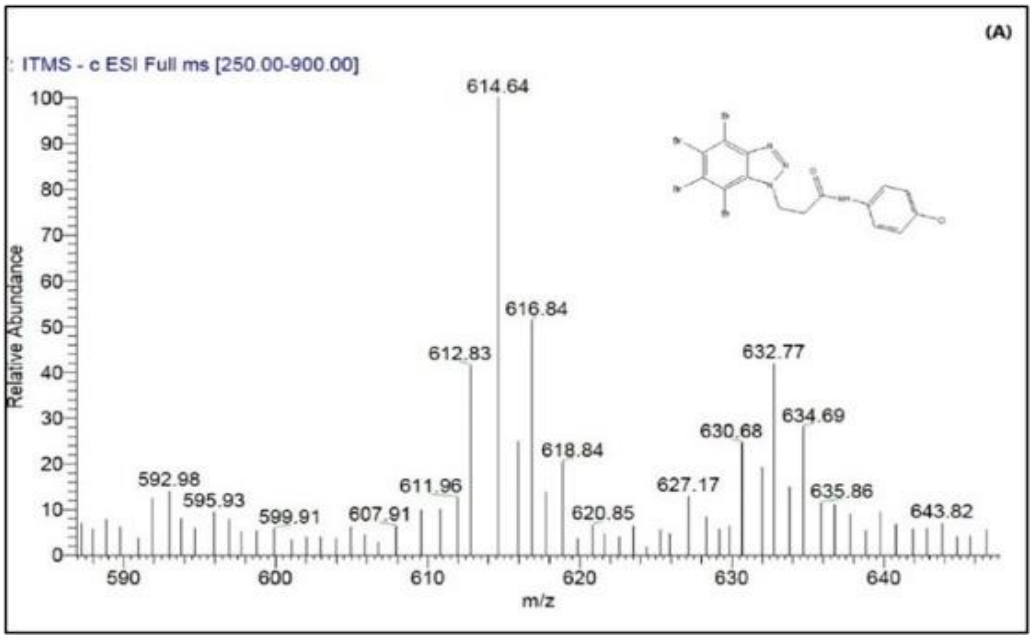


Figure 1

Dated this the 5th day of March, 2025

Sushil Kumar [IN/PA/1132]
ACCURES LEGAL
Plot No. 15, Sai Enclave, Sector 23,
Dwarka, New Delhi – 110 077, India



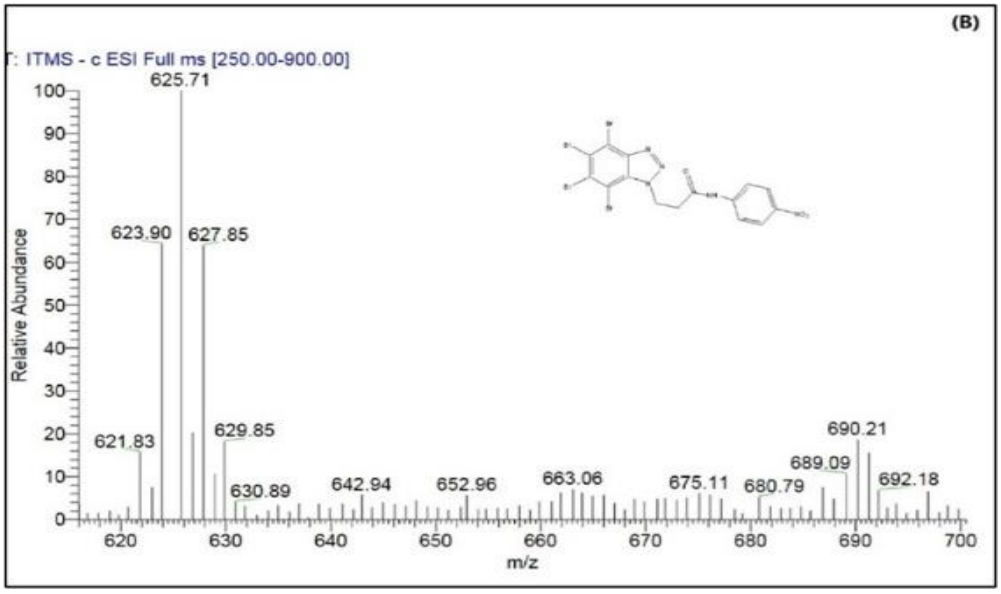


Figure 2 (A-B)

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Sushil Kumar [IN/PA/1132]
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Plot No. 15, Sai Enclave, Sector 23,
Dwarka, New Delhi – 110 077, India

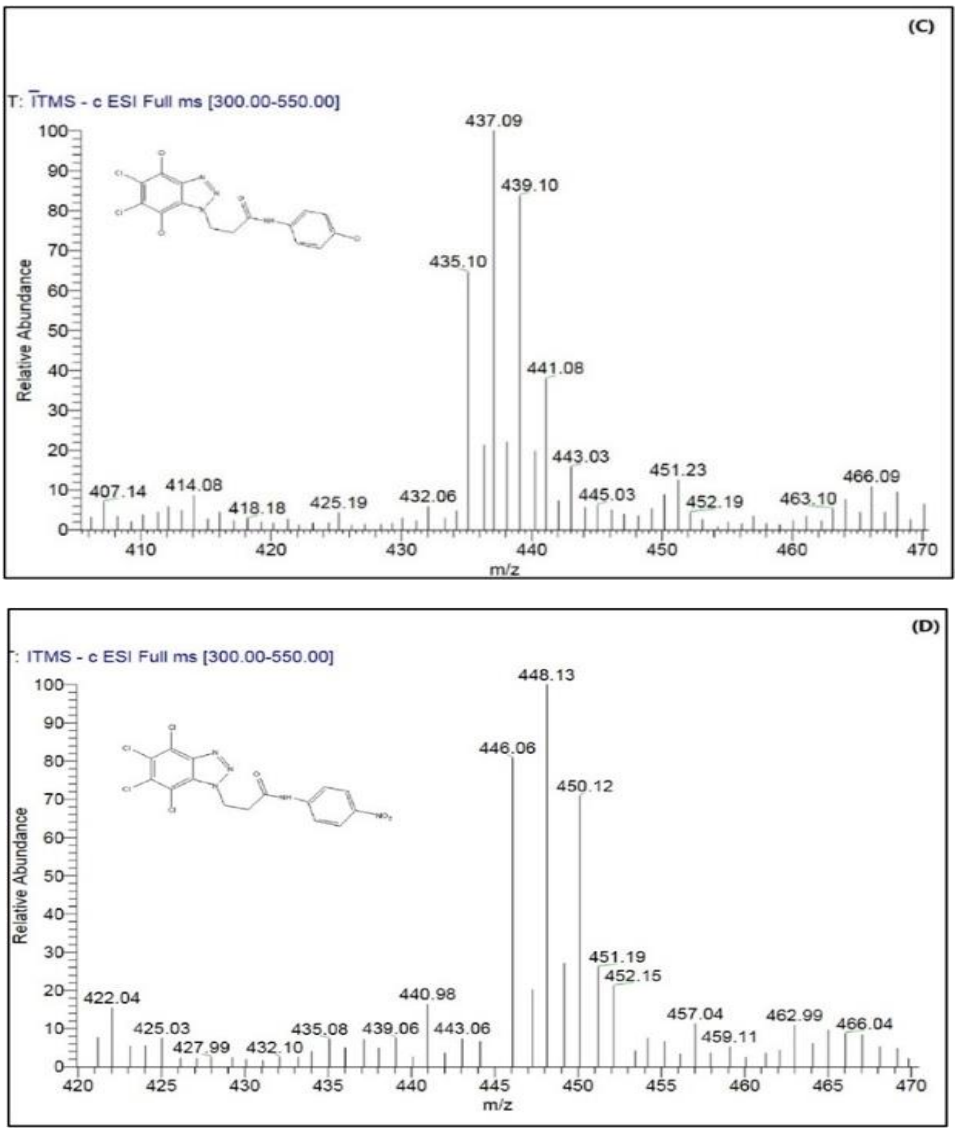
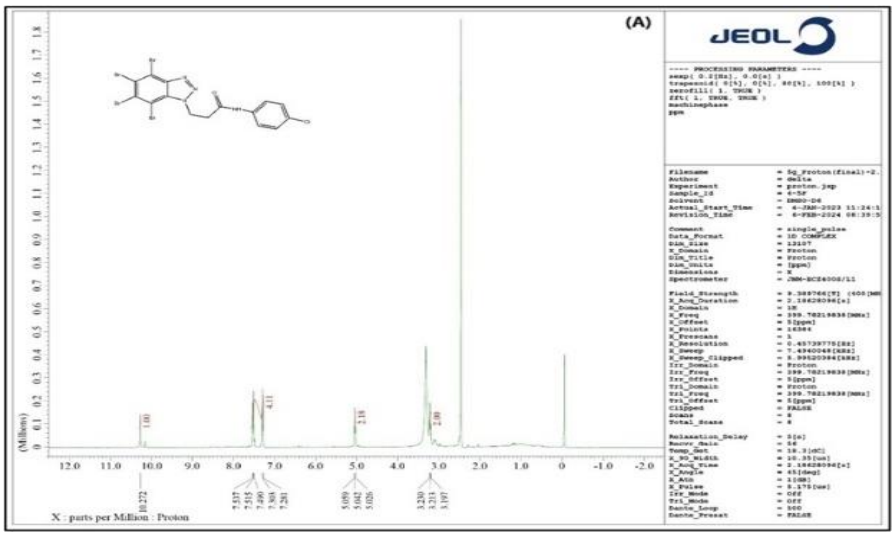


