SYNTHESIS AND EVALUATION OF SOME MANNICH BASES OF QUINAZOLINONE NUCLEUS

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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 quinazolines is beneficial to antibacterial 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 [1,12]. 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 SN2 and E2 reactions. Deutronation 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 GF254 benzene, chloroform, and methanol in the ratio 5:3:2 as the solvent system and UV chamber as the visualizing agent.
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**Table 1: Various aromatic amines used**

| Compound | Name of the aromatic amine | Ar-NH₂ |
|----------|----------------------------|--------|
| I        | p-aminobenzoic acid        |        |
| II       | 4-aminophenol              |        |
| III      | p-nitroaniline             |        |
| IV       | o-nitroaniline             |        |
| V        | 1-naphthylamine            |        |

**Table 2: Results of antimicrobial activity**

| Concentration in µg/ml | Zone of inhibition in mm M₁ | M₂ | M₃ | M₄ | M₅ | Ciprofloxacin |
|------------------------|-------------------------------|----|----|----|----|--------------|
| 200                    | 10                            | 11 | 10 | 10 | 10 | 11           |
| 400                    | 11                            | 12 | 11 | 11 | 12 | 12           |
| 600                    | 13                            | 14 | 14 | 14 | 14 | 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 III 3-((4-nitrophenylamino)methyl) quinazolin-4(3H)-one**

Yield 62%, 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 NO₂ 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.

**Compound IV 3-((2-nitrophenylamino)methyl) quinazolin-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 NO₂ stretching).

**Compound V 3-((naphthalen-1-ylamino)methyl) quinazolin-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), 1571.66 (Ar C–N stretching).
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.

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_9H_8NO_2        | 137.14           | 0.72    |
| M2            | 69      | 84-86            | C_9H_8NO         | 109.13           | 0.69    |
| M3            | 62      | 122-124          | C_9H_8N_2O       | 138.13           | 0.83    |
| M4            | 65      | 112-114          | C_9H_8N_2O       | 130.13           | 0.83    |
| M5            | 64      | 153-155          | C_9H_8N_3H       | 143.19           | 0.74    |

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AUTHORS CONTRIBUTIONS

All authors contributed equally to this work.

CONFLICT OF INTERESTS

Declared none.

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