Indian Journal of Chemistry
Vol. 46B, March 2007, pp. 550-553

Note

Synthesis and characterization of new quinazolines as potential antimicrobial agents

N C Desai*, P N Shihora & D L Moradia

University Department of Chemistry, Bhavnagar University, Bhavnagar 364 002, India

E-mail: dnisheeth@rediffmail.com

Received 29 March 2006; accepted (revised) 1 December 2006

Ethyl 4-[2-(2-chlorophenyl)-4-oxo-3-hydroquinazolin-3yl]-benzoate **1** which reacts with hydrazine hydrate in presence of methanol resulted into *N*-amino{4-[2-(2-chlorophenyl)-4-oxo(3-hydroquinazolin-3-yl)phenyl}carboxamide **2**. Compound **2** on treatment with aryl isothiocyanates in presence of acetone is converted into aryl-*N*-{[({4-[2- (2-chlorophenyl)-4-oxo(3-hydro-quinazolin-3-yl)]phenyl}carbonylamino)amino]thioxo methyl}-amides **3**. Compound **3**, in presence of sulphuric acid has yielded aryl-*N*-(5-{4-[2-(2-chlorophenyl)-4-oxo(3-hydroquinazolin-3-yl)]-phenyl}(1,3,4,thiadiazol-2-yl))amides **4a-l**. Newly synthesized compounds **4a-l** have been screened for their antibacterial and antifungal activities on *Eschericia coli, Staphylococcus aureus, Pseudomonas aeruginosa*, *Staphylococcus pyogenes, C. albicans, A. niger* and *A. clavatus.*

Keywords: Quinazoline, antibacterial activity, antifungal activity

IPC: Int.Cl.[8]

Quinazolines are nitrogen containing compounds having broad spectrum of medicinal values such as antifungal[1] anticancer[2], anti-HIV[3], antiinflammatory[4], analgesic[5], antiviral[6], antitubercular[7], antimicrobial[8], anticonvulsant[9], anticoagulant[10], anti-fibrillatory[11], cardiac stimulant[12], diuretic[13],antibacterial[14-19], etc.

Antibacterial and antifungal diseases are very common all over the world. Currently used antimicrobial agents are not effective due to the resistance developed by the microbes. And therefore, it is an ongoing effort to synthesize new antimicrobial agents. Over and above there is no permanent structure and activity relationship. In continuation to this, we have selected medicinally important quinazolines by modifying the third position, for the preparation of newer antimicrobial agents.