Figure 2 (C-D)

Dated this the 5th day of March, 2025

Sushil Kumar [IN/PA/1132]
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Plot No. 15, Sai Enclave, Sector 23,
Dwarka, New Delhi – 110 077, India



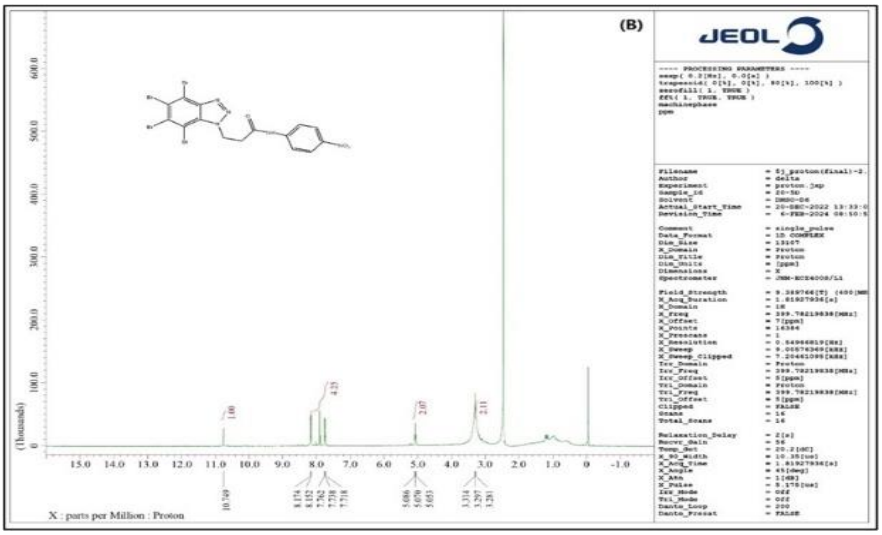
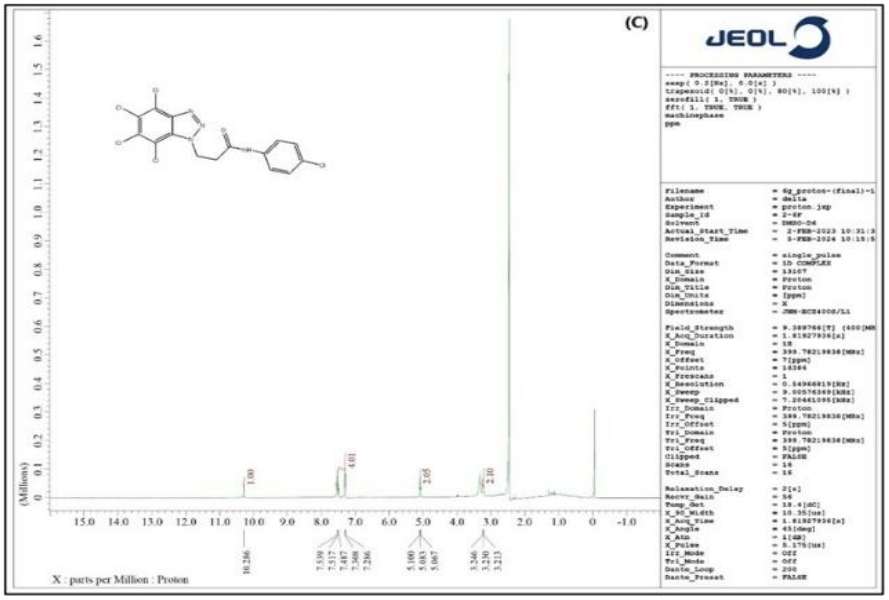


Figure 3 (A-B)

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Plot No. 15, Sai Enclave, Sector 23,
Dwarka, New Delhi – 110 077, India



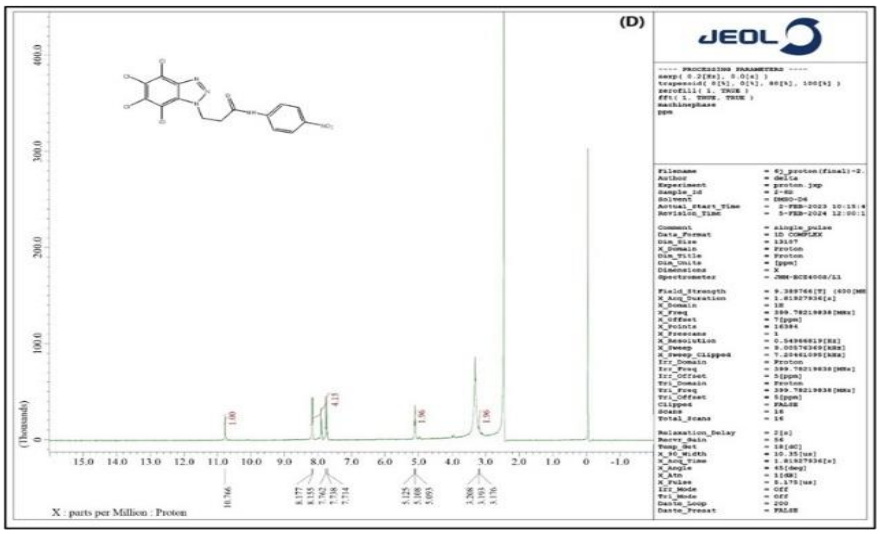
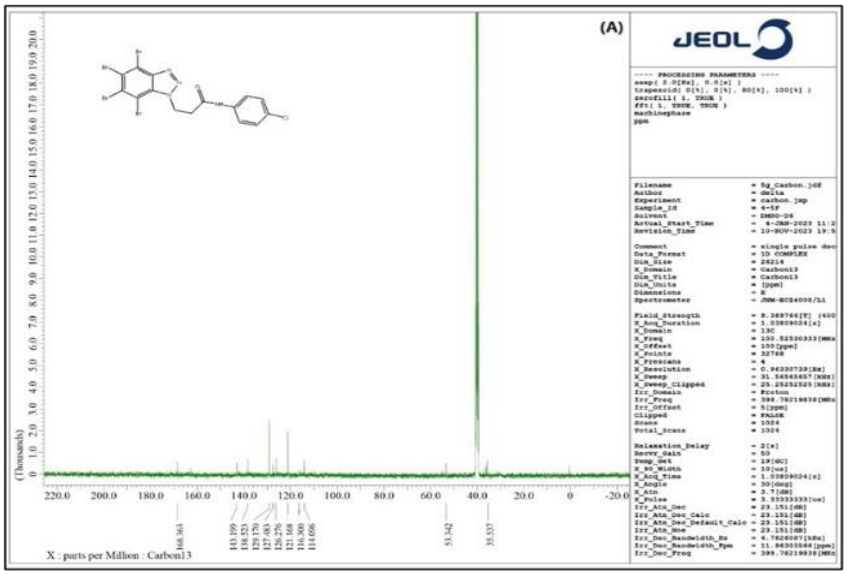


Figure 3 (C-D)

Dated this the 5th day of March, 2025

Sushil Kumar [IN/PA/1132]
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Plot No. 15, Sai Enclave, Sector 23,
Dwarka, New Delhi – 110 077, India



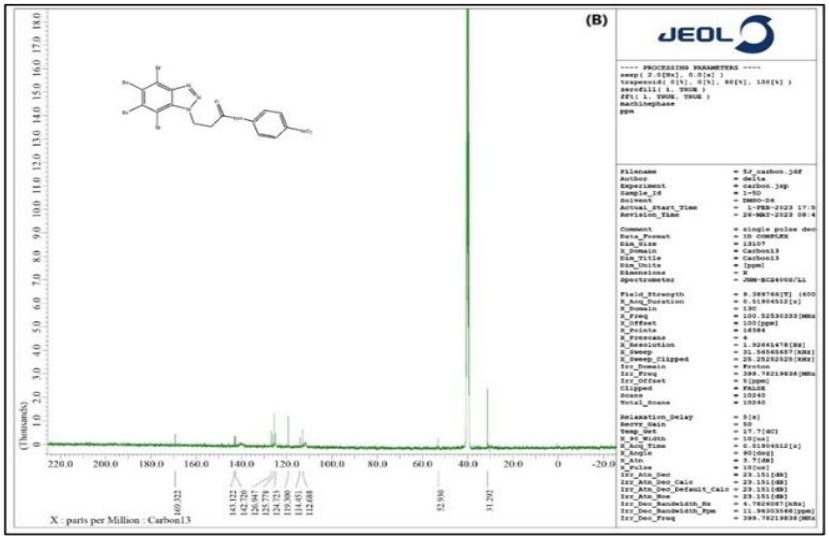


Figure 4 (A-B)

