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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and antimicrobial activity of some new 3–[5-(4-substituted) phenyl-1,3,4-oxadiazole-2yl]-2-styrylquinazoline-4(3H)-ones

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Abstract Several 3-[5-(4-substituted)phenyl-1,3,4-oxadiazole-2-yl]-2-styryl quinazoline-4(3H)-one were synthesized and screened for antibacterial activity against *Staphylococcus aureus* , *Bacillus subtilis*, *Pseudomonas aeruginosa*, and *Escherichia coli* and antifungal activity against *Aspergillus niger* and *Fusariumoxysporum* by the serial dilution technique. Compounds were prepared by reacting corresponding 2-methtyl quinazolinone and 4-subustituted benzaldehydes in glacial acetic acid. Physicochemical and spectral data were consistent with newly synthesized compounds. The prepared compounds were compared with previously synthesized 2-methyl-3-[5-(4-substituted)phenyl-1,3,4-oxadiazole-2-yl]-quinazoline-4(3H)-ones for antimicrobial activity. The present study revealed that styryl moiety at the second position of 4(3H) quinazolinone marginally increased the biological activity and exhibited better antibacterial than antifungal activities.

Introduction

One of the most frequently encountered heterocyclic molecules in medicinal chemistry is 4(3H)-quinazolinone with wide applications including antibacterial, antifungal, anticonvulsant, and anti-inflammatory activities (Armarego 1979; Gravier *et al.*, 1992; Fisnerova *et al.*, 1986). An increase in its antimicrobial activity by substituting different heterocyclic ring at the third position is also well documented in the literature. The increased antimicrobial activity obtained by

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placing a styryl moiety at the second position has also been reported. In our research we found that oxadiazole and substituted oxadiazole itself possessed antibacterial and antifungal activities (Mishra *et al.*, 2005). In an effort to observe the synergistic effect of both of these effects we synthesized new 4(3H)-qunazolinone analogues incorporating the styryl moiety and substituted oxadiazole at the second and third position of 4(3H)-qunazolinone, respectively. The present paper reports the synthesis and antimicrobial activity of 3-[5-(4-substituted) phenyl-1,3,4-oxadiazole-2-yl]-2-styryl quinazoline-4(3H)-one.

