SYNTHESIS AND INVESTIGATION OF ANTHELMINTIC, ANTIBACTERIAL AND ANTIFUNGAL ACTIVITY OF 3,3-DIPHENYL PROPANAMIDE DERIVATIVES

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INTRODUCTION

Inadequate novel antimicrobial agents and elevating bacterial resistance toward antimicrobials are a predominant topic in the field of drug development and studies [1,2]. Microbial infections have proliferated unexpectedly in the past 20 years due to antimicrobial resistance, intensification in impaired immune system patients due to HIV, cancer chemotherapy, and organ transplantation worldwide [3,4]. Despite noteworthy approach in the field of antimicrobial therapy, the increase in consumption and misuse of antibiotics have caused the emergence of bacterial resistance toward antibiotics [5,6]. In the present scenario, health problems demand to synthesize and investigate a novel class of antimicrobial agent proved to be active against microbes that are resistant toward currently used antibiotics [7]. Therefore, considering the pharmacological potential of arylopropionic acid derivatives [8-12], novel derivatives of substituted 3,3-diphenyl propionic acid were synthesized and investigated for their antibacterial, antifungal, and anthelmintic activity against housefly worms and earthworm species.

Experimental Chemistry

General

Melting points were determined by the open capillary method and were uncorrected. IR spectra were recorded on a Shimadzu 8700 Fourier-transform infrared spectrophotometer (Shimadzu, Japan) using KBr pellets. Nuclear magnetic resonance (1H-NMR) was recorded on a Bruker AC NMR spectrometer (300 MHz), (Bruker, USA) using CDCl3 as a solvent. Purity of all compounds was checked by thin-layer chromatography on pre-coated silica gel G plates (Kieselgel 0.25 mm, 60G F254, Merck, Germany) using petroleum ether/ethyl acetate as a solvent. Purity of all compounds was checked by thin-layer chromatography on pre-coated silica gel G plates (Kieselgel 0.25 mm, 60G F254, Merck, Germany) using petroleum ether/ethyl acetate as a solvent. Purity of all compounds was checked by thin-layer chromatography on pre-coated silica gel G plates (Kieselgel 0.25 mm, 60G F254, Merck, Germany) using petroleum ether/ethyl acetate as a solvent. Purity of all compounds was checked by thin-layer chromatography on pre-coated silica gel G plates (Kieselgel 0.25 mm, 60G F254, Merck, Germany) using petroleum ether/ethyl acetate as a solvent. Purity of all compounds was checked by thin-layer chromatography on pre-coated silica gel G plates (Kieselgel 0.25 mm, 60G F254, Merck, Germany) using petroleum ether/ethyl acetate as a solvent. Purity of all compounds was checked by thin-layer chromatography on pre-coated silica gel G plates (Kieselgel 0.25 mm, 60G F254, Merck, Germany) using petroleum ether/ethyl acetate as a solvent. Purity of all compounds was checked by thin-layer chromatography on pre-coated silica gel G plates (Kieselgel 0.25 mm, 60G F254, Merck, Germany) using petroleum ether/ethyl acetate as a solvent. Purity of all compounds was checked by thin-layer chromatography on pre-coated silica gel G plates (Kieselgel 0.25 mm, 60G F254, Merck, Germany) using petroleum ether/ethyl acetate as a solvent. Purity of all compounds was checked by thin-layer chromatography on pre-coated silica gel G plates (Kieselgel 0.25 mm, 60G F254, Merck, Germany) using petroleum ether/ethyl acetate as a solvent. Purity of all compounds was checked by thin-layer chromatography on pre-coated silica gel G plates (Kieselgel 0.25 mm, 60G F254, Merck, Germany) using petroleum ether/ethyl acetate as a solvent. Purity of all compounds was checked by thin-layer chromatography on pre-coated silica gel G plates (Kieselgel 0.25 mm, 60G F254, Merck, Germany) using petroleum ether/ethyl acetate as a solvent. Purity of all compounds was checked by thin-layer chromatography on pre-coated silica gel G plates (Kieselgel 0.25 mm, 60G F254, Merck, Germany) using petroleum ether/ethyl acetate as a solvent. Purity of all compounds was checked by thin-layer chromatography on pre-coated silica gel G plates (Kieselgel 0.25 mm, 60G F254, Merck, Germany) using petroleum ether/ethyl acetate as a solvent. Purity of all compounds was checked by thin-layer chromatography on pre-coated silica gel G plates (Kieselgel 0.25 mm, 60G F254, Merck, Germany) using petroleum ether/ethyl acetate as a solvent. Purity of all compounds was checked by thin-layer chromatography on pre-coated silica gel G plates (Kieselgel 0.25 mm, 60G F254, Merck, Germany) using petroleum ether/ethyl acetate as a solvent. Purity of all compounds was checked by thin-layer chromatography on pre-coated silica gel G plates (Kieselgel 0.25 mm, 60G F254, Merck, Germany) using petroleum ether/ethyl acetate as a solvent. Purity of all compounds was checked by thin-layer chromatography on pre-coated silica gel G plates (Kieselgel 0.25 mm, 60G F254, Merck, Germany) using petroleum ether/ethyl acetate as a solvent. Purity of all compounds was checked by thin-layer chromatography on pre-coated silica gel G plates (Kieselgel 0.25 mm, 60G F254, Merck, Germany) using petroleum ether/ethyl acetate as a solvent. Purity of all compounds was checked by thin-layer chromatography on pre-coated silica gel G plates (Kieselgel 0.25 mm, 60G F254, Merck, Germany) using petroleum ether/ethyl acetate as a solvent. Purity of all compounds was checked by thin-layer chromatography on pre-coated silica gel G plates (Kieselgel 0.25 mm, 60G F254, Merck, Germany) using petroleum ether/ethyl acetate as a solvent. Purity of all compounds was checked by thin-layer chromatography on pre-coated silica gel G plates (Kieselgel 0.25 mm, 60G F254, Merck, Germany) using petroleum ether/ethyl acetate as a solvent.
reaction scheme is depicted in Scheme 1, and spectral characteristics of the synthesized derivatives are listed in Table 2.