Dated this the 5th day of March, 2025

Sushil Kumar [IN/PA/1132]
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Plot No. 15, Sai Enclave, Sector 23,
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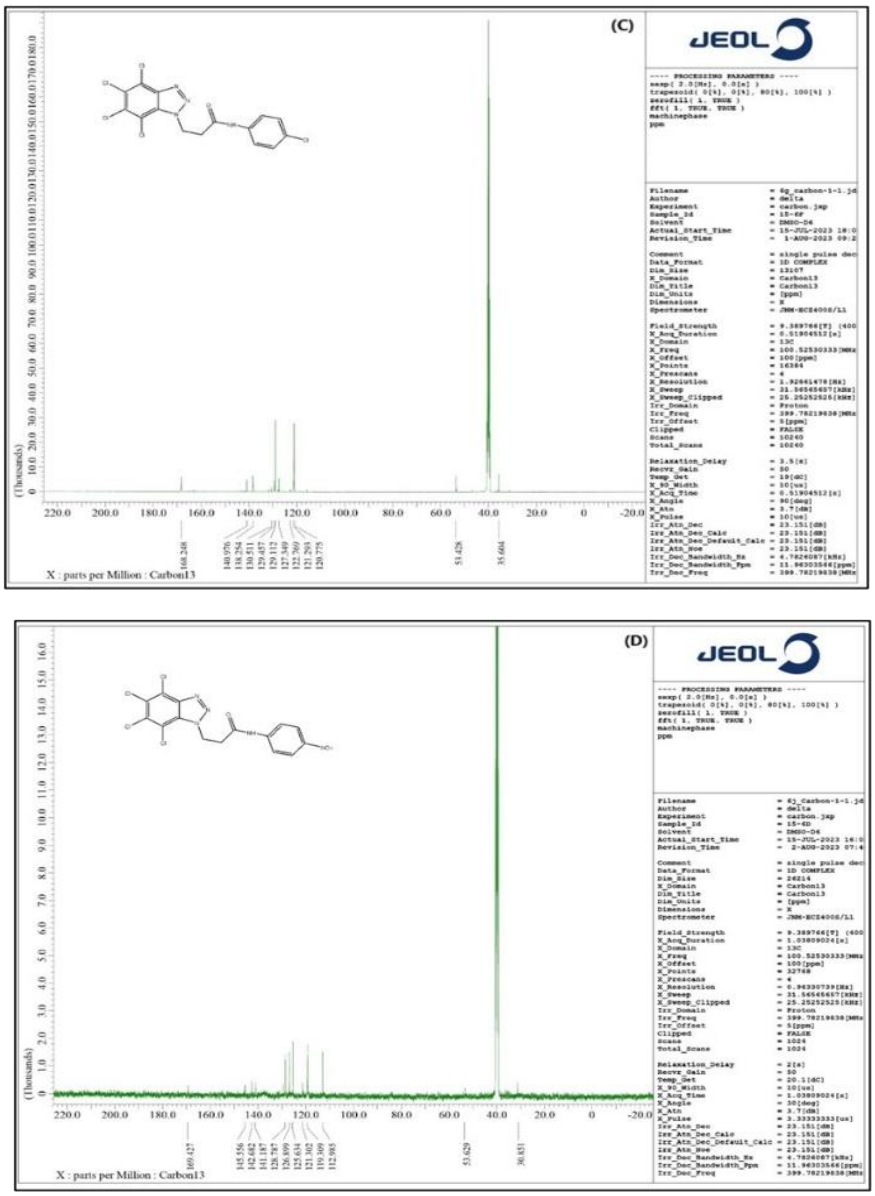


Figure 4 (C-D)

Dated this the 5th day of March, 2025

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Dwarka, New Delhi – 110 077, India

FORM 2
THE PATENT ACT, 1970
(39 of 1970)
&
THE PATENTS RULES, 2003
COMPLETE SPECIFICATION
(See section 10 and rule 13)

Title of the Invention:

TETRAHALO-BENZOTRIAZOLE DERIVATIVES AND PROCESS THEREOF FOR ANTIMICROBIAL APPLICATIONS

Applicant:

(a) Name : BIRLA INSTITUTE OF TECHNOLOGY MESRA
(b) Nationality : Indian
(c) Address : P.O. Mesra, Ranchi, Jharkhand- 835215

Preamble To The Description

Complete
The following specification particularly describes the invention and the manner in which it is to be performed.

Description (Description shall start from next page)

Claims not applicable for provisional specification. Claims should start with the preamble – "I/We claim" on separate page)

Date and Signature (to be given at the last page of specification)

Abstract of the invention (to be given along with complete specification on separate page)

TETRAHALO-BENZOTRIAZOLE DERIVATIVES AND PROCESS THEREOF FOR ANTIMICROBIAL APPLICATIONS

FIELD OF THE INVENTION

The present invention relates to synthesis of benzotriazole derivatives. More particularly, the present invention relates to a method of synthesizing multitargeting tetra-halogen derivatives of benzotriazole.

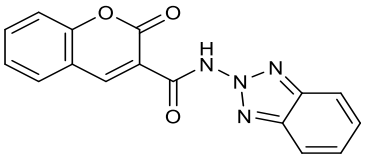
BACKGROUND OF THE INVENTION

Antibiotic-resistant bacteria and fungi pose a significant threat to public health today. It is crucial to take immediate action to combat these resistant strains and effectively treat infections. There is also a critical need for antimicrobial agents with broad-spectrum activity to combat a wide range of pathogens. Additionally, the development of environmentally friendly and non-toxic antimicrobial agents is essential to minimize negative impacts on human health and the ecosystem. Overall, the importance of advancing antimycobacterial, antibacterial and antifungal agents is vital in the fight against drug resistance, ensuring the availability of effective treatments for infectious diseases.

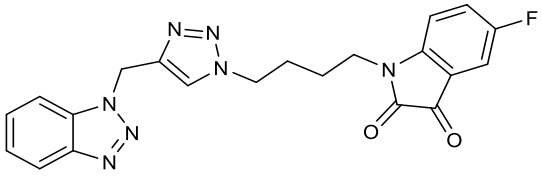
There is a clear shift from older research approaches for dealing with drug-resistant microbes, wherein this drug-resistance requires a deeper understanding of interaction between individual's body and these microbes. Production of new molecules, their derivatives, and formulations such as benzotriazole derivatives, come under such advanced approaches for combating various microbial infections including mycobacterium, bacterial, and fungal infections.

Benzotriazole is a special chemical with three nitrogen atoms (formula $C_6H_5N_3$). It's not only used in preventing metal corrosion but possesses biological properties. Benzotriazole and its different derivatives have been reported for inhibiting growth in cancer cells, acting like natural antibiotics to combat microbial infections, and protecting cells from free radical damages. Although a number of benzotriazole derivatives have been synthesized but they do not possess potential against multiple disease targets such as microbes including bacteria and viruses.

Several series of benzotriazole derivatives are designed and synthesized. Out of all synthesized derivatives, N-(2H-benzo[d][1,2,3] triazol-2-yl)-2-oxo-2H-chromene-3-carboxamide (i) and 1-(4-(4-((1H-benzo[d][1,2,3] triazol-1-yl)methyl)-1H-1,2,3-triazol-1-yl)butyl)-5-fluoroindoline-2,3-dione (ii) show exceptional antimicrobial and antifungal (targeting *Candida* species) efficacy *in vitro* compared to ciprofloxacin and fluconazole, respectively [Ahamed, et. al., J King Saud Univ Sci, 35, 102588, 2023 and Singh, et. al., J Mol Struct, 1274, 134456, 2023].

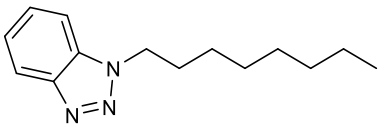


(i)

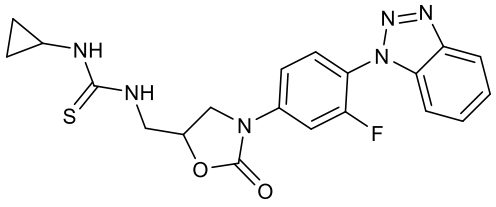


(ii)

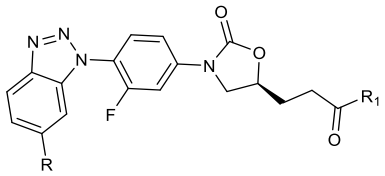
Furthermore, several series of benzotriazole derivatives is designed and synthesized. Out of all synthesized derivatives, 1-octyl-1H-benzo[d][1,2,3]triazole (iii) and 1-((3-(4-(1H-benzo[d][1,2,3]triazol-1-yl)-3-fluorophenyl)-2-oxooxazolidin-5-yl)methyl)-3-cyclopropylthiourea (iv) show antifungal (targeting *Candida* species) and antimycobacterial (*Mycobacterium tuberculosis*, and *M. avium*) potential *in vitro* compared to fluconazole and isoniazid, respectively [Jimoh, et. al., Chem Afr, 6, 383-391, 2023 and Dixit, et al., Eur J Med Chem, 41, 423-428, 2006]. In another prior art, substituted benzo-triazolyl oxazolidinone analogs are synthesized, including compounds (v) (a-d) that exhibit superior antimicrobial agents compared to standard linezolid (R = H, H, H, COOMe; R_1 = $NHCH_2CH_2CH_2OH$, $CH_2CF_2CHF_2$, OCH_2CH_2OH, OMe) [Dixit, et. al., Med Chem Lett, 15, 3002-3005, 2005].



(iii)



(iv)



(v)

However, the pre-existing methods for synthesizing compounds/ benzotriazole derivatives highlight the scarcity of synthetic processes focusing on time-efficient, safe, and simplified synthesis approaches with multitarget properties. This gap underscores the necessity for innovative approaches which can address contemporary scientific challenges effectively.

Therefore, the above-mentioned problems and challenges in development of more effective solution necessitate the requirement of synthesizing effective compounds and devising improved synthetic methods to prevent and treat global health issues due to microbial diseases.

OBJECT OF THE INVENTION

With the versatile potential of the benzotriazole moiety in creating new therapeutic analogs, the objects of the present invention include:

One object of the present invention is to provide halo-derivatives of benzotriazole compound with bioactivities against viruses and multi-drug resistant bacteria.

Another object of the present invention is to synthesize potential halo-benzotriazole compounds with non-toxic confirmations for targeting multiple disorders.

Another object of the present invention is to provide a process for synthesis of tetrahalo-benzotriazole derivative compounds in a single-step and faster reaction under non-hazardous conditions.