Material and methods

Chemistry

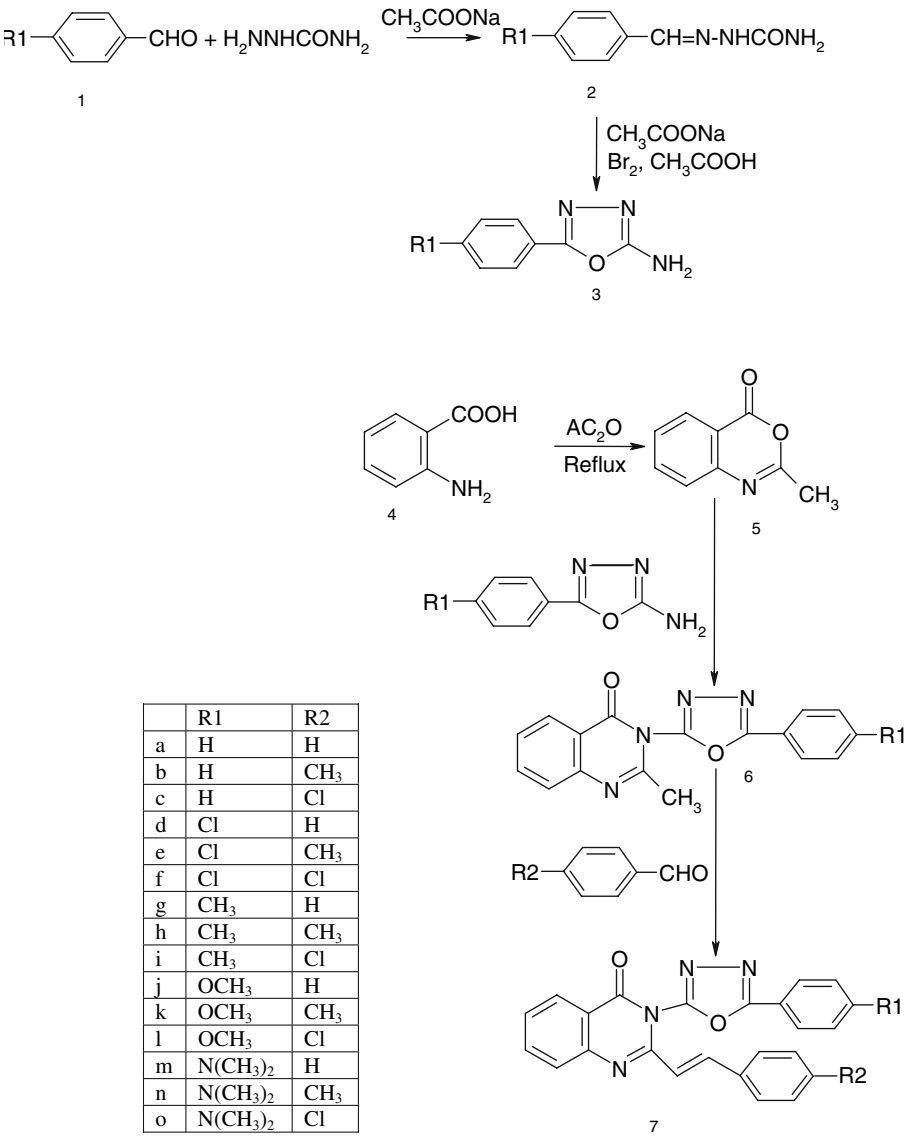
Melting points were determined in one-end-open capillary tubes on a Buchi 530 melting point apparatus and are uncorrected. Infrared (IR) and ^{13}C nuclear magnetic resonance (^{13}C NMR) spectra were recorded for the compounds on Perkin Elmer Spectrum RXI spectrophotometer in KBr pettels and a ^{13}C Advance Bruker (300 MHz) instrument, respectively. Chemical shifts are reported in parts per million (ppm) using tetramethylsilane (TMS) as an internal standard. Elemental analysis (C, N, and S) were undertaken with an Elemental Vario EL III Carlo Erba 1108 analyzer. The purity of the compounds was confirmed by thin-layer chromatography using silica gel glass plates and a benzene:ethanol (8:2) solvent system. The spots were developed in an iodine chamber and visualized under an ultraviolet lamp.

3-[5-(4-substituted)phenyl-1,3,4-oxadiazole-2-yl]-2-styrylquinazoline-4(3H)-ones (7a–o), were obtained (Fig. 1) by refluxing equimolar amounts of opportune 2-methyl-3-[5-(4-substituted)phenyl-1,3,4-oxadiazole-2-yl]-quinazoline-4(3H)-ones (6a–e) and benzaldehyde in glacial acetic acid. The structure of new compounds was elucidated by analytical as well as spectroscopic measurements. The ^{1}H NMR spectra of compounds 7 are consistent with a trans olefinic structure: β-olefinic protons appeared as doublets at δ 6.296–6.980 (J = 16.2 Hz, as required for a trans structure) while the α-olefinic hydrogen were found along with an aromatic multiplet because of the deshielding effect of the two quinazolinone nitrogens.

Synthesis of 3-[5-(4-substituted)phenyl-1,3,4-oxadiazole-2yl]-2-styrylquinazoline-4(3H)-ones was achieved based on the following procedures.

Synthesis of 4-substituted benzaldehyde semicarbazone (2)

Semicarbazide hydrochloride (0.01M) and sodium acelate (0.02M) were dissolved in 15–20 ml of distilled water placed in a flat-bottomed flask. The required aromatic aldehyde (0.01M) was dissolved in aldehyde-free alcohol. This solution was added slowly to the solution of semicarbazide hydrochloride. The separated precipitate was filtered, dried, and recrystallized from hot ethanol (95%).