**Biological screening**

**Anthelmintic activity**

**Collection of Stomoxys calcitrans and earthworms**

Houseflies (S. calcitrans) were trapped in a perforated sterile jar from recycling and waste disposable house of Moradabad Educational Trust Group of Institutions, Faculty of Pharmacy, Moradabad, Uttar Pradesh, India, and authentication was accomplished by Mr. Ramesh Kumar Gupta (Asst. Professor, Department of Pharmacology). The earthworms were collected from the soil of riverside at Ram Ganga Vihar, Moradabad, Uttar Pradesh, India.

**Housefly worm medium preparation**

The medium was prepared by adding (1.2 g) of beef extract powder in nutrient agar medium and pH was adjusted to 7.2 and sterilized in an autoclave (GPC Medical Ltd., Model AU201) at 121°C for 15 min. Amoxicillin (100 μg/mL) and clotrimazole (75 μg/mL) were added to the medium to prevent the growth of microbes. 20 mL/Petri dish of sterilized media were transferred to 60 Petri dishes and secured for solidification. Five matured female houseflies were placed inside the Petri dishes which were closed immediately and kept at room temperature. After 24 h, white colors eggs were hatched out by flies and died flies were removed. The Petri dishes were further cultured for the next 72 h evolving for the appearance of house fly worms. On generation of housefly worms, 20 worms from each dish were collected and weighed precisely in analytical balance to calculate the average weight of worm that was found to be 0.012 mg.

**Preparation of drug solutions**

Standard drug and compounds (I-VIII) were evaluated for anthelmintic potential at a concentration of 50 mg/mL and 100 mg/mL using 0.5% aq. solution of Tween 80 as a solvent.

