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SYNTHESIS AND CHARACTERIZATION OF 2-{[2-(4-OXO-2-PHENYL-4H-QUINAZOLIN-3-YL) ETHOXY] ALKYL) ARYL AMIDES/IMIDES AND THEIR EVALUATION FOR ANTIMICROBIAL ACTIVITY

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***Abstract*—2-Amino benzoic acid (anthranilic acid) on reaction with excess equivalent of benzyl chloride in dry pyridine afforded 2-phenyl benzo [d] [1,3] oxazin-4-one(I), which on heating with 2-amino ethanol (cholamine) in dry pyridine followed by acidification yielded 3-(2-hydroxy ethyl) 2- phenyl quinazolin 4(3H) one (II). Reaction of (II) with aryl amido/imido alcohols (III) in conc. H2SO4 furnished 2-{[2-(4-oxo-2-phenyl-4H-quinazolin-3-yl) ethoxy] aryl amide/imides (IV). Compounds (IV) were screened for their antimicrobial activity involving the standardized methods as recommended by the National Committee on Clinical Laboratory Standards (NCCLS).**

***Index Terms*—Anthranilic acid, Cholamine, Antimicrobial activity, dihydrofolate reductase, quinazole derivatives.**

I. INTRODUCTION

Literature survey reveals that in past quinazole compounds have been investigated in several health areas[1-10]. Interest in such compounds has increased manifolds because of their association with anticancer activity. These compounds were screened for inhibition of the enzyme dihydrofolate reductase and some quinazole derivatives were found even more potent than methotraxate as inhibitors of dihydrofolate reductase in human leukemia[11-12]. Similar analogs were found to be as potent as methotroxate dihydrofolate reductase from L1210 mouse Leukemia[13]. Very recently, quinazole compounds have been demonstrated to have definite anticancer activity against human breast carcinoma[14]. These valid observation prompted the author to undertake the synthesis of of 2-{[2-(4-oxo-2-phenyl-4H-quinazolin-3-yl)ethoxy] alkyl} aryl amides/imides (Scheme-I) for studying their antimicrobial activity involving four bacteria and six fungi.