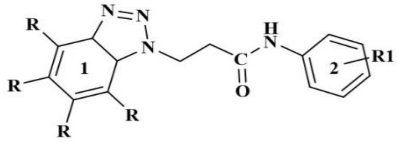
SUMMARY OF THE INVENTION

This summary is provided to introduce a selection of concepts in a simplified form that are further described below in the Detailed Description. This summary may or may not be intended to identify key features or essential features of the claimed

subject matter. Nor is this summary intended to be used to limit the claimed subject matter's scope.

Both the foregoing summary and the following detailed description provide examples and are explanatory only. Accordingly, the foregoing summary and the following detailed description should not be considered to be restrictive. Further, features or variations may be provided in addition to those set forth herein. For example, embodiments may be directed to various feature combinations and sub-combinations described in the detailed description.

According to one embodiment of the present invention, there is provided a compound of N-(aryl)-3-(perhalo-1*H*-benzo[d][1,2,3] triazol-1-yl) propenamide having formula (4-7):



(4-7)

,

wherein R is Bromine (Br) or Chlorine (Cl) and R1 is Chlorine (Cl) or Nitrogen dioxide (NO2).

According to above embodiment of the present invention, there is provided a compound of N-(aryl)-3-(perhalo-1*H*-benzo[d][1,2,3] triazol-1-yl) propenamide having formula (4-7), wherein R is Bromine (Br) or Chlorine (Cl) and R1 is Chlorine (Cl) or Nitrogen dioxide (NO2), wherein said compound is *N*-(4-chlorophenyl)-3-(perbromo-1*H*-benzo[d][1,2,3] triazol-1-yl) propenamide having the formula (4).

According to one of the above embodiments of the present invention, there is provided a compound of N-(aryl)-3-(perhalo-1*H*-benzo[d][1,2,3] triazol-1-yl) propenamide having formula (4-7), wherein R is Bromine (Br) or Chlorine (Cl) and R1 is Chlorine (Cl) or Nitrogen dioxide (NO2), wherein said compound is *N*-(4-nitrophenyl)-3-(perbromo-1*H*-benzo[d][1,2,3] triazol-1-yl) propenamide having the formula (5).

According to one of the above embodiments of the present invention, there is provided a compound of N-(aryl)-3-(perhalo-1*H*-benzo[d][1,2,3] triazol-1-yl)

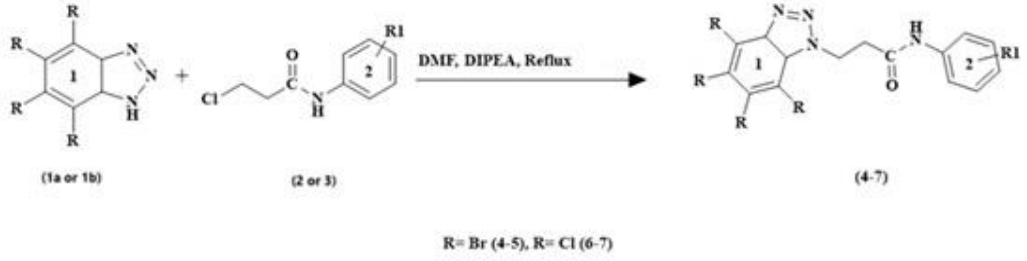
propenamide having formula (4-7), wherein R is Bromine (Br) or Chlorine (Cl) and R1 is Chlorine (Cl) or Nitrogen dioxide (NO2), wherein said compound is *N*-(4-chlorophenyl)-3-(perchloro -1*H*-benzo[d][1,2,3] triazol-1-yl) propenamide having the formula (6).

According to one of the above embodiments of the present invention, there is provided a compound of N-(aryl)-3-(perhalo-1*H*-benzo[d][1,2,3] triazol-1-yl) propenamide having formula (4-7), wherein R is Bromine (Br) or Chlorine (Cl) and R1 is Chlorine (Cl) or Nitrogen dioxide (NO2), wherein said compound is N-(4-nitrophenyl)-2-(perchloro-1H-benzo[d][1,2,3] triazol-1-yl) propenamide having the formula (7).

According to one of the above embodiments of the present invention, there is provided a compound of N-(aryl)-3-(perhalo-1*H*-benzo[d][1,2,3] triazol-1-yl) propenamide having formula (4-7), wherein R is Bromine (Br) or Chlorine (Cl) and R1 is Chlorine (Cl) or Nitrogen dioxide (NO2), wherein said compound of N-(aryl)-2-(perhalo-1*H*-benzo[d][1,2,3] triazol-1-yl)-propenamide of said formula (4-7) is synthesized by reacting a mixture of tetrachloro-benzotriazole and propenamide derivatives in dimethyl methyl formamide (DMF) with N,N-diisopropylethylamine as white powder.

According to another embodiment of the present invention, there is provided a compound of N-(aryl)-3-(perhalo-1*H*-benzo[d][1,2,3] triazol-1-yl) propenamide having formula (4-7), wherein R is Bromine (Br) or Chlorine (Cl) and R1 is Chlorine (Cl) or Nitrogen dioxide (NO2), wherein said compound of formula (4-7) exhibits improved antimicrobial activity.

According to another embodiment of the present invention, there is provided a process for synthesizing compound of N-(aryl)-3-(perhalo-1*H*-benzo[d][1,2,3] triazol-1-yl) propenamide having formula (4-7) under Scheme 1:



wherein said Scheme 1 comprises reacting 0.01-0.15 moles of precursor benzotriazole with a 0.45-3.15 M halogen source reagent in nitric acid under reflux conditions for 1-48 hours, to obtain a solution A; filtering the solution A to obtain a precipitate of tetrahalo-benzotriazoles having formula (1a or 1b), wherein R = halogen, preferably Br or Cl; recrystallizing the precipitate of formula (1a or 1b) in appropriate solvent yielding creamy or white crystals of the tetrahalo-benzotriazole having formula (1a or 1b); adding 0.033 mole an aromatic amine to 0.21 M glacial acetic acid and stirring under ice-cooled condition to obtain a solution B; mixing 0.037 M 3-chloropropionyl chloride dropwise to the solution B and stirring the mixture on ice bath for 30-60 minutes and continue stirring for an additional 1-2 hour at room temperature; pouring the stirred mixture into saline water (pH-7) solution, mixing, and filtering it to obtain another precipitate of acetamide derivative having formula (2 or 3), wherein R1 = Cl or NO_2; recrystallizing the another precipitate of formula (2 or 3) using a 2:1 mixture of ethanol and water yielding creamy or white crystals of the propenamide derivative having formula (2 or 3); mixing the derivative having formula (1a or 1b) and the derivative having formula (2 or 3) in equal ratio followed by mixing with 0.25 M dimethylformamide and 1 mM N,N-diisopropylethylamine and refluxing for 10-20 hours, preferably 15 hours; cooling the mixture of formula (1a or 1b) and formula (2 or 3) at room temperature to separate a cream-colored crude solid followed by filtering the crude solid to obtain another precipitate of formula (4-7); and recrystallizing the another precipitate of formula (4-7) using an alcohol to obtain a white powder compound having formula (4-7), wherein R = halogen, preferably Br or Cl; and R1 = Cl or NO_2, wherein said process is non-hazardous and involves single reaction for synthesizing the compound of N-(aryl)-3-(perhalo-1*H*-benzo[d][1,2,3] triazol-1-yl) propenamide having formula (4-7).

According to one exemplary embodiment of the present invention, there is provided a process for synthesizing compound of N-(aryl)-3-(perhalo-1*H*-benzo[d][1,2,3] triazol-1-yl) propenamide having formula (4-7) under Scheme 1 comprising of reacting 0.01-0.15 moles of precursor benzotriazole with a 0.45-3.15 M halogen source reagent in nitric acid under reflux conditions for 1-48 hours, to obtain a solution A; filtering the solution A to obtain a precipitate of tetrahalo-benzotriazoles having formula (1a or 1b), wherein R = halogen, preferably Br or Cl; recrystallizing the precipitate of formula (1a or 1b) in appropriate solvent yielding creamy or white crystals of the tetrahalo-benzotriazole having formula (1a or 1b); adding 0.033 mole an aromatic amine to 0.21

M glacial acetic acid and stirring under ice-cooled condition to obtain a solution B; mixing 0.037 M 3-chloropropionyl chloride dropwise to the solution B and stirring the mixture on ice bath for 30-60 minutes and continue stirring for an additional 1-2 hour at room temperature; pouring the stirred mixture into saline water (pH-7) solution, mixing, and filtering it to obtain another precipitate of acetamide derivative having formula (2 or 3), wherein R1 = Cl or NO_2; recrystallizing the another precipitate of formula (2 or 3) using a 2:1 mixture of ethanol and water yielding creamy or white crystals of the propenamide derivative having formula (2 or 3); mixing the derivative having formula (1a or 1b) and the derivative having formula (2 or 3) in equal ratio followed by mixing with 0.25 M dimethylformamide and 1 mM N,N-diisopropylethylamine and refluxing for 10-20 hours, preferably 15 hours; cooling the mixture of formula (1a or 1b) and formula (2 or 3) at room temperature to separate a cream-colored crude solid followed by filtering the crude solid to obtain another precipitate of formula (4-7); and recrystallizing the another precipitate of formula (4-7) using an alcohol to obtain a white powder compound having formula (4-7), wherein R = halogen, preferably Br or Cl; and R1 = Cl or NO_2, wherein said process is non-hazardous and involves single reaction for synthesizing the compound of N-(aryl)-3-(perhalo-1*H*-benzo[d][1,2,3] triazol-1-yl) propenamide having formula (4-7), wherein said halogen source reagent includes bromine or hydrochloric acid.