**Arraying of housefly worms**

The cultured Petri dishes containing twenty S. calcitrans worms each were selected for anthelmintic activity [13], and dishes were categorized into different groups as follows. Group-A: Marked as (ABZ) for albendazole, consisting of 4 Petri dishes having 50 mg/mL, and other 4 different Petri dishes having 100 mg/mL concentrations of albendazole. Group-(B-I): Marked as I, II, III, IV, V, VI, VII, and VIII, respectively, consisting of 4 Petri dishes/concentrations of synthesized compounds similar to the concentrations of albendazole. Group-J:

| Compound | R      | M.P. (°C) | % yield | Mol. weight (g/mol) | Rf value |
|----------|--------|-----------|---------|--------------------|----------|
| I        |        | 138–140   | 65      | 329                | 0.69     |
| II       |        | 120–121   | 62      | 315                | 0.73     |
| III      |        | 67–68     | 61      | 315                | 0.84     |
| IV       |        | 98–99     | 67      | 353.78             | 0.59     |
| V        |        | 110–112   | 63      | 335.79             | 0.65     |
| VI       |        | 68–70     | 60      | 297.29             | 0.75     |
| VII      |        | 108–109   | 61      | 373.29             | 0.86     |
| VIII     |        | 126–128   | 65      | 363.29             | 0.77     |
Scheme 1: Synthesis of 3,3-diphenyl propanamide derivatives. Reagent and condition (a) amines dissolved in diethyl ether and amino acid dissolved in 10% aq. NaOH.

Marked as a control having 0.5% aq. solution of Tween 80, used in the same concentration as mentioned in the above two groups.

Estimation of anthelmintic activity with housefly worms

In each of the 8 Petri dishes/group, well having 1 cm diameter was bored with a borer at the center and for Group-A, 50 mg/mL of albendazole solution was poured in the well of first four Petri dishes of this group followed by adding 100 mg/mL of the same in last four Petri dishes of this group. The same technique was followed for pouring the solution of synthesized compounds (I-VIII) in their respective Groups-(B-I) along with Group-J, marked as a control. All the Petri dishes were incubated at 37°C. The worms were evaluated for motility. This was done after tapping the edges of Petri dishes and allowing the worms to move freely toward the well, the worms that were alive would be seen moving. After paralysis, the worms were not able to show any motion which can be observed clearly by eyes. The unparalyzed worms were trapped toward the well, and incubation process was carried out again. Group-J, Petri dishes worms were viable for approximately 15 days with no sign of paralysis and death. The results are enlisted in Table 3.

Estimation of anthelmintic activity using earthworm species

Anthelmintic activity studies for synthesized derivatives were carried out against three different species of earthworms, Megascolex konkanensis (ICARBC 211), Pontoscolex corethruses (ICARBC 117), and Eudrilus eugeniea (ICARBC 042) following Garg and Atal method [14-17] at concentration of 50 mg/mL and 100 mg/mL, respectively, using 0.5% aq. solution of Tween 80. Three sets of Petri dishes with 4-inch diameter containing five earthworms of almost similar sizes/species (2 inches in length) in each set were prepared followed by categorization into three groups. Group-A: Marked as (ABZ) for albendazole having three sets (with respect to two different concentrations) each of three Petri dishes with three different earthworm species. Group-(B-I): Marked as I, II, III, IV, V, VI, VII, and VIII, respectively, having three sets (with respect to two different concentrations) each of the Petri dishes with five different earthworm species and Group-K: Marked as (C) for control having three sets (with respect to two different concentrations) each of three Petri dishes with five different earthworm species. The paralyzing and death time were noted, and their mean was calculated for each set. The death time was ascertained by placing the earthworms in warm water (50°C) which stimulated the movement if the worm was alive. The results are presented in Table 4.

Antibacterial and antifungal studies

The synthesized compounds (I-VIII) were screened for their antimicrobial activity by cup-plate diffusion method using the MHA medium [18-20]. The microorganisms selected for antibacterial activity were Bacillus subtilis (NCIM 2063), Staphylococcus aureus (NCIM 2079), Pseudomonas aeruginosa (NCIM 2034), and Escherichia coli (NCIM 2065) and fungal strains Candida albicans (MUCC 29), Aspergillus niger (MUCC 29), Microsporum audouinii (MUCC 545), and Trichophyton mentagrophytes (MUCC 665) were selected for antifungal activity. The synthesized compounds were tested at a concentration of 50 μg/mL. Ciprofloxacin for antibacterial activity and griseofulvin for antifungal activity were used as standard drugs at a concentration of 50 μg/mL. The results of antibacterial and antifungal studies were presented in Tables 5 and 6, respectively.

