ISBN 1-56238-454-6), 2002, M100-S12 (M7). 940, West Valley Road, Suite 1400, Wayne, PA, 19087-1898, USA.
18. A. Srivastava, R. M. Singh, *Indian J. Chem., B* **44** (2005) 1868
19. a) R.-F. Chen, C.-T. Qian, *Chin. J. Chem.* **20** (2002) 427; b) L. Wang, C. Qian, H. Tian, Y. Ma, *Synth. Commun.* **33** (2003) 1459; c) C. Rui-Fang, Q. Chang-Tao, *Chin. J. Chem.* **20** (2002) 407; d) A. Dondoni, A. Massi, S. Sabatini, *Tetrahedron Lett.* **43** (2002) 5913; e) D. Gong, L. Zhang, C. Yuan, *Heteroatom Chem.* **14** (2003) 13; f) Y. Huang, F. Yang, C. Zhu, *J. Am. Chem. Soc.* **127** (2005) 16386
20. I. Suzuki, Y. Suzumura, K. Takeda, *Tetrahedron Lett.* **47** (2006) 7861
21. Y. Ma, C. Qian, L. Wang, M. Yang, *J. Org. Chem.* **65** (2000) 3864.