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Syntheses of Biologically Active 3-[4-(4-Substituted amino-4-yl-methyl-5-thione[1,3,4]oxadiazol-2-yl-methoxy)-phenyl]-2-phenyl-3*H*-quinazolin-4-ones

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A number of Mannich base quinazoline derivatives possessing 1,3,4-oxadiazole ring have been synthesized by reacting 3-[4-(5-thione[1,3,4]-oxadiazol-2-yl-methoxy)-phenyl]-2-phenyl-3*H*-quinazolin-4-one (**V**) with different secondary amines and formaldehyde using N,N-dimethyl-formamide as the solvent to afford 3-[4-(4-substituted amino-4-yl-methyl-5-thione[1,3,4]oxadiazol-2-yl-methoxy)phenyl]-2-phenyl-3*H*-quinazolin-4-ones (**VIa-d**). The structures of the newly synthesized compounds have been established by analytical and spectral methods. The compounds have also been screened for their biological activity.

Key Words: 2-Phenyl-4-(3*H*)-quinazolin-4-one, 5-Thione[1,3,4]-oxadiazole derivatives, Biological activity.

INTRODUCTION

Quinazoline derivatives possess potent biological activity such as analgesic, antibacterial, antifungal and inflammatory[1-4]. 1,3,4-Oxadiazoles are also known to have broad spectrum of biological activities[5-8]. These compounds have been shown to possess analgesic, muscle relaxtant and tranquilising properties[9]. In the light of these interesting biological active evidences, it is worthwhile to synthesize some new quinazoline derivatives containing oxadiazole moiety to enhance their biological activity.

EXPERIMENTAL

Melting points were taken in open capillaries and are uncorrected. IR spectra were recorded on Jasco 410 plus FTIR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Jeol 300 MHz FT-NMR spectrophotometer using DMSO-d_6 as solvent and TMS as internal standard (chemical shifts in δ ppm). The mass spectra of compounds were determined with Shimadzu model No. QP 2010. The elemental analysis was carried out on a Perkin-Elmer C, H, N analyzer. The purity of the compounds was monitored by thin layer chromatography. TLC was carried out on precoated 0.2 mm silica gel $_{60}F^{254}$ plates.

2-Phenyl-3,1-benzoxazin-4-one (I): To a solution of 2-amino benzoic acid (13.7 g, 0.1 mol) in 100 mL dry pyridine, benzoyl chloride (14.0 mL, 0.1 mol) was added dropwise with constant stirring at 25-30 °C and stirred further for *ca.* 1 h. The reaction mixture was then poured into water. The solid obtained was filtered, washed with 5 % sodium bicarbonate solution and recrystallized from methanol, yield 82 %, m.p. 123 °C; IR (KBr, ν_{max}, cm^{-1}) 1762 (C=O), 1598 (C=N), 1571, 1495, 1473 (C=C, aromatic).

3-(4-Hydroxy-phenyl)-2-phenyl-3H-quinazolin-4-one (II): A mixture of compounds **I** (22.3 g, 0.1 mol) and 4-aminophenol (11.88 g, 0.11 mol) in 100 mL pyridine was refluxed for *ca.* 7 h. The reaction mixture was then allowed to cool to room temperature and left overnight. The separated solid was filtered, washed with methanol and recrystallized from ethanol, yield 50 %, m.p. 242 °C; IR (KBr, ν_{max}, cm^{-1}) 3292 (OH), 1650 (CO·N), 1604 (C=N), 1541, 1512, 1485 (C=C, aromatic).

[4-(4-Oxo-2-phenyl-4*H*-quinazolin-3-yl)-phenoxy]-acetic acid ethyl ester (III): A solution of compound **II** (3.14 g, 0.01 mol) in 100 mL dry acetone was heated in presence of anhydrous potassium carbonate (1.38 g, 0.01 mol) with ethyl chloroacetate (1.47 g, 0.012 mol) in a microwave oven for 4 min. The reaction mixture was cooled and filtered to separate out potassium chloride and unreacted potassium carbonate. Acetone was removed from the filtrate under vacuum to one-third of the initial volume. The product obtained on cooling was filtered, washed with water and recrystallized from acetone, yield 90 %, m.p. 180 °C; IR (KBr, ν_{max}, cm^{-1}) 1735 (C=O ester), 1650 (CO·N), 1606 (C=N), 1577, 1544, 1508, 1448 (C=C, aromatic); ^{1}H NMR (DMSO-d_6) δ 1.24 (t, 3H, CH_3), 4.1 (q, 2H, CH_2), 4.7 (s, 2H, O·CH_2·C), 6.9-8.6 (m, 13H, ArH). [Found (%): C, 71.96; H, 5.04; N, 6.94. $C_{24}H_{20}N_2O_4$ requires C, 72.00; H, 5.00; N, 7.00 %].