RESULTS AND DISCUSSION

The described research work comprises the synthesis of novel 3,3-diphenyl propanamide derivatives. All the structures of novel synthesized derivatives were confirmed by IR and 1H-NMR spectral.
Table 2: Spectral characteristics of synthesized compounds

| Compound | IR (KBr, ν, cm⁻¹), H-NMR (300 MHz, CDCl₃, δ, ppm) |
|----------|-------------------------------------------------|
| I        | 3500–3350 (N-H str.), 1600–1450 (C=O str.), 900–700 (C-H def.), 1690 (C=O), 1280–1278 (C-N str.), 710–690 (C-H def.), 6.8–7.2 (m, 3H, Ar-H), 7.31 (s, 1H, NH), 2.18 (2H, CH2), 2.41 (s, 3H, CH3), 4.68 δ (s, 1H, CH), 2.26 (s, 3H, CH3), 7.40 (s, 1H, -CONH) |
| II       | 3040–3000 (C-H aromatic str.), 1600–1550 (C=C str.), 900–720 (C-H def.), 1682 (C=O), 3325 (NH str., amide), 6.8–7.2 (m, 15H, Ar-H), 7.31 (s, 1H, NH), 2.18 (s, 2H, CH2), 4.68 (s, 1H, CH), 4.46 (s, 2H, CH2), 7.20 (s, 1H, -CONH) |
| III      | 1690 (C=O), 1577–1495 (C=C str.), 3450–3300 (N-H str.), 3000 (C-H str.), 2.35 (s, 3H, CH3), 7.70 (s, 1H, -CONH), 6.5–7.5 (m, 14H, Ar-H), 7.25 (s, 1H, NH), 4.52 (s, 2H, CH2) |
| IV       | 1639 (C=O str., amide), 1529 (N-H bend, amide), 880–750 (C-H def.), 1670 (C=O), 6.2–7.5 (m, 13H, Ar-H), 4.52 (s, 1H, CH), 4.56 (s, 2H, CH2), 8.0 (s, 1H, NH), 7.30 (s, 1H, -CONH) |
| V        | 3400–3350 (N-H str.), 880–750 (C-H def.), 1670 (C=O), 6.3–7.0 (m, 14H, Ar-H), 7.8 (s, 1H, NH), 4.25 (s, 1H, CH), 4.42 (s, 2H, CH2), 7.65 (s, 1H, -CONH) |
| VI       | 3500–3350 (N-H str.), 3050–3000 (C-H aromatic str.), 1600–1450 (C=C str.), 900–720 (C-H def.), 1690 (C=O), 3000–2500 (OH str.), 7.9 (s, 1H, NH), 4.28 (s, 1H, CH), 4.35 (s, 2H, CH2), 7.60 (s, 1H, -CONH), 11.0 (s, 1H, OH) |
| VII      | 1680 (C=O), 2995–2650 (OH str.), 3500–3330 (N-H str.), 4.64 (s, 1H, CH), 10.75 (s, 1H, OH), 1.43 (s, 3H, CH3), 7.40 (s, 1H, -CONH), 2.00 (s, 1H, CH), 8.10 (s, 1H, NH), 6.5–7.0 (m, 10H, Ar-H) |
| VIII     | 1675 (C=O str.), 1280–1275 (C=N str.), 3000–2500 (O-H str.), 1600–1455 (C=C str.), 11.0 (s, 1H, OH), 7.50 (s, 1H, -CONH), 8.10 (s, 1H, NH), 7.10–7.16 (m, 10H, Ar-H), 4.25 (s, 2H, CH2) |

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Table 3: Anthelmintic activity of compounds against housefly worms

| Group | Concentration (mg/mL) | Mean paralyzing time (min) | Mean death time (min) |
|-------|-----------------------|---------------------------|----------------------|
| A (ABZ) | 50 | 25.0±0.32 | 36.1±0.14 |
| B (I) | 50 | 24.2±0.13 | 35.0±0.11 |
| C (II) | 50 | 24.2±0.12 | 35.0±0.12 |
| D (III) | 50 | 24.2±0.13 | 35.0±0.13 |
| E (IV) | 50 | 24.2±0.14 | 35.0±0.15 |
| F (V) | 50 | 24.2±0.15 | 35.0±0.16 |
| G (VI) | 50 | 24.2±0.16 | 35.0±0.17 |
| H (VII) | 50 | 24.2±0.17 | 35.0±0.18 |
| I (VIII) | 50 | 24.2±0.18 | 35.0±0.19 |
| J (C) | 50 | 24.2±0.20 | 35.0±0.21 |