According to another exemplary embodiment of the present invention, there is provided a process for synthesizing compound of N-(aryl)-3-(perhalo-1*H*-benzo[d][1,2,3] triazol-1-yl) propenamide having formula (4-7) under Scheme 1 comprising of reacting 0.01-0.15 moles of precursor benzotriazole with a 0.45-3.15 M halogen source reagent in nitric acid under reflux conditions for 1-48 hours, to obtain a solution A; filtering the solution A to obtain a precipitate of tetrahalo-benzotriazoles having formula (1a or 1b), wherein R = halogen, preferably Br or Cl; recrystallizing the precipitate of formula (1a or 1b) in appropriate solvent yielding creamy or white crystals of the tetrahalo-benzotriazole having formula (1a or 1b); adding 0.033 mole an aromatic amine to 0.21 M glacial acetic acid and stirring under ice-cooled condition to obtain a solution B; mixing 0.037 M 3-chloropropionyl chloride dropwise to the solution B and stirring the mixture on ice bath for 30-60 minutes and continue stirring for an additional 1-2 hour at room temperature; pouring the stirred mixture into saline water (pH-7) solution, mixing, and filtering it to obtain another precipitate of acetamide derivative having formula (2 or 3), wherein R1 = Cl or NO_2; recrystallizing the another precipitate of formula (2 or 3)

using a 2:1 mixture of ethanol and water yielding creamy or white crystals of the propenamide derivative having formula (2 or 3); mixing the derivative having formula (1a or 1b) and the derivative having formula (2 or 3) in equal ratio followed by mixing with 0.25 M dimethylformamide and 1 mM N,N-diisopropylethylamine and refluxing for 10-20 hours, preferably 15 hours; cooling the mixture of formula (1a or 1b) and formula (2 or 3) at room temperature to separate a cream-colored crude solid followed by filtering the crude solid to obtain another precipitate of formula (4-7); and recrystallizing the another precipitate of formula (4-7) using an alcohol to obtain a white powder compound having formula (4-7), wherein R = halogen, preferably Br or Cl; and R1 = Cl or NO_2, wherein said process is non-hazardous and involves single reaction for synthesizing the compound of N-(aryl)-3-(perhalo-1*H*-benzo[d][1,2,3] triazol-1-yl) propenamide having formula (4-7), wherein said appropriate solvent is selected from acetic acid or nitromethane.

According to another exemplary embodiment of the present invention, there is provided a process for synthesizing compound of N-(aryl)-3-(perhalo-1*H*-benzo[d][1,2,3] triazol-1-yl) propenamide having formula (4-7) under Scheme 1 comprising of reacting 0.01-0.15 moles of precursor benzotriazole with a 0.45-3.15 M halogen source reagent in nitric acid under reflux conditions for 1-48 hours, to obtain a solution A; filtering the solution A to obtain a precipitate of tetrahalo-benzotriazoles having formula (1a or 1b), wherein R = halogen, preferably Br or Cl; recrystallizing the precipitate of formula (1a or 1b) in appropriate solvent yielding creamy or white crystals of the tetrahalo-benzotriazole having formula (1a or 1b); adding 0.033 mole an aromatic amine to 0.21 M glacial acetic acid and stirring under ice-cooled condition to obtain a solution B; mixing 0.037 M 3-chloropropionyl chloride dropwise to the solution B and stirring the mixture on ice bath for 30-60 minutes and continue stirring for an additional 1-2 hour at room temperature; pouring the stirred mixture into saline water (pH-7) solution, mixing, and filtering it to obtain another precipitate of acetamide derivative having formula (2 or 3), wherein R1 = Cl or NO_2; recrystallizing the another precipitate of formula (2 or 3) using a 2:1 mixture of ethanol and water yielding creamy or white crystals of the propenamide derivative having formula (2 or 3); mixing the derivative having formula (1a or 1b) and the derivative having formula (2 or 3) in equal ratio followed by mixing with 0.25 M dimethylformamide and 1 mM N,N-diisopropylethylamine and refluxing for 10-20 hours, preferably 15 hours; cooling the mixture of formula (1a or 1b) and formula (2 or 3) at room temperature to separate a cream-colored crude solid followed by

filtering the crude solid to obtain another precipitate of formula (4-7); and recrystallizing the another precipitate of formula (4-7) using an alcohol to obtain a white powder compound having formula (4-7), wherein R = halogen, preferably Br or Cl; and R1 = Cl or NO_2, wherein said process is non-hazardous and involves single reaction for synthesizing the compound of N-(aryl)-3-(perhalo-1*H*-benzo[d][1,2,3] triazol-1-yl) propenamide having formula (4-7), wherein said aromatic amine is selected from 4-chloro aniline or 4-nitro aniline.

According to one of the above embodiments of the present invention, there is provided a process for synthesizing compound of N-(aryl)-3-(perhalo-1*H*-benzo[d][1,2,3] triazol-1-yl) propenamide having formula (4-7) under Scheme 1 comprising of reacting 0.01-0.15 moles of precursor benzotriazole with a 0.45-3.15 M halogen source reagent in nitric acid under reflux conditions for 1-48 hours, to obtain a solution A; filtering the solution A to obtain a precipitate of tetrahalo-benzotriazoles having formula (1a or 1b), wherein R = halogen, preferably Br or Cl; recrystallizing the precipitate of formula (1a or 1b) in appropriate solvent yielding creamy or white crystals of the tetrahalo-benzotriazole having formula (1a or 1b); adding 0.033 mole an aromatic amine to 0.21 M glacial acetic acid and stirring under ice-cooled condition to obtain a solution B; mixing 0.037 M 3-chloropropionyl chloride dropwise to the solution B and stirring the mixture on ice bath for 30-60 minutes and continue stirring for an additional 1-2 hour at room temperature; pouring the stirred mixture into saline water (pH-7) solution, mixing, and filtering it to obtain another precipitate of acetamide derivative having formula (2 or 3), wherein R1 = Cl or NO_2; recrystallizing the another precipitate of formula (2 or 3) using a 2:1 mixture of ethanol and water yielding creamy or white crystals of the propenamide derivative having formula (2 or 3); mixing the derivative having formula (1a or 1b) and the derivative having formula (2 or 3) in equal ratio followed by mixing with 0.25 M dimethylformamide and 1 mM N,N-diisopropylethylamine and refluxing for 10-20 hours, preferably 15 hours; cooling the mixture of formula (1a or 1b) and formula (2 or 3) at room temperature to separate a cream-colored crude solid followed by filtering the crude solid to obtain another precipitate of formula (4-7); and recrystallizing the another precipitate of formula (4-7) using an alcohol to obtain a white powder compound having formula (4-7), wherein R = halogen, preferably Br or Cl; and R1 = Cl or NO_2, wherein said process is non-hazardous and involves single reaction for synthesizing the compound of N-(aryl)-3-(perhalo-1*H*-benzo[d][1,2,3] triazol-1-yl) propenamide having formula (4-7), wherein said creamy or white crystals of tetrahalo-

benzotriazole having formula (1a or 1b), is tetrabromo-benzotriazole or tetrachloro-benzotriazole.

According to one of the above embodiments of the present invention, there is provided a process for synthesizing compound of N-(aryl)-3-(perhalo-1*H*-benzo[d][1,2,3] triazol-1-yl) propenamide having formula (4-7) under Scheme 1 comprising of reacting 0.01-0.15 moles of precursor benzotriazole with a 0.45-3.15 M halogen source reagent in nitric acid under reflux conditions for 1-48 hours, to obtain a solution A; filtering the solution A to obtain a precipitate of tetrahalo-benzotriazoles having formula (1a or 1b), wherein R = halogen, preferably Br or Cl; recrystallizing the precipitate of formula (1a or 1b) in appropriate solvent yielding creamy or white crystals of the tetrahalo-benzotriazole having formula (1a or 1b); adding 0.033 mole an aromatic amine to 0.21 M glacial acetic acid and stirring under ice-cooled condition to obtain a solution B; mixing 0.037 M 3-chloropropionyl chloride dropwise to the solution B and stirring the mixture on ice bath for 30-60 minutes and continue stirring for an additional 1-2 hour at room temperature; pouring the stirred mixture into saline water (pH-7) solution, mixing, and filtering it to obtain another precipitate of acetamide derivative having formula (2 or 3), wherein R1 = Cl or NO_2; recrystallizing the another precipitate of formula (2 or 3) using a 2:1 mixture of ethanol and water yielding creamy or white crystals of the propenamide derivative having formula (2 or 3); mixing the derivative having formula (1a or 1b) and the derivative having formula (2 or 3) in equal ratio followed by mixing with 0.25 M dimethylformamide and 1 mM N,N-diisopropylethylamine and refluxing for 10-20 hours, preferably 15 hours; cooling the mixture of formula (1a or 1b) and formula (2 or 3) at room temperature to separate a cream-colored crude solid followed by filtering the crude solid to obtain another precipitate of formula (4-7); and recrystallizing the another precipitate of formula (4-7) using an alcohol to obtain a white powder compound having formula (4-7), wherein R = halogen, preferably Br or Cl; and R1 = Cl or NO_2, wherein said process is non-hazardous and involves single reaction for synthesizing the compound of N-(aryl)-3-(perhalo-1*H*-benzo[d][1,2,3] triazol-1-yl) propenamide having formula (4-7), wherein said creamy or white crystals of the propenamide derivative having formula (2 or 3) is 3-chloro-N-(4-chlorophenyl) propenamide (2) or 2-chloro-N-(4-nitroophenyl) propenamide (3).