	R1	R2
a	H	H
b	H	CH_3
c	H	Cl
d	Cl	H
e	Cl	CH_3
f	Cl	Cl
g	CH_3	H
h	CH_3	CH_3
i	CH_3	Cl
j	OCH_3	H
k	OCH_3	CH_3
l	OCH_3	Cl
m	$N(CH_3)_2$	H
n	$N(CH_3)_2$	CH_3
o	$N(CH_3)_2$	Cl

Fig. 1 Scheme for the synthesis of the title compounds (7a–o)

Synthesis of 2-amino-5-aryl-1,3,4-oxadiazols (3)

Semicarbazone (2) (0.01M) and sodium acetate (0.02M) was dissolved in 30–40 ml of glacial acetic acid with continuous stirring. Bromine (0.7 ml in 5 ml of GAA) was added slowly, and the solution was stirred for 1 h and then poured onto crushed ice. The resulting solid was separated, dried, and recrystallized from hot ethanol (95%).

Synthesis of 2-methyl benzoxazin -4(3H)-one (5)

Anthranilic acid (4) (0.01M, 1.8g) was taken in acetic anhydride and refluxed under anhydrous conditions for 4 h. Excess acetic anhydride was then distilled off under reduced pressure. The obtained product was immediately used for next step.

Synthesis of 2-methyl-3-[5-(4-substituted)phenyl-1,3,4-oxadiazole-2-yl]-quinazoline-4(3H)-ones (6)

To the mixture of benzoxazinone (5) 2-amino-5-aryl -1,3,4-oxadiazole (0.01M) in 10 ml of glacial acetic acid was added and refluxed under anhydrous condition for 4 h. After cooling it was poured into crushed ice. The solid separated out was filtered thoroughly washed with cold distilled water, dried, and recrystallized from hot ethanol (95%).

Synthesis of the title compounds (7)

Equimolar amounts (0.012M) of 2-methyl-3-[5-(4-substituted)phenyl-1,3,4-oxadiazole-2-yl]-quinazoline-4(3H)-one and opportune benzaldehyde were reacted in glacial acetic (5.2 mL) under reflux for 18 h. A sticky oily matter was obtained, which was then purified to remove impurities to obtain the final product, which was dried and recrystallized from hot ethanol. The physicochemical and spectral properties of the title compounds are presented in Tables 1 and 2 respectively.

Table 1 Physicochemical properties of 3-[5-substituted 1,3,4-thiadiazole -2 yl] quinazoline-4(3H)-ones

Comp.	Molecular formula	Mol. wt.	m.p. (°C)	% yield
7a	$C_{24}H_{16}N_4O_2$	392	210	23.29
7b	$C_{25}H_{18}N_4O_2$	406	240*	12.74
7c	$C_{24}H_{15}N_4O_2Cl$	426.5	238–240	8.9
7d	$C_{24}H_{15}N_4O_2Cl$	426.5	195*	19.8
7e	$C_{25}H_{17}N_4O_2Cl$	440.5	215	17.3
7f	$C_{24}H_{14}N_4O_2Cl_2$	461	185*	22.05
7g	$C_{25}H_{18}N_4O_2$	406	195–197	21.94
7h	$C_{26}H_{20}N_4O_2$	420	185*	15.15
7i	$C_{25}H_{17}N_4O_2Cl$	440.5	260*	46.93
7j	$C_{25}H_{18}N_4O_3$	422	210*	6.65
7k	$C_{26}H_{20}N_4O_3$	436	218–220	9.2
7l	$C_{25}H_{17}N_4O_3Cl$	456.5	215*	27.47
7m	$C_{26}H_{21}N_5O_2$	435	180*	4
7n	$C_{27}H_{23}N_5O_2$	449	183–185	5.8
7o	$C_{26}H_{20}N_5O_2Cl$	469.5	180*	3.7

*Compound decomposed at mentioned temperature.

