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Short communication

Synthesis of 4-aryl-7,7-dimethyl-1,2,3,4,5,6,7,8-octahydroquinazoline-2-one/thione-5-one derivatives and evaluation as antibacterials

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Abstract

A novel, ecofriendly, one pot solvent free method for the synthesis of 4-aryl-7,7-dimethyl-1,2,3,4,5,6,7,8-octahydroquinazoline-2-one/thione-5-one derivatives is described which devoids the use of any organic solvents and auxiliaries. All the synthesized compounds were screened for their in vitro antibacterial activity against standard strains of *Staphylococcus aureus*, *Escherichia coli* and *Pseudomonas aeruginosa*.

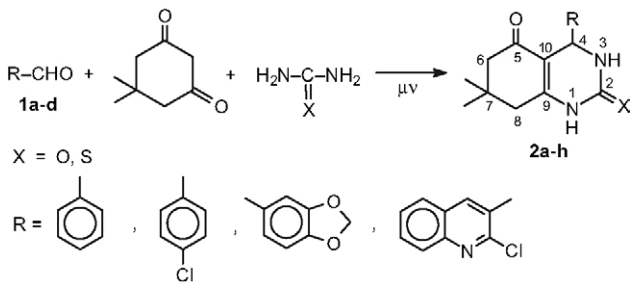
Keywords: Quinazolines; Solvent free; Antibacterial activity; Microwave irradiation

1. Introduction

In disease conditions in which pain and inflammation are the accompanying manifestations analgesic and antiinflammatory drugs are prescribed. These manifestations are often encountered in microbial infections of man. Quinazolines and condensed quinazolines exhibit potent antimicrobial [1–4], analgesic [5] and antiinflammatory [6] activities. Keeping in view the diverse therapeutic [7] activities of quinazolines and as part of our ongoing development of efficient protocols for the preparation of bioactive heterocycles [8–11] the present study describes a simple, novel, high yielding, solvent free methodology for synthesis of the title compounds and to screen them for their in vitro antibacterial activity.

2. Chemistry

Several methods for the synthesis of quinazolines are reported in literature [12,13] involving a refluxing solvent like benzene or xylene with azeotropic water removal, refluxing in ethanol/acetic acid mixtures [14,15] and by reaction in alkali media but all have resorted to harsh conditions such as low yield, longer reaction times, and use of expensive and hazardous chemicals with side product formation. The introduction of microwave assisted organic synthesis (MAOS) has had a significant impact on synthetic chemistry. Many practical benefits [16] observed for microwave (MW) conditions have motivated a large and continuing survey of nearly all classes of thermal reactions for improvement by MW heating. The synthesis of the title compounds is outlined in Scheme 1. The preparation of **2a**–**h** was carried out by heating an equimolar amount of aldehyde **1a**–**d**, 5,5-dimethyl-1,3-cyclohexanedione (dimedone) and urea/thiourea in the absence of solvent and catalyst under microwave irradiation employing neat reaction conditions.



Scheme 1. Synthesis of quinazoline derivatives via Biginelli Reactions.

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3. Pharmacology

3.1. Antibacterial activity

All the synthesized compounds were tested for their in vitro antibacterial activity against standard strains of bacteria by the cup-plate agar diffusion method [17] and Broth Microdilution MIC method [18].

4. Results and discussion

4.1. Chemistry

In light of the improvement MAOS has bestowed upon various thermal reactions reinvestigation of the classical procedure (via modified Biginelli [19,20] reaction by the cyclocondensation of dimedone, aldehyde **1a–d** and urea/thiourea in presence of conc. HCl in refluxing ethanol for long hours) for the synthesis of the title compounds seemed warranted. Initial efforts focussed on optimizing MW condition for the formation of quinazoline derivatives using acidic alumina, based on prior investigations of the conventional thermal heating. The product was formed in good yield within just few minutes of MWI. The reaction was also attempted over neutral alumina which gave appreciable yields without much compromise in reaction time. Since the solid support methodology requires an appreciable amount of solvent for the adsorption of reagents and elution of products an environmentally benign solvent free neat synthesis of octahydroquinazoline derivatives was attempted without using acid, solvent and solid support. When equimolar amount of neat reactants were subjected to MWI for only few minutes excellent yield of products were obtained after tituration with only few drops of methanol (Table 1). In addition, the use of several heterocyclic aldehydes, led to the synthesis of some novel quinazoline derivatives belonging to Biginelli series of condensation products. The structure of the products were confirmed on the basis of spectroscopic and analytical data.