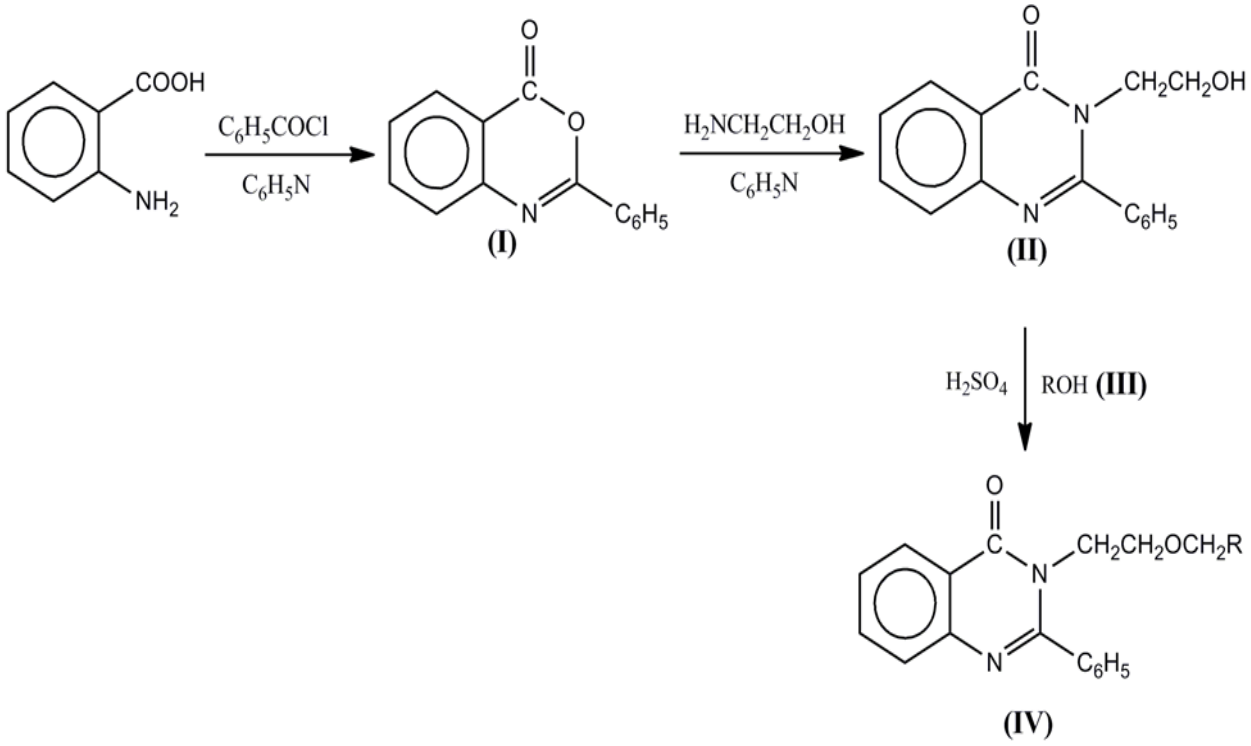
II. EXPERIMENTAL SECTION

Melting points were determined in open capillary tubes in a Toshniwal (japan) electrical melting point apparatus and therefore the values reported are uncorrected. The IR spectra were recorded on an FTIR Perkin Elmer (model) spectrometer using KBr discs (cm-1). The 1HNMR and 13CNMR spectra were recorded in CDCl3 on a Bruker instrument at 300 MHz and 75 MHz, respectively. Chemical shifts are expressed in δ scale downfield from TMS, which was used as an internal standard. The mass spectra (FAB) were recorded on JEOL SX102/ DA-600 mass spectrometer using Argon as FAB gas. The purity of the compounds was checked by Thin Layer Chromatography (TLC) using silica gel-G (Acme), and the spots were visualized by iodine vapours. The intermediates viz; 2-phenylbenzo [d] [1, 3] oxazin-4-one (I), 3-(2-hydroxyethyl)-2-phenyl quinazolin 4(3H) one (II) and aryl amido/imidoalcohols (III) were synthesized involving the established protocols[15 – 22].

III. SYNTHESIS OF 2-{[2-(4-OXO-2-PHENYL-4H-QUINAZOLIN-3-YL)ETHOXY]ALKYL]ARYL AMIDES/IMIDES (IV)

A mixture consisting of 3-(2-hydroxyethyl)-2-phenyl-quinazolin 4(3H) one (II) (0.01 mole) and an appropriate aryl amido/imidoalcohol (III) (0.01 mole) were dissolved in conc. H2SO4 by stirring carefully and cautiously. While dissolving the contents were occasionally cooled. A dark solution resulted which were stirred for one hour mechanically and subsequently left as such under refrigeration overnight. It was poured into ice-cold water (250ml) slowly with filtered of and washed with cold water repeatedly in order to remove the sulphonated product. The resultant solid wad dried in vacuo and recrystallized from dilute ethanol. The target compounds

synthesized in this way are recorded in Table-1 alongwith their characterization data.

