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Research Article

SYNTHESIS AND EVALUATION OF SOME MANNICH BASES OF QUINAZOLINONE NUCLEUS

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ABSTRACT

Objective: In the present work, a series of five Mannich bases of quinazolinone nucleus synthesized by treating quinazolinones with various aromatic amines.

Methods: A series of Mannich bases of quinazolinone synthesized by refluxing quinazolinone with anthranilic acid, amine, and formaldehyde in ethanol. The chemical structures of synthesized compounds were confirmed by thin-layer chromatography using the suitable solvent system and characterized by melting point and IR. The compounds screened for their antibacterial activity and antioxidant activity.

Results: Antioxidant activity of the synthesized compounds was done using 2,2-diphenyl-1-picrylhydrazyl (DPPH) radicals scavenging method. Compounds II and III showed values at 53% and 36%, respectively, when compared to that of standard ascorbic acid 24% at 10 µg/ml. Compounds II and IV showed excellent activity against Gram-negative organism *Escherichia coli* using ciprofloxacin as standard.

Conclusion: All the synthesized compounds were screened for antimicrobial activity by cup plate by measuring inhibition zone using *E. coli* at a concentration range of 200–600 mcg/ml, and antioxidant activity was determined by DPPH method.

Key words: Mannich reaction, Quinazolinone, Antimicrobial, 2,2-Diphenyl-1-picrylhydrazyl method.

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INTRODUCTION

Quinazolinone [1,2] is the versatile nitrogen-containing heterocyclic compounds possessing a broad spectrum of biological and pharmacological activities such as analgesic, anti-inflammatory [3], antibacterial [4], diuretic, antihypertensive, antimalarial [5,6], sedative, hypoglycemic, antibiotic, and antitumor. As our interest in the search for biological heterocycles, we sought an unexplored, synthetically accessible heterocyclic template (quinazolinone) [7,8] capable of bearing some potential pharmacophore to elicit and enhance inherent biological activity. Earlier reports [3] have shown that the presence of alkyl, aryl, and heteroaryl group at second and third positions of quinazolinones is beneficial to anti-inflammatory activity [9]. Furthermore, quinazoline-4(3H)-ones substituted at 3rd position with heterocyclic moieties are beneficial to bacterial activities.

Mannich bases [10] have explored in the area of antibacterial and antifungal drugs. Various Mannich bases have shown antimicrobial activity. Given antimicrobial property of quinazoline moiety and Mannich bases, it envisaged that the combined effect of all entities would result in increased antimicrobial activity [11,12]. It has studied that attempts to alkylate simple aldehydes, ketones, and esters may be rendered ineffective by the occurrence of competing for reaction, notably Aldol and Claisen condensation as well as SN_2 and E_2 reactions. Deprotonation of aldehydes, ketones, and esters allows for direct alkylation of these compounds, while deprotonation of dithione derivatives of aldehydes offers an indirect method for replacing the aldehydic proton with alkyl groups.

METHODS

The melting points of the synthesized compounds were determined in open capillary tubes and were uncorrected. IR spectra were recorded using Perkin–Elmer instrument using KBr pellets techniques. Thin-layer chromatography (TLC) was performed using precoated alumina-silica gel GF_{254}, benzene, chloroform, and methanol in the ratio 5:3:2 as the solvent system and UV chamber as the visualizing agent.

General procedure

Synthesis of quinazolinone

Quinazolinone [13] was synthesized from anthranilic acid (2-aminobenzoic acid) 0.01 mole and formamide 0.0015 mole which was heated at 180°C for 4 h and cooled. The solid product thus obtained was broken up and recrystallized from hot water.

Synthesis of Mannich bases

Mannich bases [14] was synthesized from a mixture of quinazolinone 0.01 mole, various aromatic amines (as shown in Table 1) 0.01 mole, and formaldehyde 1.62 ml in ethanol 15 ml and refluxed for 4 h. It was then poured on to the crushed ice for cooling. The precipitated solid was filtered and recrystallized from aqueous ethanol.

Scheme of work

1. Condensation, at 180°C for 4 h
2. Cyclization
3. Mannich reaction with HCHO and Ar-NH_2.

Physical data of synthesized compounds (I to V)

Compound I 4-((4-oxoquinazolin-3(4H)-yr)methylaminobenzoic acid

Yield 57%, melting point 133-135˚c, IR (KBr, cm^{-1}) 3368.86 (quinazolinone ring, quinolineringAr-NH), 1011.71 (aliphatic C-N stretching), 1676.90 (Ar C=C stretching), 1250.16 (Ar C–N stretching), 1519.29 (Ar COOH stretching).