[4-(4-Oxo-2-phenyl-4*H*-quinazolin-3-yl)-phenoxy]-acetic acid hydrazide (IV): Compound **III** (4.0 g, 0.01 mol) and 2 mL of 99 % hydrazine hydrate in 500 mL of ethanol was refluxed for *ca.* 8 h. The reaction mixture was then allowed to cool to room temperature. The separated white coloured crystalline solid was filtered, washed with ethanol and recrystallized from ethanol, yield 85 %, m.p. 220 °C; IR (KBr, ν_{max}, cm^{-1}) 3315, 3272 (NH·NH_2), 1674 (C=O amide), 1652 (CO·N), 1603 (C=N), 1585, 1508, 1450 (C=C, aromatic); ^{1}H NMR (DMSO-d_6) δ 4.3 (s, 2H, NH_2), 4.4 (s, 2H, O·CH_2·C), 6.9-8.6 (m, 13H, ArH), 9.3 (s, 1H, NH). [Found (%): C, 68.45; H, 4.79; N, 14.52. $C_{22}H_{18}N_4O_3$ requires C, 68.39; H, 4.66; N, 14.50 %].

3-[4-(5-Thione-[1,3,4]oxadiazol-2-ylmethoxy)-phenyl]-2-phenyl-3*H*-quinazolin-4-one (V): Compound **IV** (3.86 g, 0.01 mol) was added to a solution of potassium hydroxide (0.56 g, 0.01 mol) in absolute ethanol (40 mL). Carbon disulphide (0.9 mL, 0.015 mol) was added dropwise with continuous stirring over a period of 0.5 h. The reaction mixture was then refluxed until the evolution of H_2S gas almost ceased. The solvent was removed under reduced pressure and the residue obtained was dissolved in water and acidified with dilute hydrochloric acid. The solid obtained was filtered, washed with water and recrystallized from ethanol,

yield 74 %, m.p. 165 °C; IR (KBr, ν_{max}, cm^{-1}) 3290 (NH), 1668 (CO·N), 1600 (C=N), 1583, 1508, 1448 (C=C, aromatic), 1120 (C=S); ^{1}H NMR (DMSO-d_6) δ 5.2 (s, 2H, O·CH_2·C), 6.9-8.6 (m, 13H, ArH), 14.0 (s, 1H, NH). [Found (%): C, 64.49; H, 3.81; N, 13.11. $C_{23}H_{16}N_4O_3S$ requires C, 64.48; H, 3.73; N, 13.08 %].

3-[4-(4-Substituted amino-1-yl-methyl-5-thione-[1,3,4]oxadiazol-2-yl-methoxy)-phenyl]-2-phenyl-3*H*-quinazolin-4-ones (VIa-d): 2-Phenyl-3-[4-(5-thione[1,3,4]oxadiazol-2-yl-methoxy)-phenyl]- 3*H*-quinazolin-4-one (**V**; 0.256 g, 0.0006 mol) was dissolved in 1.0 cm^3 N,N-dimethyl formamide. A slight excess of formaldehyde (0.050 mL, 0.00067 mol) and appropriate secondary amine (0.0006 mol) was added with vigorous stirring. The reaction mixture was stirred at room temperature (30 °C) for 24 h. The white colour product obtained was filtered, washed with water and recystallized from ethanol, **VIa**: IR (KBr, ν_{max}, cm^{-1}) 1647 (CO·N), 1602 (C=N), 1556, 1508, 1448 (C=C, aromatic), 1114 (C=S); ^{1}H NMR (DMSO-d_6) δ 2.6 (t, 4H, CH_2·N·CH_2), 3.5 (t, 4H, CH_2·O·CH_2), 4.9 (s, 2H, N·CH_2·N), 5.3 (s, 2H, O·CH_2·C), 7.0-8.6 (m, 13H, ArH); ^{13}C NMR (DMSO-d_6) δ 23.15, 25.3, 50.7, 60.0, 115.2, 121.0, 122.3, 122.6, 123.1, 126.9, 128.8, 132.0, 132.2, 132.6, 134.4, 138.7, 153.7, 157.8, 164.5, 167.1, 178.1; MS (m/z): 527 [M^+], 371, 327, 313, 223, 205, 179, 166, 146, 118, 109, 105, 90, 77.