Table 2 Spectroscopic data of the title compounds (7–o)

Comp.	IR spectra (cm^{-1})	^1H NMR
7a	1672 (C=O), 1590 (C=N), 1145 (C-O-C)	6.9 (1H, βCH), 7.05–8.45 (m,15H, 2Ph & H5–8, αCH)
7b	1674.2 (C=O),1585 (C=N), 1142.5 (C-O-C)	2.47 (s, 3H, Me); 6.9 (d, 1H, βCH); 7.11–8.47 (m, 14H, 2Ph & H5–8, αCH)
7c	1662.8 (C=O), 1594.5 (C=N), 1149.8 (C-O-C)	6.92 (1H, βCH), 7.10–8.46 (m,14H, 2Ph & H5–8, αCH)
7d	1670.8 (C=O), 1601.8 (C=N), 1146.5 (C-O-C)	6.90 (1H, βCH), 7.11–8.44 (m,14H, 2Ph & H5–8, αCH)
7e	1650 (C=O), 1590.7 (C=N), 1150 (C-O-C)	2.35 (s, 3H, Me); 6.93 (d, 1H, βCH); 7.05–8.48 (m, 13H, 2Ph & H5–8, αCH)
7f	1678 (C=O), 1585.5 (C=N), 1145 (C-O-C)	6.90 (d, 1H, βCH); 7.90–8.48 (m, 13H, 2Ph & H5–8, αCH)
7g	1671.3 (C=O), 1603.2 (C=N), 1154.2 (C-O-C)	2.35 (s, 3H, Me); 6.92 (d, 1H, βCH); 7.06–8.49 (m, 14H, 2Ph & H5–8, αCH)
7h	1658.9 (C=O), 1573.6 (C=N), 1150 (C-O-C)	2.28 (s, 6H, 2Me); 6.93 (d, 1H, βCH); 7.11–8.48 (m, 13H, 2Ph & H5–8, αCH)
7i	1676.6 (C=O), 1584.7 (C=N), 1145 (C-O-C)	2.35 (s, 3H, Me); 6.9 (d, 1H, βCH); 7.10–8.45 (m, 13H, 2Ph & H5–8, αCH)
7j	1657.8 (C=O), 1599.1 (C=N), 1168.9 (C-O-C)	3.89 (s, 3H, OMe); 6.92 (d, 1H, βCH); 7.09–8.47 (m, 14H, 2Ph & H5–8, αCH)
7k	1671.5 (C=O), 1589.7 (C=N), 1142 (C-O-C)	2.37 (s, 3H, Me); 3.88 (s, 3H, OMe) 6.92 (d, 1H, βCH); 7.03–8.17 (m, 14H, 2Ph & H5–8, αCH)
7l	1672.4 (C=O), 1597.1 (C=N), 1172 (C-O-C)	3.88 (s, 3H, OMe); 6.91 (d, 1H, βCH); 7.11–8.45 (m, 13H, 2Ph & H5–8, αCH)
7m	1687 (C=O), 1588.5 (C=N), 1163.3 (C-O-C)	3.12 (s, 6H, NMe_2); 6.90 (d, 1H, βCH); 7.05–8.44 (m, 14H, 2Ph & H5–8, αCH)
7n	1686.4 (C=O), 1591.3 (C=N), 1164 (C-O-C)	2.36 (s, 3H, Me); 3.10 (s, 6H, NMe_2); 6.91 (d, 1H, βCH); 7.08–8.48 (m, 13H, 2Ph & H5–8, αCH)
7o	1685.8 (C=O), 1592.5 (C=N), 1162.6 (C-O-C)	3.11 (s, 6H, NMe_2) 6.90 (d, 1βCH); 7.07–8.47 (m, 13H, 2Ph & H5–8, αCH)