Table 1
Comparison of reaction times and yields for compounds **2a–h**

Compounds	R	X	M.p. (°C)	Neat synthesis (microwave)[a]	
				Time (min)	Yield (%)
2a	Phenyl	O	289–291	2.5	91
2b[b]	Phenyl	S	160–162	2.8	90
2c[b]	4-Chlorophenyl	O	>300	1.8	92
2d	4-Chlorophenyl	S	218–220	2.2	90
2e	Piperonyl	O	>300	2.3	89
2f	Piperonyl	S	208–210	3.0	88
2g	2-Chloro-3-quinolyl	O	>300	3.2	86
2h	2-Chloro-3-quinolyl	S	298–300	3.5	85

[a] Microwave heating (800 W, 2450 MHz, 95–105 °C, 30 s).
[b] **2b** and **2c** were synthesized conventionally [22,23] and not by this methodology.

Table 2
In vitro antibacterial activity of compounds **2a–h** and the reference drug Norfloxacin

Compounds/drug (μg ml^{-1})	Diameter of zone of inhibition (mm)		
	S. aureus ATCC 25923	*E. coli* ATCC 25922	*P. aeruginosa* ATCC 27853
2a (50)	16.0	23.0	26.0
2b (50)	16.0	23.0	25.0
2c (50)	16.0	23.0	26.0
2d (50)	16.0	24.0	26.0
2e (50)	17.0	24.0	26.0
2f (50)	16.0	23.0	26.0
2g (50)	16.0	23.0	25.0
2h (50)	16.0	23.0	26.0
Norfloxacin (**4**)	18.0	28.0	28.0

4.2. Antibacterial activity

All the synthesized compounds **2a–h**, dissolved in dimethylformamide (DMF) and tested at a concentration of 50 μg ml^{-1} by cup plate agar dilution method (Table 2) were found to be active against *Staphylococcus aureus ATCC 25923*, *Escherichia coli ATCC 25922* and *Pseudomonas aeruginosa ATCC 27853*. All the compounds showed antibacterial activity at different concentrations when tested by Broth Microdilution MIC method (Table 3). Norfloxacin was used as the standard drug.

5. Conclusions

Hence we have developed an easy and convenient synthetic route for the preparation of quinazoline derivatives by coupling microwaves using solvent free technique, thus minimizing the use of hazardous solvents and external catalyst which makes it an efficient protocol for organic chemists. Further the compounds were shown to have antibacterial activity against gram-negative and gram-positive bacteria. Further investigations to increase their antibacterial activity and improve the pharmokinetic performance of these new quinazoline derivatives may result in potent antibacterials becoming available for commercial exploitation.

6. Experimental protocols

6.1. Chemistry

Melting points were determined on a Thomas Hoover melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer FT IR-1710 spectrophotometer. ^{1}H NMR were recorded in $CDCl_3$ on Bruker Avance Spectrospin 300 (300 MHz) instrument using TMS as internal standard. Elemental analysis was performed on a Heraeus CHN Rapid Analyzer. Microwave irradiation was carried out in a Kenstar Microwave Oven, Model No. OM 9925E (2450 MHz, 800 W). Temperature of the reaction mixture was measured

Table 3
Antibacterial activity of different compounds (**2a–h**) and Norfloxacin by Broth Microdilution MIC method

Concentration used (μg ml^{-1})	Compounds																										
	2a			**2b**			**2c**			**2d**			**2e**			**2f**			**2g**			**2h**			Norfloxacin		
	Antibacterial activity against standard strains																										
	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3
0.5	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+
1.0	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+
2.0	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+
4.0	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	+
8.0	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–
16.0	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–
32.0	–	–	+	–	–	+	–	–	+	–	–	+	–	–	+	–	–	+	–	–	+	–	–	+	–	–	–
64.0	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–

1 = *E. coli* ATCC 25922.
2 = *P. aeruginosa* ATCC 27853.
3 = *S. aureus* ATCC 25923.
+ = resistant.
– = susceptible.

through AZ, Mini Gun Type, Non Contact IR Thermometer, Model No. 8868. Mass spectra was recorded using micromass time of Flight Massspectrometer Model LCT using ES+. Silica gel plates (Merck) were used for analytical chromatography. Solvents and reagents were purchased from the commercial vendors in the appropriate grade and were used without further purification.

