Antibacterial and Antifungal Activities of Some Novel 2,3-Disubstituted Quinazolin-4(3H)-ones

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A series of novel 2,3-disubstituted quinazolin-4(3*H*)-ones have been synthesized by condensing the aromatic primary amino group of quinazoline with different aldehydes and ketones. When these compounds were evaluated for antibacterial and antifungal activities, all the compounds inhibited the growth of bacteria and fungi significantly. The compounds VII and IX exhibited equipotent activity with the standard ciprofloxacin against *Shigella flexneri*, and *Pseudomonas aeruginosa*, and the compound VIII exhibited equivalent activity to ciprofloxacin against *Bacillus subtilis* and *Citrobacter ferundii*. The compounds V, VI and IX were found to be equipotent with the standard clotrimazole against *Aspergillus niger* and *Microsporum gypseum*; and the compound VI was equipotent with standard clotrimazole against *Trichophyton mentagrophytes*.

Quinazolines and condensed quinazolines received the attention of medicinal chemists due to its wide range of biological activities which include analgesic and antiinflammatory[1,2], antibacterial[3,4], antifungal[5,6], antihistaminic[7,8], antihypertensive[9,10], anticancer[11,12] and antiepileptic[13] activities. Schiff bases were reported to possess potent antimicrobial activity[14]. In the present study it was envisaged that a drug molecule possessing the above mentioned pharmacophore could be of advantage since it might possess potent antibacterial and antifungal activities. The title compounds, 2,3-disubstituted quinazolin-4(3*H*)-ones were prepared by condensing the aromatic primary amino group of quinazoline with different aldehydes and ketones. The starting material 3-amino-2-substituted quinazolines were synthesized from anthranilic acid[15]. The title compounds were screeened for antibacterial and antifungal activities.

Melting points were taken in open capillary tubes on a Thomas Hoover melting point apparatus and were uncorrected. IR spectra were recorded on a Perkin Elmer - 841 grating spectrometer in KBr. ^{1}H NMR spectra were recorded on a varian EM-360 spectrometer (300 MHz) employing tetramethylsilane as the internal reference. Mass spectra on varian Atlas CH-7 mass spectrometer at 70-eV. Elemental analysis were performed on a Carlo Erba elemental analyzer.

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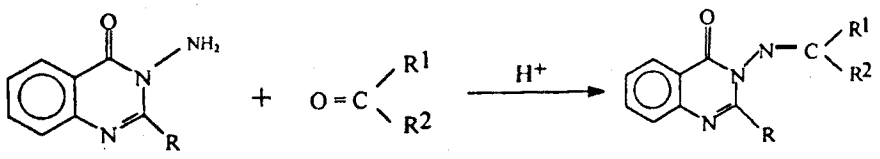
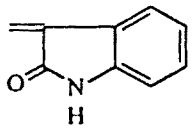
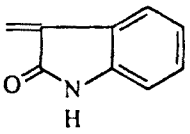
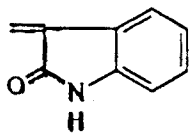
The title compound, 2-phenyl-3-(2-butylidene) quinazolin-4(3*H*)-one (I)[15] was prepared by taking a mixture of 3-amino-2-phenyl quinazolin-4(3*H*)-one 1.18 g (0.005 mol) and ethylmethyl ketone 0.36 g (0.005 mol) in 25 ml of methanol and 1 ml of glacial acetic acid. The mixture was refluxed for 17 h and cooled, the seperated solid was recrystallized from benzene and methanol. Yield: 0.9 g (75%), m.p. 192-194°, **IR** (KBr) (cm^{-1}: 1660 (C=O), 1590 (C=N), 1560 (C=C), 1260 (C-N), 770, 700 (C-H). **^{1}H NMR** ($CDCl_3$) δ (ppm): 1.2-1.4 (3H, t, CH_2 - $C\underline{H}_3$), 1.5-1.6 (3H, s, CH_3), 4-4.4 (2H, q, $C\underline{H}_2$-CH_3), 7.4-7.8 (5H, m, Ar-H), 8.1-8.3 (4H, m, Ar-H); MS (m/e): 291M$^+$; Anal. ($C_{18}H_{17}N_3O$) C,H,N. Similarly the compounds **II** and **III** were synthesized using cinnamaldehyde and isatin. Compound **II**: reaction time: 15 h; yield: 1.7 gm (71%); m.p. 252-254°; mol.formula $C_{23}H_{17}N_3O$; mol. wt: 351. Compound **III**: reaction time: 16 h; yield: 0.9 gm (76%); m.p. 172-174°; mol.formula-$C_{22}H_{14}N_4O_2$; mol.wt: 366.