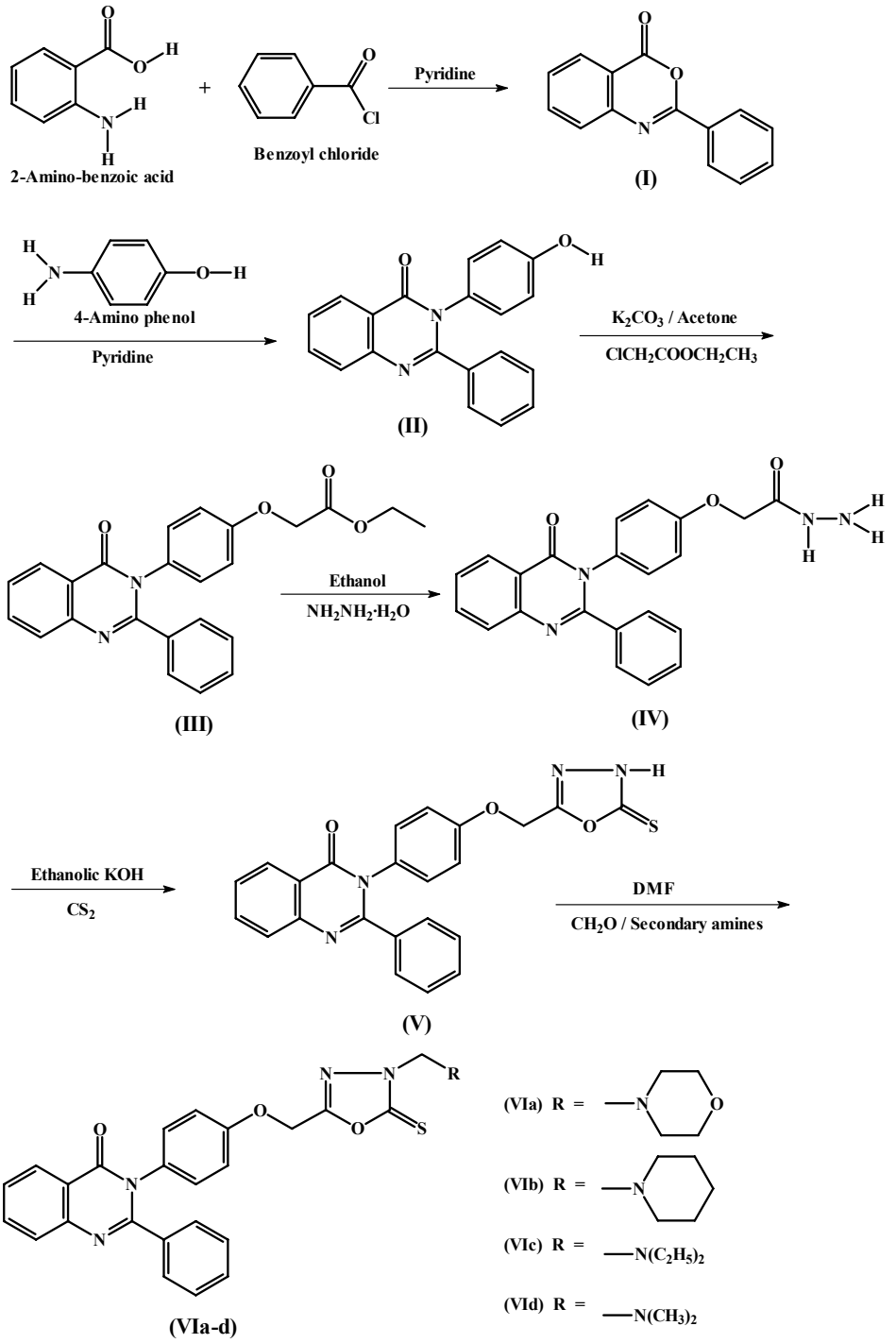
The characterization data of compounds (**VIa-d**) have been given in Table-1.