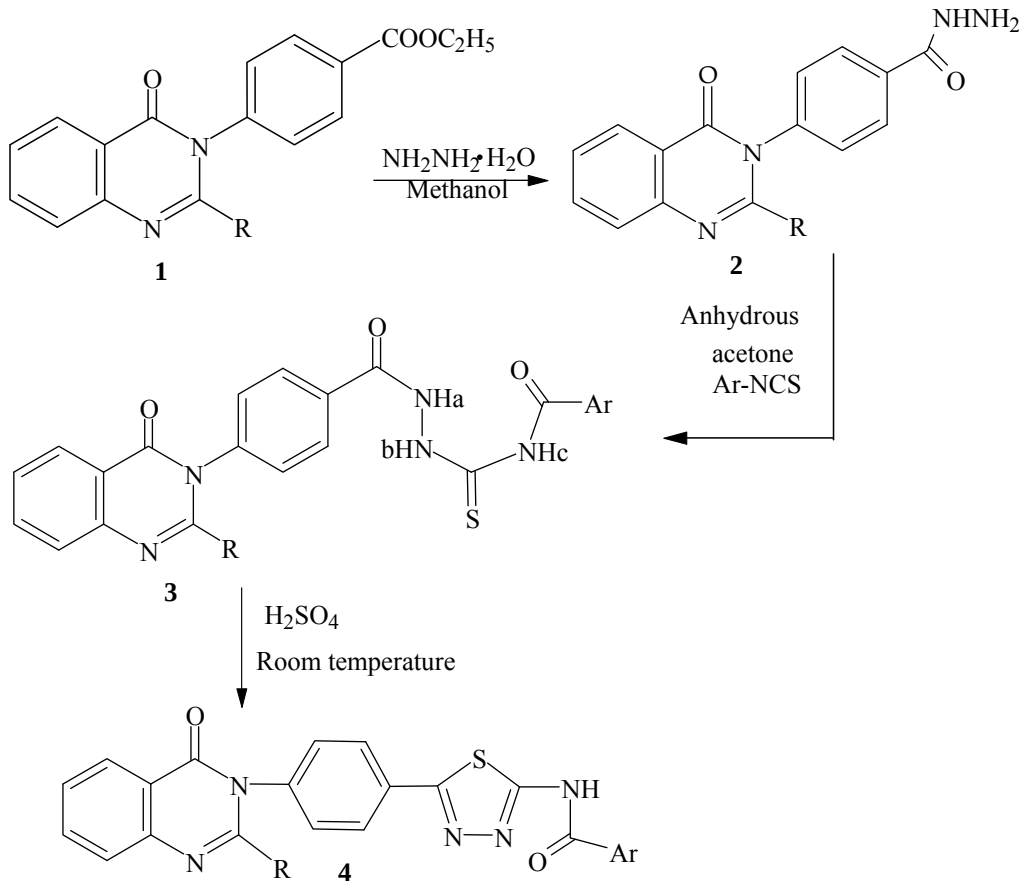
The present paper describes the synthesis of aryl-*N*-(5-{4-[2-(2-chlorophenyl)-4-oxo(3-hydroquinazolin-3-yl)]phenyl}(1,3,4,thiadiazol-2-yl))amides **4a-l** (**Scheme I**). These compounds were screened for antibacterial and antifungal activities by broth dilution method. Compound **4** was prepared by the reaction of H_2SO_4 with aryl-*N*-{[({4-[2-(2-chlorophenyl)-4-oxo(3-hydroquinazolin-3-yl)]phenyl}carbonylamino)-amino]thioxomethyl}amides **3**. Compound **3** was obtained by the condensation of **2** and aryl isothiocyanates in presence of anhydrous acetone. Compound **2** was synthesized by the reaction between ethyl 4-[2-(2-chlorophenyl)-4-oxo-3-hydroquinazolin-3yl]benzo-ate and hydrazine hydrate. Compound **4a** was characterized with the help of elemental analysis, IR, ^{1}H NMR and mass spectral analysis. IR spectra of this compound exhibited absorption bands at 1660 and 1690 cm^{-1}, which indicated the presence of carbonyl group. The ^{1}H NMR of compound **4a** showed signals at δ 6.8-7.9 for aromatic protons and due to the cyclization of **3,** one signal at δ 12.90 of –CONH- proton was obtained. In the mass spectrum of the compound, base peak appeared at *m/z* 105 and molecular ion peak was observed at *m/z* 535.5. Details of the characterized data of compound **4** are reported in (**Table I**).

Biological activity

Antibacterial activity. Antibacterial activity was carried out by broth dilution method[25,26]. The strains used for the activity were procured from Institute of Microbial Technology, Chandigarh. The compounds **4a-l** were screened for their antibacterial activity against *Eschericia coli, Staphylococcus aureus, Pseudomonas aeruginosa* and *Staphylococcus pyogenes* at concentrations of 1000, 500, 200, 100, 50, 25, 12.5 µg/mL respectively (**Table II**).

Antifungal activity. Same compounds were tested for antifungal activity against *C. albicans, A. niger and A. clavatus* at concentrations of 1000, 500, 200, and 100 µg/mL respectively (**Table II**). The results are recorded in the form of primary and secondary screening. Each synthesized drug was diluted obtaining 1000 µg/mL concentration, as a stock solution.

The synthesized drugs found to be active in this primary screening were further tested in a second set of dilution against all microorganisms. Secondary screening: The drugs found active in primary screening were similarly diluted to obtain 100, 50,



Scheme 1

R= 2-Chlorophenyl, Ar= Different aryl groups

25 µg/mL concentrations, 10 µL suspension from each well was further inoculated on appropriate media and growth was noted after 24 and 48 hr. The lowest concentration, which showed no growth after spot subculture was considered as MBC/MFC for each drug. The highest dilution showing at least 99% inhibition is taken as MBC/MFC. The result of this test is affected by the size of the inoculum. The test mixture should contain 10^8 organisms/mL. The standard drug used in the present study was gentamycin for evaluating antibacterial activity which showed (0.25, 0.05, 0.5 and 1 µg/mL MBC against *S. aureus*, *S. pyogenes* and *P. aeruginosa* respectively. K nystatin was used as the standard drug for antifungal activity, which showed 100 µg/mL MFC against fungi, used for the antifungal activity.