According to one exemplary embodiment of the present invention, there is provided a process for synthesizing compound of N-(aryl)-3-(perhalo-1*H*-benzo[d][1,2,3] triazol-1-

yl) propenamide having formula (4-7) under Scheme 1 comprising of reacting 0.01-0.15 moles of precursor benzotriazole with a 0.45-3.15 M halogen source reagent in nitric acid under reflux conditions for 1-48 hours, to obtain a solution A; filtering the solution A to obtain a precipitate of tetrahalo-benzotriazoles having formula (1a or 1b), wherein R = halogen, preferably Br or Cl; recrystallizing the precipitate of formula (1a or 1b) in appropriate solvent yielding creamy or white crystals of the tetrahalo-benzotriazole having formula (1a or 1b); adding 0.033 mole an aromatic amine to 0.21 M glacial acetic acid and stirring under ice-cooled condition to obtain a solution B; mixing 0.037 M 3-chloropropionyl chloride dropwise to the solution B and stirring the mixture on ice bath for 30-60 minutes and continue stirring for an additional 1-2 hour at room temperature; pouring the stirred mixture into saline water (pH-7) solution, mixing, and filtering it to obtain another precipitate of acetamide derivative having formula (2 or 3), wherein R1 = Cl or NO_2; recrystallizing the another precipitate of formula (2 or 3) using a 2:1 mixture of ethanol and water yielding creamy or white crystals of the propenamide derivative having formula (2 or 3); mixing the derivative having formula (1a or 1b) and the derivative having formula (2 or 3) in equal ratio followed by mixing with 0.25 M dimethylformamide and 1 mM N,N-diisopropylethylamine and refluxing for 10-20 hours, preferably 15 hours; cooling the mixture of formula (1a or 1b) and formula (2 or 3) at room temperature to separate a cream-colored crude solid followed by filtering the crude solid to obtain another precipitate of formula (4-7); and recrystallizing the another precipitate of formula (4-7) using an alcohol to obtain a white powder compound having formula (4-7), wherein R = halogen, preferably Br or Cl; and R1 = Cl or NO_2, wherein said process is non-hazardous and involves single reaction for synthesizing the compound of N-(aryl)-3-(perhalo-1*H*-benzo[d][1,2,3] triazol-1-yl) propenamide having formula (4-7), wherein said alcohol is ethanol.

According to one of the above embodiments of the present invention, there is provided a process for synthesizing compound of N-(aryl)-3-(perhalo-1*H*-benzo[d][1,2,3] triazol-1-yl) propenamide having formula (4-7) under Scheme 1 comprising of reacting 0.01-0.15 moles of precursor benzotriazole with a 0.45-3.15 M halogen source reagent in nitric acid under reflux conditions for 1-48 hours, to obtain a solution A; filtering the solution A to obtain a precipitate of tetrahalo-benzotriazoles having formula (1a or 1b), wherein R = halogen, preferably Br or Cl; recrystallizing the precipitate of formula (1a or 1b) in appropriate solvent yielding creamy or white crystals of the tetrahalo-benzotriazole having formula (1a or 1b); adding 0.033 mole an aromatic amine to 0.21

M glacial acetic acid and stirring under ice-cooled condition to obtain a solution B; mixing 0.037 M 3-chloropropionyl chloride dropwise to the solution B and stirring the mixture on ice bath for 30-60 minutes and continue stirring for an additional 1-2 hour at room temperature; pouring the stirred mixture into saline water (pH-7) solution, mixing, and filtering it to obtain another precipitate of acetamide derivative having formula (2 or 3), wherein R1 = Cl or NO_2; recrystallizing the another precipitate of formula (2 or 3) using a 2:1 mixture of ethanol and water yielding creamy or white crystals of the propenamide derivative having formula (2 or 3); mixing the derivative having formula (1a or 1b) and the derivative having formula (2 or 3) in equal ratio followed by mixing with 0.25 M dimethylformamide and 1 mM N,N-diisopropylethylamine and refluxing for 10-20 hours, preferably 15 hours; cooling the mixture of formula (1a or 1b) and formula (2 or 3) at room temperature to separate a cream-colored crude solid followed by filtering the crude solid to obtain another precipitate of formula (4-7); and recrystallizing the another precipitate of formula (4-7) using an alcohol to obtain a white powder compound having formula (4-7), wherein R = halogen, preferably Br or Cl; and R1 = Cl or NO_2, wherein said process is non-hazardous and involves single reaction for synthesizing the compound of N-(aryl)-3-(perhalo-1*H*-benzo[d][1,2,3] triazol-1-yl) propenamide having formula (4-7), wherein said white powder compound having formula (4-7) is *N*-(4-chlorophenyl)-3-(perbromo-1*H*-benzo[d][1,2,3] triazol-1-yl) propenamide (4); *N*-(4-nitrophenyl)-3-(perbromo-1*H*-benzo[d][1,2,3] triazol-1-yl) propenamide (5); *N*-(4-chlorophenyl)-3-(perchloro -1*H*-benzo[d][1,2,3] triazol-1-yl) propenamide (6); or *N*-(4-nitrophenyl)-3-(perchloro -1*H*-benzo[d][1,2,3] triazol-1-yl) propenamide (7).

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 depicts scheme 1 for synthesizing *N*-(aryl)-2-(perhalo-1*H*-benzo[d][1,2,3] triazol-1-yl)- propanamide (4-7).

Figure 2 depicts the Mass Spectrum of **(A)** *N*-(4-chlorophenyl)-3-(perbromo-1*H*-benzo[d][1,2,3] triazol-1-yl)propanamide (4); **(B)** *N*-(4-nitrophenyl)-3-(perbromo-1*H*-benzo[d][1,2,3] triazol-1-yl)propanamide (5); **(C)** *N*-(4-chlorophenyl)-3-(perchloro-1*H*-benzo[d][1,2,3] triazol-1-yl)propanamide (6); and **(D)** *N*-(4-nitrophenyl)-3-(perchloro-1*H*-benzo[d][1,2,3] triazol-1-yl)propanamide (7).

Figure 3 depicts the 1H NMR Spectrum of **(A)** *N*-(4-chlorophenyl)-3-(perbromo-1*H*-benzo[d][1,2,3] triazol-1-yl)propanamide (4); **(B)** *N*-(4-nitrophenyl)-3-(perbromo-1*H*-benzo[d][1,2,3] triazol-1-yl)propanamide (5); **(C)** *N*-(4-chlorophenyl)-3-(perchloro-1*H*-benzo[d][1,2,3] triazol-1-yl)propanamide (6); and **(D)** *N*-(4-nitrophenyl)-3-(perchloro-1*H*-benzo[d][1,2,3] triazol-1-yl)propanamide (7).

Figure 4 depicts the ^{13}C NMR spectrum of **(A)** *N*-(4-chlorophenyl)-3-(perbromo-1*H*-benzo[d][1,2,3] triazol-1-yl)propanamide (4); **(B)** *N*-(4-nitrophenyl)-3-(perbromo-1*H*-benzo[d][1,2,3] triazol-1-yl)propanamide (5); **(C)** *N*-(4-chlorophenyl)-3-(perchloro-1*H*-benzo[d][1,2,3] triazol-1-yl)propanamide (6); and **(D)** *N*-(4-nitrophenyl)-3-(perchloro-1*H*-benzo[d][1,2,3] triazol-1-yl)propanamide (7).

DETAILED DESCRIPTION OF THE INVENTION

In the present invention, following a meticulous analysis of structure-activity relationships (SAR) and utilizing modeling studies from existing benzotriazole derivatives, a synthetic scheme for benzotriazoles is devised, wherein the synthesis process is optimized for simplicity and uniformity, resulting in an efficient and straightforward method of benzotriazole derivatives synthesis.

The present invention focuses on the streamlined synthesis of multifunctional compounds via a single-step process, emphasizing efficiency, safety, and time reduction. Herein, a highly simplified single stepped process is involved in synthesizing the potent compounds, focusing on their efficacy against microbes: mycobacteria (*M. smegmatis)*, gram positive bacteria (*S. aureus* and *B. subtilis)*, gram negative bacteria (*E. coli* and *P. aeruginosa)*, and fungi (*C. albicans* and *A. niger).*

According to one embodiment of the present invention, structural confirmation of synthesized benzotriazole derivatives is done through spectral analysis followed by extensive biological studies, and non-toxicity confirmation of the synthesized compounds through oral toxicity studies based on OECD guidelines.

Synthesis of Tetrahalo-benzotriazole Amides Derivatives:

A general process for synthesizing tetrahalo-benzotriazole amides involves simple steps having single reaction. The process shown in Scheme 1 [Figure 1] is a fast and non-toxic synthetic method.

Synthesizing Tetrahalo-benzotriazole (1) -

Tetrahalo-benzotriazole derivatives are synthesized by reacting 0.01-0.15 moles of a precursor benzotriazole with 0.45-3.15 M halogen source reagent in nitric acid under reflux conditions for 1-48 hours to obtain solution A, followed by its filtration and recrystallization, yielding tetrahalo-benzotriazole (1a or 1b).

EXAMPLE 1

Synthesis of tetrabromo-benzotriazole (1a) - Initially, tetrabromo-benzotriazole is synthesized by reacting 11.9 g benzotriazole (0.10 mole) with 23 ml bromine (0.45 mole), and 150 ml nitric acid under reflux conditions for 48 hours. It is followed by filtering the precipitate and recrystallizing with acetic acid to yield creamy crystals [Yield:75%, m.p: 264˚-266˚C].

EXAMPLE 2

Synthesis of tetrachloro-benzotriazole (1b) - Tetrachloro-benzotriazole is synthesized by reacting 4.76 g benzotriazole (0.040 mole) with 525 ml of hydrochloric acid and 175 ml of nitric acid under reflux conditions for 4 hours. It is followed by filtering the precipitate and recrystallizing with nitromethane to yield white crystals [Yield:80%, m.p:259-261˚C].