Compound II 3-((4-hydroxyphenylamino)methyl) quinazoline-4(3H)-one

Yield 69%, melting point 84-86°C, infrared (IR) (KBr, cm^{-1})3061.54 (quinazolinone ring, quinoline ring Ar-NH), 1037.14(Aliphatic C-N stretching), 1612.97 (Ar C=C stretching), 1260.45 (Ar C–N stretching), 3370.30 (Ar OH stretching).

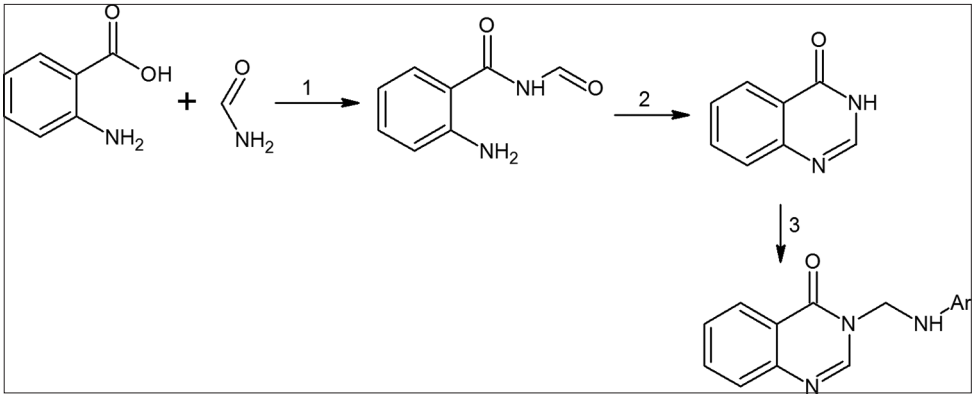
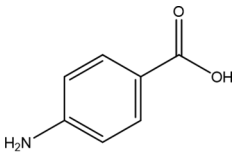
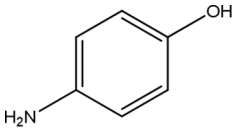
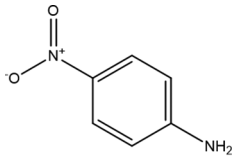
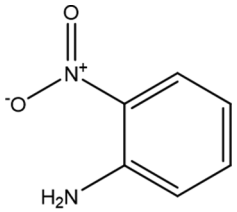
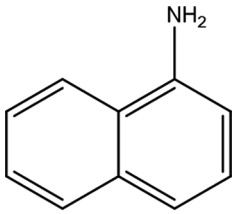


Table 1: Various aromatic amines used

Compound	Name of the aromatic amine	Ar-NH_2
I	p-aminobenzoic acid	 p-amino benzoic acid
II	4- aminophenol	 4- amino phenol
III	p- nitroaniline	 p- nitro aniline
IV	o- nitroaniline	 o- nitro aniline
V	1-naphthylamine	 1-naphthylamine

Compound III 3-((4-nitrophenylamino)methyl) quinazoiln-4(3H)-one

Yield62%, melting point 122-124°C, IR (KBr, cm^{-1}) 3364.54 (quinazolinone ring, quinoline ring Ar-NH), 1186.37 (aliphatic C-N stretching), 1599.74 (Ar C=C stretching), 1263.79 (Ar C–N stretching), 1530.49 (Ar NO_2 stretching).

Table 2: Results of antimicrobial activity

Concentration in μg/ml	Zone of inhibition in mm					
	M_1	M_2	M_3	M_4	M_5	Ciprofloxacin
200	10	11	10	11	10	11
400	11	13	11	12	11	12
600	13	14	12	14	12	14

Table 3: Results of antioxidant activity

Compound	Concentration/% inhibition			
	10 μg/ml	20 μg/ml	30 μg/ml	40 μg/ml
I	12.9	42	56	74
II	53	67.2	75.2	83
III	36	51.2	65	85.7
IV	34.5	24	63.5	88
V	33	35	44	87
Ascorbic acid	24	48	63	88

Compound IV 3-((2-nitrophenylamino)methyl) quinazoiln-4(3H)-one

Yield 65%, melting point 112-114°C, IR (KBr, cm^{-1}) 3373.33 (quinazolinone ring, quinoline ring Ar-NH), 1155.32 (aliphatic C-N stretching), 1618.86 (Ar C=C stretching), 1340.01 (Ar C–N stretching), 1503.81 (Ar NO_2 stretching).