*6.1.1. General procedure for the synthesis of 4-Aryl-7,7-dimethyl-1,2,3,4,5,6,7,8-octahydroquinazoline-2-one/thione-5-one (**2a–h**)*

6.1.1.1. Neat microwave method. Equimolar amount of 0.024 mol of aldehyde **1a–d**, dimedone and urea/thiourea were taken in an Erlenmeyer Flask and was subjected to microwave irradiation. On completion of reaction as monitored by TLC examination at an interval of 30 s, the sticky solid obtained was titurated with few drops of methanol to afford the desired product **2a–h** which was recrystallized from methanol.

*6.1.2. 4-Phenyl-7,7-dimethyl-1,2,3,4,5,6,7,8-octahydroquinazoline-2,5-dione (**2a**)*

IR (KBr): 3325 (NH), 1664 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.96 (s, 3H, CH_3); 1.08 (s, 3H, CH_3); 2.12–2.38 (m, 4H, CH_2); 5.01 (s, 1H, H-4); 7.14–7.38 (m, 5H, Ar-H); 8.0 (s, 1H, NH); 10.6 (s, 1H, NH); Anal. Calcd. for $C_{16}H_{18}N_2O_2$ (M^+: *m/e* 270): C, 71.11; H, 6.66; N, 10.37. Found: C, 72.07; H, 6.78; N, 10.51.

*6.1.3. 4-Phenyl-7,7-dimethyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline-2-thione (**2b**)*

IR (KBr): 3443 (NH), 1662 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.97 (s, 3H, CH_3); 1.08 (s, 3H, CH_3); 2.13–2.46 (m, 4H, CH_2); 4.75 (s, 1H, H-4); 7.09–7.29 (m, 5H, Ar-H); 7.90 (s, 1H, NH); 10.81 (s, 1H, NH); Anal. Calcd. for $C_{16}H_{18}N_2OS$ (M^+: *m/e* 286): C, 67.13; H, 6.29; N, 9.79. Found: C, 67.26; H, 6.38, N, 9.72.

*6.1.4. 4-(4-Chlorophenyl)-7,7-dimethyl-1,2,3,4,5,6,7,8-octahydroquinazoline-2,5-dione (**2c**)*

IR (KBr): 3436 (NH), 1635 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.96 (s, 3H, CH_3); 1.13 (s, 3H, CH_3); 2.12–2.39 (m, 4H, CH_2); 5.04 (s, 1H, H-4); 7.14–7.28 (m, 4H, Ar-H); 7.92 (s, 1H, NH); 10.52 (s, 1H, NH). Anal. Calcd. for $C_{16}H_{17}ClN_2O_2$ (M^+: *m/e* 304.5): C, 63.05; H, 5.58; N, 9.19. Found: C, 63.18; H, 5.45; N, 9.03.

*6.1.5. 4-(4-Chlorophenyl)-7,7-dimethyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline-2-thione (**2d**)*

IR (KBr): 3440 (NH), 1635 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.98 (s, 3H, CH_3); 1.10 (s, 3H; CH_3); 2.15–2.48 (m, 4H, CH_2); 4.72 (s, 1H, H-4); 7.14–7.43 (m, 4H, Ar-H); 7.82 (s, 1H, NH); 10.63 (s, 1H, NH); Anal. Calcd. for $C_{16}H_{17}ClN_2OS$ (M^+: *m/e* 320.5): C, 59.90; H, 5.30; N, 8.73. Found: C, 60.02; H, 5.56; N, 8.86.