Synthesizing Propenamide Derivatives (2-3)-

An aromatic amine is added to 0.21 M glacial acetic acid and stirred under ice-cooled condition to obtain a solution B, followed by addition of 3-chloropropionyl chloride to it. The mixture is stirred on an ice bath for 30-60 minutes and left to stir for an additional 1-2 hours at room temperature. The reaction mixture is then poured into a saline water solution and filtered. The resulting product is recrystallized using a 2:1 mixture of ethanol and water, yielding creamy white crystals of 3-chloro-N-(substituted phenyl) propenamide (2-3).

EXAMPLE 3

Synthesizing 3-chloro-*N*-(4-chlorophenyl) propenamide (2) - 4-Chloro aniline (0.033 mole) is added carefully to glacial acetic acid (12.5 ml) and stirred under ice-cooled condition. Subsequently, 0.037 M 3-chloropropionyl chloride (3.56 ml) is added dropwise to the solution. The mixture is stirred in an ice bath for 30 minutes and left to stir for 2 hours at room temperature. The progress of the reaction is monitored using a preparative TLC plate. The reaction mixture is then poured into a saline water solution (pH-7) and filtered. The resulting product is recrystallized using a 2:1 mixture of ethanol and water, yielding creamy white crystals of (2) 3-chloro-N-(4-chlorophenyl) propanamide [Yield: 78%, m.p.: 121-123˚C].

EXAMPLE 4

Synthesizing 2-chloro-*N*-(4-nitroophenyl) propenamide (3) - 4-nitro aniline (0.033 mole) is added carefully to glacial acetic acid (12.5 ml) and stirred under ice-cooled condition. Subsequently, 0.037 M 3-chloropropionyl chloride (3.56 ml) is added dropwise to the solution. The mixture is stirred in an ice bath for 30 minutes and left to stir for 2 hours at room temperature. The progress of the reaction is monitored using a preparative TLC plate. The reaction mixture is then poured into a saline water solution (pH-7) and filtered. The resulting product is recrystallized using a 2:1 mixture of ethanol and water, yielding creamy white crystals of (3) 2-chloro-N-(4-nitrophenyl) propanamide [Yield: 65%, m.p.: 154-156 ˚C].

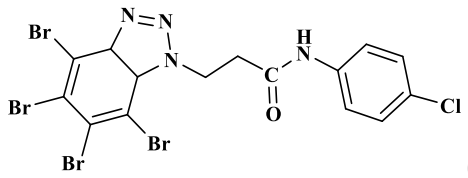
Preparation of *N*-(aryl)-2-(perhalo-1*H*-benzo[d][1,2,3] triazol-1-yl)-amides (4-7):

Tetrahalo-benzotriazole (1a/1b) is mixed with respective propenamide (2/3) in 1:1 ratio followed by mixing with 0.25 M dimethylformamide (DMF), and 1 mM N,N-diisopropylethylamine and refluxing for 10-20 hours. Further, cooling at room temperature separates a cream-colored crude solid which is isolated through filtration followed by its recrystallization using ethanol producing a white powder compound (4-7).

EXAMPLE 5

Preparation of *N*-(4-chlorophenyl)-3-(perbromo-1*H*-benzo[d][1,2,3] triazol-1-yl) propenamide (4) - 1 mM tetrabromobenzotriazole (1a) (0.434 gm) is mixed with 1 mM 3-chloro-N-(4-chlorophenyl) propanamide (2) in 20 mL DMF, and 1 mM N,N-

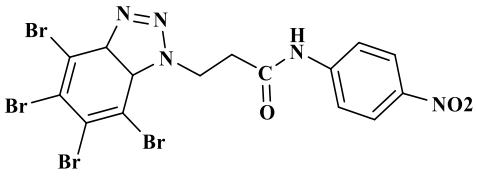
diisopropylethylamine (0.26 gm) and refluxed for 15 hours. The solution is allowed to cool to room temperature which separates a cream-colored crude solid and isolated through filtration. Recrystallization is done using ethanol which produces a white powder compound (4).



(4)

EXAMPLE 6

Preparation of *N*-(4-nitrophenyl)-3-(perbromo-1*H*-benzo[d][1,2,3] triazol-1-yl) propenamide (5) - 1 mM tetrabromobenzotriazole (1a) (0.434 gm) is mixed with 1 mM 2-chloro-N-(4-nitroophenyl) propanamide (3) in 20 mL DMF, and 1 mM N,N-diisopropylethylamine (0.26 gm) followed by refluxing for 15 hours. The solution is allowed to cool to room temperature which separates a cream-colored crude solid and isolated through filtration. Recrystallization is done using ethanol which produces a white powder compound (5).

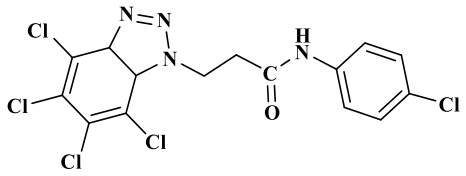


(5)

EXAMPLE 7

Preparation of *N*-(4-chlorophenyl)-3-(perchloro -1*H*-benzo[d][1,2,3] triazol-1-yl) propenamide (6):

1 mM tetrachlorobenzotriazole (1b) (0.256 gm) is mixed with 1 mM 3-chloro-N-(4-chlorophenyl) propanamide (2) in 20 mL DMF, and 1 mM N,N-diisopropylethylamine (0.26 gm) followed by refluxing for 15 hours. The solution is allowed to cool to room temperature which separates a cream-colored crude solid and isolated through filtration. Recrystallization is done using ethanol which produces a white powder compound (6).

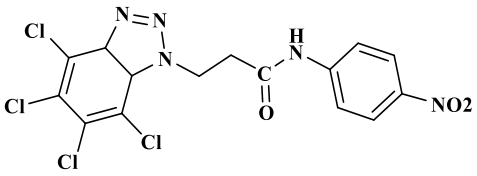


(6)

EXAMPLE 8

Preparation of *N*-(4-nitrophenyl)-3-(perchloro -1*H*-benzo[d][1,2,3] triazol-1-yl) propenamide (7):

1 mM tetrachlorobenzotriazole (1b) (0.256 gm) is mixed with 1 mM 2-chloro-N-(4-nitrophenyl) propanamide (3) in 20 mL DMF, and 1 mM N,N-diisopropylethylamine (0.26 gm) followed by refluxing for 15 hours. The solution is allowed to cool to room temperature which separates a cream-colored crude solid and isolated through filtration. Recrystallization is done using ethanol which produces a white powder compound (7).



(7)

According to another embodiment of the present invention, structural confirmation of synthesized benzotriazole derivatives is done through spectral analysis followed by extensive biological studies, and non-toxicity confirmation of the synthesized compounds through oral toxicity studies based on OECD guidelines.

In the present invention, high quality chemicals and reagents are used in synthesis and chemical purity of the product(s) is assessed via melting point and thin-layer chromatography followed by mass spectra are acquired using a JEOL spectrophotometer (400 MHz), with values reported in ppm relative to tetramethyl-silane, and using deuterated-DMSO as the solvent and LC-MS, respectively [Figure 2 (A-D)].

Further, structural elucidation through Nuclear magnetic resonance [NMR (^{1}H NMR and ^{13}C NMR)] [Figures 3 (A-D) and 4 (A-D)]. Determination of the Structure of Synthesized Compound using Nuclear Magnetic Resonance (NMR) Spectroscopy:

EXAMPLE 9

N-(4-chlorophenyl)-3-(perbromo-1*H*-benzo[d][1,2,3] triazol-1-yl) propanamide (4) - ^{1}H NMR spectrum [Figure 3A] of compound 4 shows a singlet of 1 proton assigned to the NH substituent at δ10.27. Compound 4 shows a multiplet of 4 protons assigned to the aromatic protons at δ 7.54-7.28. A triplet of 2 protons assigned to the methylenic protons of NH-CO-CH_2-CH_2 at δ 5.04 is observed for the compound 4. Similarly, a triplet of 2 protons is assigned to the methylenic protons of NH-CO-CH_2-CH_2 at δ 3.21 for compound 4.

White Solid; Reaction time (hour):15; Yield (%):78; m.p.:206-208 ˚C; ^{1}H-NMR (400 MHz, DMSO- d_6) δ: 10.27 (s, 1H; NH-CO-CH_2-CH_2), 7.54-7.28 (m, 4H; Ar-H), 5.04 (t, 2H; NH-CO-CH_2-CH_2), 3.21 (t, 2H; NH-CO-CH_2-CH_2);^{13}C-NMR (101 MHz, DMSO- d_6) δ: 168.4, 143.2, 138.5, 129.2, 127.5, 126.3, 121.2, 116.3, 114.1, 53.3, 35.5; For $C_{15}H_9Br_4ClN_4O$ LC-MS: *m/z* = 614.64 $[M-1H]^+$; Elemental Analysis: C, 29.23; H, 1.47; Br, 51.86; Cl, 5.75; N, 9.09; O, 2.60; Found: C, 29.22; H, 1.48; Br, 51.87; Cl, 5.74; N, 9.08; O, 2.59.

EXAMPLE 10

N-(4-nitrophenyl)-3-(perbromo-1*H*-benzo[d][1,2,3] triazol-1-yl) propanamide (5) - ^{1}H NMR spectrum [Figure 3B] of compound 5 shows a singlet of 1 proton assigned to the NH substituent at δ 10.75. Compound 5 shows a multiplet of 4 protons assigned to the aromatic protons at δ 8.17-7.72. A triplet of 2 protons assigned to the methylenic protons of NH-CO-CH_2-CH_2 at δ 5.07 is observed for compound 5. Similarly, a triplet of 2 protons is assigned to the methylenic protons of NH-CO-CH_2-CH_2 at δ 3.30 for compound 5.