Compound V 3-((naphthalen-1-ylamino)methyl) quinazoiln-4(3H)-one

Yield 65%, melting point 153-155°C, IR (KBr, cm^{-1}) 3206.06 (quinazolinone ring, quinoline ring Ar-NH), 1226.72 (aliphatic C-N stretching), 1659.99 (Ar C=C stretching), 1371.66 (Ar C–N stretching).

Antimicrobial activity

In vitro antibacterial activity of the synthesized compounds, I to V, were evaluated by cup-plate method against the bacterial strain *E. coli* using agar media at the concentration range of 200–600 μg/ ml. A control experiment was carried out under similar condition using ciprofloxacin as standard. The turbidimetric method was used to check the antibacterial activity of the synthesized compounds at different concentration using ciprofloxacin as the positive control and dimethylformamide as the negative control. The zone of inhibition was measured which showed all the synthesized compounds showed better inhibition as compared to the standard. The values are tabulated in Table 2.

Table 4: Physicochemical parameters of the synthesized compounds

Compound code	% yield	Melting point °C	Molecular formula	Molecular weight	Rf value
M1	57	133-135	$C_7H_7NO_2$	137.14	0.72
M2	69	84-86	C_6H_7NO	109.13	0.69
M3	62	122-124	$C_6H_6N_2O_2$	138.13	0.83
M4	65	112-114	$C_6H_6N_2O_2$	138.13	0.83
M5	64	153-155	$C_{10}H_7NH_2$	143.19	0.74

Anti oxidant activity

Determination of 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging activity

The DPPH assay method is based on the reduction of DPPH, a stable free radical. The free radical DPPH with an odd electron gives a maximum absorption at 517 nm (purple color).

When antioxidants react with DPPH, which is a stable free radical it becomes paired off in the presence of a hydrogen donor, and as a consequence, the absorbance decreased from the DPPH radical to the DPPH-H form, resulting in decolorization (yellow color) with respect to the number of electrons captured. The lower absorbance of the reaction mixture indicates higher free radical scavenging activity.

Preparation of DPPH

0.1 g of DPPH dissolved in 50 ml of methanol. Pipette out 1 ml of the solution and dilute to 10 ml with methanol. Pipette out 10 ml and dilute to 50 ml with methanol (20 µg/ml).

Preparation of stock solution

Take of 0.1 g of the sample and dissolve in 100 ml of the methanol (1000 µg/ml).

Procedure

Take 1, 2, 3, 4, and 5 ml of the stock solution and dilute with methanol to get concentrations of 50, 40, 20, and 10 µg/ml, respectively. Add 6 ml of the prepared DPPH to the resulting solution. Incubate the reaction mixture at room temperature for 30 min. The absorbance of the reaction mixture read at 517 nm. Ascorbic acid used as the standard. The percentage of free radical scavenging calculated and the results are tabulated in Table 3.

RESULTS AND DISCUSSION

A novel series of I to V derivatives have been synthesized and screened for their *in vitro* antibacterial and antioxidant activities. The results of the physical data of the final synthesized compounds are presented in Table 4.

The antibacterial activity results revealed that all compounds showed a significant activity against bacterial strain *E. coli*. Compounds II and IV showed excellent activity against Gram-negative organism *E. coli*. In the antioxidant activity, compounds II and III showed a highly significant activity which was comparable with the standard drug ascorbic acid. The results are presented in Tables 2 and 3.

The structures of the newly synthesized compounds were established on the basis of spectral data and elemental analysis. The compounds were purified by recrystallization from appropriate solvents. The completions of the reactions were monitored by TLC. The antibacterial activity of the compounds showed excellent activity against *E. coli*. The compounds also displayed significant antioxidant activity.

CONCLUSION

Further studies can be done to get biologically more useful compounds in this series. The antioxidant activity of all the synthesized compounds showed moderate activity.

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AUTHORS CONTRIBUTIONS

All authors contributed equally to this work.

CONFLICT OF INTERESTS

Declared none.

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