Compounds **4e** and **4i** are considered to be active against *S. pyogenes*. The antibacterial activity of both compounds were enhanced due to the introduction of chloro and methyl group in the heterocyclic frame work. Compounds **4c** was active against *C. albicans and A. clavatus*. Due to the presence of nitro group consequently **4k** is active against *C. albicans and A. clavatus.* The enhancement of the activity of this compound is due to the presence of chlorine atom in the frame work. From the activity data, it was observed that minor change in molecular configuration of these compounds profoundly influences the activity.

Experimental Section

Melting points for resultant compounds were determined in open capillary tubes using a Toshniwal melting point apparatus and are uncorrected. IR spectra were recorded in KBr on a FT IR 9201 VC spectrophotometer; ^{1}H NMR spectra in $CDCl_3$ on DRX (200 MHz) and DRX (300 MHz) spectrometer using TMS as internal standard. Mass spectra was recorded on Q-TOF Micro Mass. Purity of these compounds were checked by TLC. Compounds ethyl

Table I — Physical constants and characterization data of compounds, **1**, **2**, **3** and **4a-l**

Compd	Ar	m.p °C	Yield (%)	Found (%) Calcd C	H	N	S	^{1}H NMR ($CDCl_3$) (δ, ppm)
1	-	120	60	68.23 (68.15	4.23 4.18	5.43 5.40)		7.1-8.0 (m, 12H, ArH), 4.29 (t, 2H, -OCH_2-)
2	-	170	62	64.53 (64.49	3.86 3.73	14.33 14.20)		7.1-7.95 (m, 12H, ArH), 8.0 (s, 1H, -CONH-), 2.0 (s, 2H, -NH-NH_2)
3	C_6H_5	130	67	62.63 (62.87	4.89 3.60	12.91 12.89	5.55 5.51)	7.0-7.9 (m, 12H, ArH), 10.90 (s, 1H,-$CONH_a$), 10.52 (s, 1H, -$CONH_b$), 12.90 (s, 1H, -$CONH_c$)
4a	C_6H_5	145	70	64.98 (64.87	3.38 3.20	13.06 12.80	5.98 5.95)	7.0-7.9 (m, 17H, ArH), 12.80 (s, 1H, -CONH-)
4b	C_6H_5-CH_2	178	65	65.51 (65.48	3.66 3.60	12.73 12.65	5.83 5.81)	7.0-7.9 (m, 17H, ArH), 12.49 (s, 1H, -CONH-), 3.44 (s, 2H, -$COCH_2$-Ar)
4c	*m*-NO_2-C_6H_5	192	67	59.95 (59.91	2.49 2.30	12.33 12.23	5.51 5.45)	7.17-8.1 (m, 16H, ArH), 12.9 (s, 1H, -CONH-)
4d	*o*-Cl-C_6H_5	173	72	61.06 (61.05	3.00 2.98	12.27 12.11	5.62 5.61)	6.94-7.8 (m, 16H, ArH), 12.7 (s, 1H, -CONH-)
4e	*m*-Cl-C_6H_5	180	65	61.06 (61.04	3.00 2.95	12.29 12.13	5.62 5.60)	7.42-7.9 (m, 16H, ArH), 12.8 (s, 1H, -CONH-)
4f	*p*-Cl-C_6H_5	162	77	61.06 (61.03	3.00 2.99	12.25 12.20	5.62 5.60)	6.50-7.8 (m, 16H, ArH), 12.8 (s, 1H, -CONH-)
4g	*o*,*m*-Cl_2-C_6H_3	162	77	57.58 (57.55	2.66 2.64	11.57 11.42	5.30 5.28)	7.32-8.1 (m, 15H, ArH), 12.7 (s, 1H, -CONH-)
4h	$C_8H_4NO_2$-CH_2	162	59	62.08 (62.04	3.09 3.05	13.57 13.42	5.18 5.15)	7.88-8.0 (m, 16H, ArH), 12.5 (s, 1H, -CONH-), 4.50 (s, 2H, -$COCH_2$-N)
4i	*p*-CH_3-C_6H_5	192	85	65.51 (65.50	3.66 3.62	12.73 12.60	5.83 5.80)	7.2-7.8 (m, 16H, ArH), 12.6 (s, 1H, -CONH-), 2.35 (s, 3H, Ar-CH_3)
4j	*p*-OCH_3-C_6H_5	142	65	63.65 (63.60	3.56 3.50	12.11 12.01	5.66 5.62)	7.2-7.8 (m, 16H, ArH), 12.8 (s, 1H, -CONH-), 3.95 (s, 3H, Ar-OCH_3)
4k	*p*-NO_2-C_6H_4-CH_2	183	79	60.55 (60.52	3.21 3.20	12.11 12.01	5.38 5.35)	7.5 -8.1 (m, 16H, ArH), 12.7 (s, 1H, -CONH-), 3.46 (s, 2H, Ar-CH_2 -CO)
4l	*p*-Cl-C_6H_4-CH_2	174	67	61.64 (61.63	3.27 3.20	12.34 12.24	5.48 5.44)	7.0 -7.9 (m, 16H, ArH), 12.5 (s, 1H, -CONH-), 3.44 (s, 2H, Ar-CH_2 -CO)