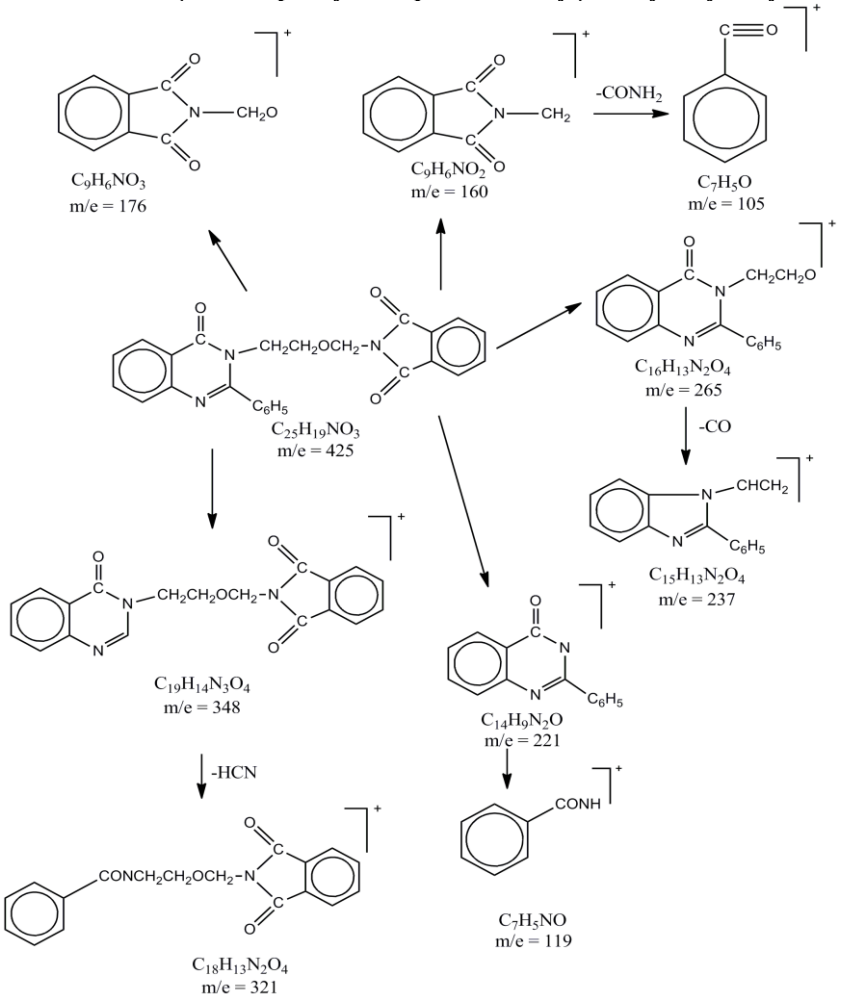


Scheme I: Reactions involving synthesis of the target compounds 2-{[2-(4-oxo-2-phenyl-4H-quinazolin-3-yl)ethoxy]alkyl]aryl amides/imides (IV)

TABLE-1
Characterization data of 2-{[2-(4-oxo-2-phenyl-4H-quinazolin-3-yl)ethoxy] alkyl]aryl amides/imides (IV)

Compd. no.	R	m.p. (°c)	Yield (%)	Molecular formula	Analysis	
					Nitrogen %age	
					Calcd.	Found
IV a	Phthalimidomethyl	138	60	$C_{25}H_{19}N_3O_4$	9.88	9.76
IV b	Phthalimidoethyl	158	65	$C_{26}H_{21}N_3O_4$	9.57	9.64
IV c	Benzamidomethyl	139 - 140	55	$C_{24}H_{21}N_3O_3$	10.52	10.52
IV d	Benzamodobenzyl	193 - 194	45	$C_{30}H_{25}N_3O_3$	8.84	8.74
IV e.	Benzamido-p-methoxybenzyl	162	50	$C_{31}H_{27}N_3O_4$	8.32	8.20

Mass spectral pattern of 2-{[2-(4-oxo-2-phenyl-4H-quinazolin-3-yl)ethoxy]alkyl] aryl amides/imides (IV)



- Mass (FAB): M+425, other spectral peaks are (m/e) 348,321, 265, 237, 221, 119, 160, 105, 176 (Base peak appeared at 265)
- IR (KBr) (in cm-1): 1685 (tert. amido C=O), 1715 (imide C=O), 1644 (C=N), 1077 (C-O-C)
- 1HNMR (DMSO-D6) (in ppm): 7.15-7.86(m, 13H, Ar-H), 5.18 (s, 2H, OCH2N), 3.90 (t, 2H, O-CH2) 3.45 (t, 2H, N-CH2)
- 13CNMR (CDCl3) (In ppm): 72.5, 76.5, 78.4, 115.2, 117.4, 119.1, 121.5, 125.4, 131.2, 135.4, 137.3, 141.7, 170.2, 175.5

IV. BIOLOGICAL ACTIVITY

All the target compounds (IV a-e) were evaluated for their antimicrobial activity against four bacteria viz; Eschericia coli, Pseudomonas aeruginosa, Staphylococcus aureus, and Klebsiella pneumoniae as well as six fungi viz; Candida albicans, Cryptococcus neoformans, Sporothrix schenkii, Trichophyton mentagrophyte, Aspergillus flavus, and Candida paraplosis involving the broth dilution method in vitro, as recommended by NCCLS. Gentamycin and fluconazole were taken as standard drugs for antibacterial and antifungal activity assay of the investigational compounds. Two compounds viz; IV a and IV b showed measurable level of antibacterial activity against Staphylococcus aureus, thus showing the selectivity of activity since other compounds of this category failed to elicit any observable level of antibacterial activity against Escherichia coli, Pseudomonas aeruginosa and Klebsiella Pneumoniae. Only one compound (IV a) showed, antifungal activity against Candida albucans to the moderate level. All other compounds were found less significant against all the six fungi.

V. CONCLUSION

In summary we can say that, we have synthesized some novel antibacterial and antifungal compounds, but only two of them are active as antibacterial and one as antifungal agent. These compounds warrant further study by changing the substituents and introducing some polar active groups. We may

also conclude that the binding capacity and approach of the active molecule to the target cell also depends on the size of the drug molecule and since phthalimidomethyl and phthalimidoethyl are smaller groups as compared to the groups of other target compounds therefore the target compounds with these groups show some antibacterial antifungal activity.

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