The title compound, 2-mercapto-3-(1-phenyl-3-propylidene) quinazolin-4(3*H*)-one (**V**)[15] was prepared by taking a mixture of 3-amino-2-mercapto quinazolin-4(3*H*)-one 1.16 g (0.006 mol) and cinnamaldehyde 0.79 g (0.006 mol) in 20 ml of dimethylformamide and 2 ml acetic anhydride, it was refluxed for 17 h and cooled. The reaction mixture was poured into methanol and the solid obtained was recrystal-



R = -Ph, -SH, -SCH3 (I-IX)

Compd	R	$=C<^{R^1}_{R^2}$
I	-Ph	$=C<^{CH_3}_{CH_2\text{-}CH_3}$
II	-Ph	= CH-CH=CH 
III	-Ph	
IV	-SH	$=C<^{CH_3}_{CH_2\text{-}CH_3}$
V	-SH	= CH-CH=CH 
VI	-SH	
VII	-SCH_3	$=C<^{CH_3}_{CH_2\text{-}CH_3}$
VIII	-SCH_3	= CH-CH=CH 
IX	-SCH_3	

Scheme 1: Structures of title compounds.

TABLE 1: ANTIBACTERIAL AND ANTIFUNGAL ACTIVITIES OF TEST COMPOUNDS.

Micro Organisms	Zone of Inhibition (in mm) of test compounds (100 μg/ml)									Standard 10 μg/ml
	I	II	III	IV	V	VI	VII	VIII	IX	
Salmonella typhi	11	12	8	14	13	13	14	12	12	24
Shigella flexneri	15	13	16	18	17	17	23	20	24	23
Escherichia coli	14	10	11	11	10	13	12	14	15	25
P. aeruginosa	16	14	17	17	19	16	24	21	23	24
Pseudomonas	13	13	11	12	14	11	12	10	18	23
B. subtilis	17	16	16	18	15	16	20	22	20	22
Proteus vulgaris	11	13	14	11	13	14	16	17	16	24
Citrobacter ferundii	22	21	24	19	20	16	23	25	19	24
Klebs pneumoniae	10	16	13	13	14	11	12	10	15	25
S. aureus	12	10	11	10	12	11	14	13	18	25
Candidia albicans	16	16	13	16	16	18	17	16	15	27
Aspergillus niger	17	15	14	22	26	27	23	20	26	25
M. gypseum	18	16	19	23	25	24	22	18	24	25
T. mentagrophytes	16	19	17	21	20	26	21	22	23	26

lized from dimethyl formamide. Yield: 0.8 g (69%), m.p. 220-222°. **IR** (KBr) (cm^{-1}): 3050, 2900 (Ar-CH), 1680 (C=O), 1600 (C=C), 1440 (ring C=N), 960 (S-H), 700 (C-S), 750 (C-H). **^{1}H NMR** ($CDCl_3$) δ (ppm): 3.2-3.3 (1H, s, SH), 4.9-5.1 (1H, d, -CH), 5.7-5.9 (1H, 2d, =CH), 6.4-6.6 (1H, d, -CH), 7.4-7.8 (5H, m, Ar-H), 8.2-8.5 (4H, m, Ar-H); MS (m/e): 307M$^+$: Anal. ($C_{17}H_{13}N_3OS$) C,H,N. Similarly the compounds IV and VI were synthesized using ethylmethyl ketone and isatin. Compound **IV**: reaction time: 16 h; yield: 1.4 g (72%); m.p. 310-312°; mol.formula-$C_{12}H_{13}N_3OS$; mol. wt: 247. Compound **VI**: reaction time: 50 h; yield: 0.85 mg (73%); m.p.>320°; mol.formula-$C_{16}H_{10}N_4O_2S$; mol. wt: 322.