*6.1.6. 4-Piperonyl-7,7-dimethyl-1,2,3,4,5,6,7,8-octahydroquinazoline-2,5-dione (**2e**)*

IR (KBr): 3390 (NH), 1658 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.95 (s, 3H, CH_3); 1.04 (s, 3H, CH_3); 2.17–2.42 (m, 4H, CH_2); 5.08 (s, 1H, H-4); 5.90 (s, 2H, OCH_2); 6.76–6.82 (m, 3H, Ar-H); 8.05 (s, 1H, NH); 10.76 (s, 1H, NH); Anal. Calcd. for $C_{17}H_{18}N_2O_4$ (M^+: *m/e* 314): C, 64.96; H, 5.73; N, 8.91. Found: C, 64.82; H, 5.60; N, 8.98.

*6.1.7. 4-Piperonyl-7,7-dimethyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline-2-thione (**2f**)*

IR (KBr): 3430 (NH), 1655 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.97 (s, 3H, CH_3); 1.07 (s, 3H, CH_3); 2.15–2.48 (m, 4H, CH_2); 4.63 (s, 1H, H-4); 5.93 (s, 2H, OCH_2); 6.66–6.78 (m, 3H, Ar-H); 8.01 (s, 1H, NH); 10.52 (s, 1H, NH); Anal. Calcd. for $C_{17}H_{18}N_2O_3S$ (M^+: *m/e* 330): C, 61.81; H, 5.45; N, 8.48. Found: C, 61.70; H, 5.49; N, 8.52.

*6.1.8. 4-(2-Chloro-3-quinolyl)-7,7-dimethyl-1,2,3,4,5,6,7,8-octahydroquinazoline-2,5-dione (**2g**)*

2-Chloro-3-quinoline aldehyde was prepared according to the literature method [21]. IR (KBr): 3378 (NH), 1640 (C=C)

cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.98 (s, 3H, CH_3); 1.12 (s, 3H, CH_3); 2.21–2.35 (m, 4H, CH_2); 5.18 (s, 1H, H-4); 7.21–7.82 (m, 5H, quinolyl); 7.88 (s, 1H, NH); 10.30 (s, 1H, NH); Anal. Calcd. for $C_{19}H_{18}ClN_3O_2$ (M^+: *m/e* 355.5): C, 64.13; H, 5.06; N, 11.81. Found: C, 64.25; H, 5.20; N, 11.70.

*6.1.9. 4-(2-Chloro-3-quinolyl)-7,7-dimethyl-5-oxo-1,2,3,4,5,6,7,8-octahydro-quinazoline-2-thione (**2h**)*

IR (KBr): 3431 (NH), 1650 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.00 (s, 3H, CH_3); 1.17 (s, 3H, CH_3); 2.18–2.42 (m, 4H, CH_2); 5.05 (s, 1H, H-4); 7.14–7.63 (m, 5H, quinolyl); 8.11 (s, 1H, NH); 11.31 (s, 1H, NH); Anal. Calcd. for $C_{19}H_{18}ClN_3OS$ (M^+: *m/e* 371.5): C, 61.37; H, 4.84; N, 11.30. Found: C, 61.28; H, 4.96; N, 11.14.

6.2. Antibacterial activity

All the synthesized compounds **2a**–**h** were tested for their in vitro antibacterial activity against *S. aureus ATCC 25923*, *E. coli ATCC 25922* and *P. aeruginosa ATCC 27853* by the cup–plate agar diffusion method. The compounds were dissolved in DMF and were tested at a concentration of 50 μg ml^{-1}. Norfloxacin (4 μg ml^{-1}) was used as standard. The inoculum of each of the standard bacterial strains was prepared by transferring a single well-isolated colony taken from overnight culture on nutrient agar plate in 10 ml of nutrient broth. The resulting suspension was vortexed for 15 s and incubated at 37 ± 1 °C for 4 h. The turbidity was adjusted to match the 0.5 McFarland standard. Mueller Hinton Agar plates were inoculated with the inoculum using a sterile cotton swab and allowed to dry for 5 min. Cups of 8 mm diameter were made on these plates with the help of a sterile pasteur pipette. Hundred microlitres solution of the compounds was added to each cup. One cup each was inoculated with the solvent and Norfloxacin on each of the plates. The plates were incubated aerobically at 37 ± 1 °C for 24 h. After incubation, the inhibition zone diameter around each cup was measured using a ruler. Further, the MIC of these compounds and Norfloxacin was determined by using the standard protocol of NCCLS Broth Microdilution MIC method [18].

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