R = 2-Chlorophenyl

4-[2- (2-chlorophenyl)-4-oxo-3-hydroquinazolin-3yl] benzoate **1**, and *N*-amino{4-[2-(2-chlorophenyl) -4-oxo(3-hydroquinazolin-3yl]phenyl} carboxamide **2** are given in literature[20-24].

Aryl-*N*-{[({4-[2-(2-chlorophenyl)-4-oxo(3-hydroquinazolin-3-yl)]phenyl}carbonylamino)amino]-thioxomethyl}amides 3. Compound **2** (0.02 mole) and aryl-isothiocyanate (0.02 mole) in dry acetone (20 mL) were stirred for an hr at room temp and further washed with water and dried to generate **3a**, m.p. 130°C, yield : 67%. Anal. Found: C 62.87, H 3.60, N 12.89. Calcd for $C_{29}H_{20}ClN_5O_3S$: C 62.63, H 4.89, N 12.91%. IR(KBr): 1645 (>C=O), 1660(>C=O), 1590(>C=N), 3230(>N-H); ^{1}H NMR: δ 7.0-7.9 (m, 12H, ArH), 10.90 (s, 1H,-$CONH_a$) 10.52 (s, 1H, -$CONH_b$), 12.90 (s, 1H, -$CONH_c$).

Aryl-*N*-(5-{4-[2-(2-chlorophenyl)-4-oxo(3-hydroquinazolin-3-yl)]phenyl} (1,3,4,thiadiazol-2-yl)) amides 4a-l. Compound **3** (0.01 mole) was added to cold conc. sulphuric acid (25 mL). The mixture was stirred at room temp for 2 hr. The resultant solid mass was poured onto crushed ice (100 g) with stirring. The product was filtered, washed with water and dried. The characterization data of compound **4a** prepared according to this procedure was given in **Table I**, m.p. 145°C, yield : 70%. Anal. Found: C 64.87, H 3.20, N 12.80. Calcd. for $C_{29}H_{18}ClN_5O_2S$: C 64.98, H 3.38, N 13.06%. IR(KBr): 1660(>C=O), 1696(>C=O), 1580 (>C=N), 3156(>N-H); ^{1}H NMR: δ 7.0-7.9 (m, 12H, ArH), 12.80 (s, 1H, -CONH-). MS: [M^+] at *m/z* 535.5 and other prominent peaks are appeared at 531.40, 413.27, 336.08, 256.31, 228.28, 202.19, 105, 81.03.

Table II — Antimicrobial activity of compounds **4a-l**

	Antibacterial activity is expressed in the form of Minimal Bactericidal Concentration (MBC)				Antifungal activity is expressed in the form of Minimum Fungicidal Concentration (MFC)		
Compd	*E. coli* MTCC 443	*P. aeruginosa* MTCC 1688	*S. aureus* MTCC 96	*S. pyogenus* MTCC 442	*C. albicans* MTCC 227	*A. niger* MTCC 282	*A. clavatus* MTCC 1323
4a	500	1000	1000	100	1000	1000	1000
4b	100	1000	500	500	1000	1000	1000
4c	1000	1000	500	100	100	500	100
4d	500	1000	100	50	1000	1000	1000
4e	100	100	100	25	1000	1000	1000
4f	500	500	1000	100	1000	1000	1000
4g	500	500	100	100	1000	1000	1000
4h	1000	500	50	50	1000	500	1000
4i	50	500	50	25	1000	500	1000
4j	100	500	100	50	1000	100	1000
4k	200	1000	200	100	100	200	100
4l	1000	500	1000	500	1000	1000	1000