The title compound, 2-methylthio-3-(2-butylidene) quinazolin-4(3H)-one (VII)[15] was prepared by taking a mixture of 3-amino-2-methylthio quinazolin-4(3*H*)-one 1.04 g (0.005 mol) and ethylmethyl ketone 0.36 g (0.005 mol) in 25 ml of acetic acid. The mixture was refluxed for 24 h and the reaction mixture was poured into water. The solid obtained was recrystallized from methanol. Yield: 0.85 g (81%), m.p. 142-143°. **IR** (KBr) (cm^{-1}): 2900, 2420, 2280, (Ar-CH), 1660 (C=O), 1530 (C=N), 1300 (ring C=C), 680 (C-S). **^{1}H NMR** ($CDCl_3$) δ (ppm): 1.2-1.5 (3H, t, CH_2-$C\underline{H}_3$), 1.6-1.7 (3H, s, CH_3), 2.6-2.7 (3H, s, SCH_3), 4.1-4.4 (2H, q, $C\underline{H}_2$-CH_3), 8.1-8.4 (4H, m, Ar-H); MS (m/e): 261M$^+$: Anal. ($C_{13}H_{15}N_3OS$) C,H,N. Similarly the compounds **VIII** and **IX** were synthesized using cinnamaldehyde and isatin. Compound VIII: reaction time: 20 h: yield: 0.7 g (72%); m.p. 130-132°; mol.formula-$C_{18}H_{15}N_3OS$; mol. wt: 321. Compound IX: reaction time: 30 h yield: 0.8 g (77 %); m.p. 218-220°; mol.formula-$C_{17}H_{12}N_4O_2S$; mol. wt: 336.

The title compounds (I-IX) were screened for antibacterial and antifungal activities by agar-cup plate method[16]. At a concertration of 100 μg/ml using DMF as a solvent against the following bacteria, *Shigella flexneri, Salmonella typhi, Escherichia coli, Pseudomonas, Proteus vulgaris, Klebs. pneumoniae, S. aureus. P. aeruginosa, B. subtilis, Citrobacter freundii* and following fungi, *Candida albicans, Aspergillus niger, M. gypseum, T. mentagrophytes*. All bacteria were grown on Mueller-Hinton agar (Hi-media) plates (37°, 24 h) and fungi were grown on Sabouraud Dextrose agar (Hi-media) plates (26°, 48-72 h). The zone of inhibition (in mm) of each strain was recorded and the antibacterial activity has been compared with known standard drug ciprofloxacin at 10 μg/ml concentration and the antifungal activity with clortrimazole at 20 μg/ml concentration.

All the test compounds exhibited moderate to good antibacterial and antifungal activities. The compounds VII and IX exhibited equipotent activity with the standard ciprofloxacin against *S. flexneri* and *P. aeruginosa*; and the compound VIII exhibited equipotent activity with ciprofloxacin against *S. subtilis* and *C. freundii*. The compounds V, VI and IX were found to be equipotent with the standard clotrimazole against *A niger* and *M. gypseum*; and the compound VI was equipotent with standard clotrimazole against T. mentagrophytes.

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Spectrophotometric Investigations on the Assay of Phenothiazine Drugs

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A rapid, accurate and sensitive spectrophotometric method for the quantitative determination of four phenothiazine drugs either in pure form or in pharmaceutical preparations has been developed. The method is based on the development of red coloured products by the interaction of phenothiazines with diazotised anthranilic acid in hydrochloric acid medium. The reaction proceeds via the oxidation of the phenothiazine nucleus into a semiquinonoid radical. The optimum reaction conditions and other analytical parameters are evaluated. The common excipients employed do not interfere in the determination of phenothiazine drugs. Results of analysis of pure drugs and their dosage forms by the proposed method are in good agreement with those of the official method.

Phenothiazines are widely used as anticholinergic, antihistaminic and antipsychotic drugs[1]. Phenothiazine drugs are analysed spectrophotometrically using various analytical reagents, which include, hexacyanoferrate (III)[2], N-

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