The results in Table 4 revealed the anthelmintic potential of synthesized compounds against earthworm species. The standard drug, albendazole in three earthworm species, namely M. konanensis, P. corethruses, and E. eugeniea at dose of 50 and 100 mg/mL caused paralysis at 12.32±0.40, 10.34±0.22, 13.10±0.11, 12.15±0.12, and 10.54±0.10 min and death at 17.02±0.10, 14.10±0.25, 16.11±0.12, 14.35±0.22, 16.45±0.14, and 14.1±0.20 min, respectively. The compounds VII and VIII in the same three earthworm species at a dose of 50 and 100 mg/mL declined the time of paralysis and death compared to that of albendazole. Therefore, it can be concluded that compounds VII and VIII are more effective anthelmintic agents than albendazole.

All the synthesized compounds (I-VIII) at a dose of 50 µg/mL were screened for their antibacterial and antifungal activity by the cup-plate diffusion method using ciprofloxacin and griseofulvin as a standard drug at the same dose of 50 µg/mL. The results of antibacterial in Table 5 expressed that all the compounds exhibited moderate to good activity against Gram-negative bacterial strains (E. coli and P. aeruginosa) and minimal potential against Gram-positive bacterial strains (S. aureus and E. faecalis). The compounds IV, VII, and VIII represented 4.5–13.6% higher activity against E. coli and 10–30% higher activity against P. aeruginosa in comparison to ciprofloxacin. Hence, it can be concluded that these derivatives exhibited maximum activity.
activity against Gram-negative bacterial strains as compared to the standard drug. Table 6 expressed the results of antifungal activity of synthesized compounds and results revealed that all the compounds were more active against \( C.\ albicans \) and \( A.\ niger \) in comparison with \( M.\ audouinii \) and \( T.\ mentagrophytes \) and the compounds IV, VII, and VIII, exhibited 5-20\% higher activity than griseofulvin against \( C.\ albicans \) and 15.78–31.5\% higher activity against \( A.\ niger \) in comparison with standard drug griseofulvin.

**Table 6: Antifungal activity of compounds**

| Compound | Diameter of the zone of inhibition (mm) |
|----------|----------------------------------------|
|           | Candida albicans | Microsporum audouinii | Aspergillus niger | Trichophyton mentagrophytes |
| I        | 18              | 16                      | 16               | 15                        |
| II       | 17              | 14                      | 15               | 17                        |
| III      | 19              | 17                      | 18               | 13                        |
| IV       | 21              | 16                      | 22               | 19                        |
| V        | 20              | 17                      | 17               | 16                        |
| VI       | 18              | 15                      | 18               | 18                        |
| VII      | 22              | 17                      | 24               | 20                        |
| VIII     | 24              | 17                      | 25               | 20                        |
| Control  | -               | -                       | -                | -                         |
| Griseofulvin | 20            | 18                      | 19               | 21                        |

**CONCLUSION**

This research demonstrated the synthesis of substituted 3,3-diphenyl propanamide derivatives. Anthelmintic activity was evaluated using housefly worms method and earthworm species model. The results of anthelmintic studies indicated good level of activity. The derivatives bearing amino acid moiety in the structure exhibited maximum anthelmintic, antibacterial, and antifungal activity. However, one fluoro, chloro substituted derivative represented maximum antibacterial and...
antifungal activity in comparison with a standard drug. The findings suggested that amino acids derivatives of 3,3-diphenyl propanamide have magnificent future scope for further design and discovery as effective anthelmintics and antimicrobial agents.

**AUTHOR’S CONTRIBUTION**

The research methodologies were designed by Sachin Chaudhary and synthesis of the derivatives was performed by Harish Chandra Verma, Mandeep Kumar Gupta, and Sachin Chaudhary. The biological screening was performed by Ramesh Kumar Gupta. Amit Kumar and Abdel-Nasser El-Shorbagi contributed in designing of the manuscript.

**CONFLICTS OF INTEREST**

The authors have no conflicts of interest during the research.

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