Microbiological evaluation

All the glass apparatus used was sterilized before use. The liquid dilution technique was used to determine the minimum inhibitory concentration (MIC) of the synthesized compounds. Bacterial strain of *Staphylococcus aureus* (MTCC no. 96), *Bacillus subtilus* (MTCC no. 619), *Pseudomonas aeruginosa* (MTCC no. 424) and *Escherichia coli* (MTCC no. 40) and fungal strains of *Aspergillus niger* (MTCC no. 1344) and *Fusarium oxysporum* obtained from Institute of Microbial Technology, Chandigarh were used in the present study. Nutrient broth (beef extract 1 g, yeast extract 2 g, peptone 5 g, sodium chloride 5 g, distilled water q.s. 1000 ml) was used as growth medium for bacteria and Sabouraund's medium (dextrose 40 g, peptone

Table 3 Antibacterial and antifungal activity of synthesized compounds (7a–o)

Code	Antibacterial (μg/ml)				Antifungal (μg/ml)	
	S. aureus	B. subtilis	P. aeruginosa	E. coli	A. niger	F. oxysporum
7a	82	80	90	76	143	152
7b	NA	NA	NA	NA	NA	NA
7c	NA	NA	NA	NA	NA	NA
7d	79	75	86	70	130	141
7e	NA	NA	NA	NA	NA	NA
7	NA	NA	NA	NA	NA	NA
7f	NA	NA	NA	NA	NA	NA
7g	85	83	92	81	145	156
7h	NA	NA	NA	NA	NA	NA
7i	NA	NA	NA	NA	NA	NA
7j	NA	NA	NA	NA	NA	NA
7k	NA	NA	NA	NA	NA	NA
7l	NA	NA	NA	NA	NA	NA
7m	88	83	94	79	155	166
7n	NA	NA	NA	NA	NA	NA
7o	NA	NA	NA	NA	NA	NA
NF	6	5	8	4	–	–
CT	–	–	–	–	6	8

NA = not significantly active

10 g, distilled water q.s. 1000 ml) was used for fungus growth. Cook's procedure of serial dilution and observation for presence of growth was used in the determining the MIC. Dimethylformamide was used as the solvent for the compounds. A blank test was done to check the antimicrobial activity of DMF. Norfloxacin (NF) and clotrimazole (CT) were used as the standard drugs for antibacterial and antifungal activity, respectively, because these compounds are easily soluble in DMF.

Results and discussion

The synthesized 2-styryl quinazolinones 7a–o were screened for their antimicrobial activity by the serial dilution method to evaluate the minimum inhibitory concentration Table 3.

All of the precursors (6a–e) of the title compounds showed antibacterial activity in the range of 88–130 μg/mL for *Staphylococcus aureus*, 84–129 μg/mL for *Bacillus subtilis*, 95–138 μg/mL for *Pseudomonas aeruginosa*, and 80–120 μg/mL for *Escherichia coli*. It was observed that styrylation of 2-methyl-3-[5-phenyl-1,3,4-oxadiazole-2-yl]quinazoline-4(3H)-one marginally increased its antimicrobial activity Table 4. Only nonsubstituted styryl compounds showed activity. Substitution either by electron-releasing or electron-attracting moieties at the styryl group resulted in loss of activity. Compound 7d was found to be the most active compound

Table 4 Antibacterial and antifungal activity of compounds (6a–e)

Code	Antibacterial (μg/ml)				Antifungal (μg/ml)	
	S. aureus	B. subtilis	P. aeruginosa	E. coli	A. niger	F. oxysporum
6a (R=H)	130	127	135	120	185	192
6b (R=Me)	127	122	138	115	165	180
6c (R=Cl)	89	84	98	82	172	184
6d (R=OMe)	90	85	100	80	165	175
6e ($R=N(CH_3)_2$	88	88	95	84	170	179
NF	6	5	8	4	–	–
CT	–	–	–	–	6	8

of the prepared series. All active compounds showed better antibacterial than antifungal activity in the range 70–195 μg/ml. In conclusion the presented results reveal that synthesized 2-styryl-quinazoline-4(3H)-one exhibited better antibacterial than antifungal activity and that styrylation slightly increases the biological activity.

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