TABLE-1
PHYSICAL DATA OF COMPOUNDS

Compd.	R	m.p. (ºC)	Yield (%)	m.f.	Elemental analysis (%): Calcd. (Found)		
					C	H	N
VIa	Morpholino	195	58	$C_{28}H_{25}N_5O_4S$	63.75 (63.78)	4.74 (4.83)	13.28 (13.31)
VIb	Piperidino	187	52	$C_{29}H_{27}N_5O_3S$	66.28 (66.30)	5.14 (5.21)	13.33 (13.39)
VIc	Diethylamino	192	61	$C_{28}H_{27}N_5O_3S$	65.49 (65.50)	5.26 (5.35)	13.64 (13.64)
VId	Dimethylamino	160	56	$C_{26}H_{23}N_5O_3S$	64.32 (64.35)	4.74 (4.82)	14.43 (14.45)

RESULTS AND DISCUSSION

2-Amino benzoic acid was reacted with benzoyl chloride in pyridine to give 2-phenyl-3,1-benzoxazin-4-one (**I**)[10,11] which on heating with 4-aminophenol gave 3-(4-hydroxy-phenyl)-2-phenyl-3*H*-quinazolin-4-one (**II**)[12]. Esterification of **II** with ethyl chloroacetate in presence of potassium carbonate in acetone by microwave irradiation yielded [4-(4-oxo-2-phenyl-4*H*-quinazolin-3-yl)phenoxy]acetic acid ethyl ester (**III**). The compound (**III**) was condensed with hydrazine hydrate in ethanol to give [4-(4-oxo-2-phenyl-4*H*-quinazolin-3-yl)phenoxy]acetic acid hydrazide (**IV**) in good yields. The compound (**IV**) on treatment with ethanolic KOH and


2-Amino-benzoic acid
Benzoyl chloride
Pyridine
(I)
4-Amino phenol
Pyridine
(II)
K2CO3 / Acetone
ClCH2COOCH2CH3
(III)
Ethanol
NH2NH2·H2O
(IV)
Ethanolic KOH
CS2
(V)
DMF
CH2O / Secondary amines
(VIa-d)
(VIa) R =
(VIb) R =
(VIc) R = N(C2H5)2
(VId) R = N(CH3)2

Scheme-I

carbon disulphide furnished 3-[4-(5-thione[1,3,4]oxadiazol-2-yl-methoxy)phenyl]-2-phenyl-3*H*-quinazolin-4-one (**V**). The reaction of compound **V** with different secondary amines and formaldehyde using N,N-dimethyl formamide afforded Mannich base 3-[4-(4-substituted amino-1-yl-methyl-5-thione[1,3,4]oxadiazol-2-yl-methoxy)phenyl]-2-phenyl-3*H*-quinazolin-4-ones (**VIa-d**) (**Scheme-I**):

Biological activity

Antibacterial activity: All the newly synthesized quinazolin-4-ones (**VIa-d**) were screened *in vitro* for their antibacterial activity against *Staphylococcus aureus*, *Escherichia coli*, *Bacillus subtilis* and *Salmonella typhosa* by the ditch-plate technique[13] using concentrations of 2 mg/mL. Nutrient agar was employed as culture media and DMF was used as solvent control for antibacterial activity.

Antifungal activity: The compounds (**VIa-d**) synthesized were screened for their antifungal activity against *Aspergillus niger, Candida albicans*, *Cryptococcus neoformans* and *Thielaviopsis paradoxa* by paper-disc diffusion method[14] at concentrations of 2 mg/mL. Nutrient agar was employed as culture media and DMF was used as solvent control for antifungal activity.

The known compounds such as ampicillin, amoxicillin, norfloxacin, penicillin and griseofulvin were used for comparison purpose. The diameter of zone of inhibition was measured in mm. The antibacterial and antifungal screening data are recorded in Table-2.

TABLE-2
BIOLOGICAL ACTIVITY DATA

Compd.	Zone of inhibition (mm)							
	Antibacterial activity				Antifungal activity			
	S. aureus	*E. coli*	*B. subtilis*	*S. typhosa*	*A. niger*	*C. albicans*	*C. neoformans*	*T. paradoxa*
VIa	12	8	12	10	11	10	14	15
VIb	15	14	10	15	14	9	10	11
VIc	15	9	14	12	16	17	11	10
VId	17	14	12	16	17	15	12	16

From Table-2 it can be seen that the compounds **VIb**, **VIc** and **VId** showed good activity against *Staphylococcus aureus*, compounds **VIb** and **VId** showed good activity against *Salmonella typhosa*. The compounds **VIc** and **VId** showed remarkable activity against *Aspergillus niger* and *Candida albicans* and the compounds **VIa** and **VId** showed remarkable activity against *Thielaviopsis paradoxa*.

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