For antibacterial activity, in present protocol 100 µg/mL is considered as moderately active, 50 µg/mL is considered as good activity and 25 µg/mL is considered as active as compared to the standard drug gentamycin. For antifungal activity, 200µg/mL is considered as moderately active, 100 µg/mL is considered as active as compared to standard drug K nystatin.

Acknowledgement

The authors express their sincere thanks to the Head, Department of Chemistry, Bhavnagar University, Bhavnagar for providing research facilities.

References

1 Robert J A & Russell H E, *J Med Chem*, 15, **1972**, 335.
2 Desai N C, Shah B R, Bhatt J J, Patel H H, Undavia N K & Trivedi P B, *Indian J Chem*, 34B, **1995**, 201.
3 Desai N C, Undavia N K, Trivedi P B, Dave D & Vyas G D, *Indian J Chem*, 36, **1998**, 1280.
4 Khili M A, Soliman R, Furghuli A M& Bekhit A A, *Arch Pharm (Weighnein, Germany)*, 327, **1994**, 27.
5 Gursoy A, Buyuktimkin S, Demirayak S & Ekinci A C, *Arch Pharm (Weighnein, Germany)*, 323, **1990**, 623.
6 Panday V K, Misra D & Shukla S, *Ind Drug*, 31, **1994**, 532.
7 Joshi V & Chardhari R P, *Indian J Chem*, 26B, **198**7, 602.
8 Wasfy A A F, *Indian J Chem*, 42B, **2003**, 3102.
9 Zilberminto LG, Bv *Estestr Nauch Insti Permskmsk Univ*, 141, **1964**, 67; *Chem Abstr*, 64, **1966**, 1220.
10 Seth P K & Parmar S S, *Can J Pharmacol*, 43, **1965**, 1019.
11 Umino S, Kariyone K, Zenno H & Kamiya T, *Japanese Pat,* 12, **1970**, 670; *Chem Abstr*, 68, **1968**, 2195.
12 Shetty B V, *US Pat*, **1970**, 3,549,634; *Chem Abstr*, 75, **1971**, 5940.
13 Otto H & Houlohan w w, *Swiss Pat,* **1971**, 499,544*; Chem Abstr*, 75, **1971**, 20435.
14 Panday V K, Lohani H C, Shanker K, & Dovel D C, *Indian Drugs,* 20, **1983**, 315.
15 Pandey V K, Gupta M & Mishra D, *Ind Drugs,* 33, **1996**, 409.
16 Sen Gupta A K, & Misra Hemant K, *Indian J Pharm Sci*, ب9(11), **1980**, 1313.
17 Mosad S M, Mohammed K I, Ahmed M A & Abdel-Hamide S G, *J Apllied Sci*, 4 (2), **2004**, 302.
18 Trova M P, Zhang N & Kitchen D B, *Chem Abstr*, 129, **1982**, 41144_a.
19 Udupi R H, Ramesh B & Bhatt A R, *Indian Heterocycl Chem*, 8, **1999**, 301.
20 Pandey V K, Pathak L P M & Mishra S K, *Indian J Chem*, 44B, **2005**, 1940.
21 Desai N C, Shah M D, Keshav K A, Saxena A K, *Indian J Chem*, 40B, **2001**, 201.
22 Desai N C, Bhatt J J, Shah B R, Undavia N K & Trivedi P B, *IL Farmaco*, 51(5), **1996**, 361.
23 Desai N C, Bhatt J J, Patel H H, Undavia N K & Trivedi P B, *Indian J Chem*, 34B, **1995**, 201.
24 Shivarama B H, Prasanna C S, Roy K S, Shridhra K & Bhat U G, *Indian J Chem*, 43B, **2004**, 2174.
25 Robert C, Medical Microbiology, ELBS and E & S., Living stone, Briton 11th edn., **1970**, 895-901.
26 National committee for clinical laboratory standard: Reference method for broth dilution antifungal susceptibility testing of yeasts approved standard M27A, NCCLS, Wayne PA, **1997**.