White Solid; Reaction time (hour):15; Yield (%):72; m.p.:199-201˚C; ^{1}H-NMR (400 MHz, DMSO- d_6) δ: 10.75 (s, 1H; NH-CO-CH_2-CH_2), 8.17-7.72 (m, 4H; Ar-H), 5.07 (t, 2H; NH-CO-CH_2-CH_2), 3.30 (t, 2H; NH-CO-CH_2-CH_2); ^{13}C-(NMR 101 MHz, DMSO- d_6) δ: 169.3, 143.1, 142.7, 126.9, 125.8, 124.7, 119.3, 114.5, 112.7, 52.9, 31.3; For $C_{15}H_9Br_4N_5O_3$ LC-MS : *m/z* = 625.71 $[M-1H]^+$; Elemental Analysis: . C, 28.74; H, 1.45; Br, 50.98; N, 11.17; O, 7.66; Found: C, 28.73; H, 1.47; Br, 50.99; N, 11.18; O, 7.65.

EXAMPLE 11

N-(4-chlorophenyl)-3-(perchloro -1*H*-benzo[d][1,2,3] triazol-1-yl) propanamide (6) - ^{1}H NMR spectrum [Figure 4C] of compound 6 shows a singlet of 1 proton assigned to the NH substituent at δ 9.41 to 10.29. Compound 6 shows a multiplet of 4 protons assigned to the aromatic protons at δ 7.54-7.29. A triplet of 2 protons assigned to the methylenic protons of NH-CO-CH_2-CH_2 at δ 5.08 is observed for compound 6. Similarly, a triplet of 2 protons is assigned to the methylenic protons of NH-CO-CH_2-CH_2 at δ 3.23 for compound 6.

White Solid; Reaction time (hour):15; Yield (%):70; m.p.:189-191 ˚C; ^{1}H-NMR 400 MHz, DMSO- d_6) δ: 10.29 (s, 1H; NH-CO-CH_2-CH_2), 7.54-7.29 (m, 4H; Ar-H), 5.08 (t, 2H; NH-CO-CH_2-CH_2), 3.23 (t, 2H; NH-CO-CH_2-CH_2); ^{13}C-NMR (101 MHz, DMSO- d_6) δ: 168.2, 141.0, 138.3, 130.5, 129.5, 129.1, 127.3, 122.8, 121.3, 120.8, 53.4, 35.6, for $C_{15}H_9Cl_5N_4O$, LC-MS: *m/z* = 437.09 $[M-1H]^+$; Elemental Analysis: C, 41.09; H, 2.07; Cl, 40.42; N, 12.78; O, 3.65; Found: C, 41.10; H, 2.08; Cl, 40.41; N, 12.79; O, 3.66.

EXAMPLE 12

N-(4-nitrophenyl)-3-(perchloro -1*H*-benzo[d][1,2,3] triazol-1-yl) propanamide (7) - ^{1}H NMR spectrum [Figure 3D] of compound 7 shows a singlet of 1 proton assigned to the NH substituent at δ 10.77. Compound 7 shows a multiplet of 4 protons assigned to the aromatic protons at δ 8.18-7.71. A triplet of 2 protons assigned to the methylenic protons of NH-CO-CH_2-CH_2 at δ 5.11 is observed for compound 7. Similarly, a triplet of 2 protons is assigned to the methylenic protons of NH-CO-CH_2-CH_2 at δ 3.19 for compound 7.

White Solid; Reaction time (hour):15; Yield (%):73; m.p.:198-200 ˚C; ^{1}H-NMR (400 MHz, DMSO- d_6) δ: 10.77 (s, 1H; NH-CO-CH_2-CH_2), 8.18-7.71 (m, 4H; Ar-H), 5.11 (t, 2H; NH-CO-CH_2-CH_2), 3.19 (t, 2H; NH-CO-CH_2-CH_2); ^{13}C-NMR (101 MHz, DMSO- d_6) δ: 169.4, 145.6, 142.7, 141.2, 128.8, 126.9, 125.6, 121.3, 119.3, 113.0, 53.6, 30.9, for $C_{15}H_9Cl_4N_5O_3$, LC-MS: *m/z* = 448.13 $[M-1H]^+$; Elemental Analysis: C, 40.12; H, 2.02; Cl, 31.58; N, 15.60; O, 10.69; Found: C, 40.11; H, 2.03; Cl, 31.59; N, 15.61; O, 10.68.

Evaluation of Bioactivity Potential of Synthesized Compounds (4-7):

Antimicrobial potential and non-toxic nature of the synthesized derivative compounds is determined *in vitro.*

EXAMPLE 13

Antimicrobial Study - Compounds (4-7) are tested against various microbes: Mycobacteria (*M. smegmatis*); gram (+ve) bacteria: *S. aureus* and *B. subtilis;* gram (-ve) bacteria: *E. coli* and *P. aeruginosa*; fungi - Candida *albicans, Aspergillus niger.* Newly synthesized derivatives (4-7) are extensively assessed for their antimycobacterial, antibacterial, and antifungal properties. The minimum inhibitory concentrations (MICs) are determined against a diverse range of microorganisms, including *M. smegmatis* (ATCC 607), *S. aureus* (NCIM 2122), *B. subtilis* (MTCC 121), *E. coli* (MTCC 118), *P. aeruginosa* (MTCC 647), *C. albicans* (MTCC 227), and *A. niger* (NCIM 1056). The 2-fold serial dilution method is employed to assess the antimycobacterial and antibacterial efficacy. Pyrazinamide, streptomycin, and fluconazole are used as comparative controls. This comprehensive evaluation across diverse microbial strains provides valuable insights into the potential of these derivatives as potent agents against various microbial activities.

Antimycobacterial MICs are determined using activated *M. smegmatis*. The synthesized compounds and the standard are tested over four days at 37°C. Mueller-Hinton broth is used for bacterial investigations, and Sabouraud dextrose broth is employed for antifungal assessments. Test substances are prepared at a concentration of 10000 µg/mL in a 2–10% DMSO range (1 mg/100 µL in DMSO each). Serial dilutions from 0.781 to 100 µg/mL are carried out to determine the MICs.

The MICs, evaluated by the absence of color change after incubation with Alamar blue reagent, indicate no microbial growth. Absorbance measurements are performed at 570 and 600 nm using a Biotech Synergy XT plate reader. The synthesized compounds show equivalent antimicrobial activity when compared to the respective standard drugs for their inhibition. The MIC values are presented in Table 1.

Table 1: MIC values (µg/mL) of compounds (4-7) and the respective standard drugs for antimycobacterial, antimicrobial, and antifungal activity.

Compound	Microorganism (MIC)						
	Mycobacteria	Gram +ve bacteria		Gram -ve bacteria		Fungal strain	
	M. smegmatis	*S. aureus*	*B. subtilis*	*E. coli*	*P. aeruginosa*	*C. albicans*	*A. niger*
4	1.95	6.25	6.25	6.25	6.25	12.5	12.5
5	1.95	6.25	6.25	6.25	6.25	12.5	12.5
6	1.95	6.25	6.25	6.25	6.25	12.5	12.5
7	1.95	6.25	6.25	6.25	6.25	12.5	12.5
Pyrazinamide (antimycobacteria)	0.975	-	-	-	-	-	-
Streptomycin (antibacterial)	-	6.250	6.250	3.125	3.125	-	-
Fluconazole (antifungal)	-	-	-	-	-	12.5	12.5

EXAMPLE 14

In vivo acute oral toxicity - The acute oral toxicity assessments of compounds (4-7) are conducted in strict adherence to OECD guideline 420, revealing no instances of fatalities across all tested levels, spanning up to and including 2000 mg/kg body weight. In alignment with established criteria, the findings unequivocally affirm the non-toxic nature of all Compound (4-7) variants.

Initially, healthy young adult female Swiss albino mice, which have never given birth and are not pregnant, housed at a temperature of 22±3°C and relative humidity below 30%, with a 12-hour light/dark cycle. After being randomly selected, the mice are marked and kept in cages for at least seven days to acclimate to laboratory conditions before experimentation. Following OECD Guideline No. 420 for acute oral toxicity, three mice per group are fasted for approximately 4 hours before receiving a 2000 mg/kg suspension of compounds (4-7) via oral gavage respectively, with additional fasting for 2 hours post-dosing. The mice are observed at 1, 2, 4, 8, 12, and 24-hour intervals for skin changes, morbidity, aggressiveness, increased oral secretion, and sensitivity to sound and pain. Mortality data are collected over a 14-day period following the administration of compounds (4-7).

According to another embodiment of the present invention, wherein said process synthesizing novel compounds in a single-step pathway not only expedites the synthesis but also offers significant advantages, including the ability to target multiple disorders effectively and ensuring a non-toxic confirmation.

While the invention is amenable to various modifications and alternative forms, some embodiments have been illustrated through examples in the drawings and are described in detail above. The intention, however, is not to limit the invention to those examples, and the invention is intended to cover all modifications, equivalents, and alternatives to the embodiments described in this specification.

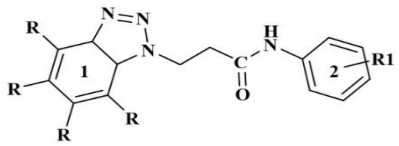
The embodiments in the specification are described progressively and the focus of description in each embodiment is the difference from other embodiments. For the same or similar parts of each embodiment, reference may be made to each other.

It will be appreciated by those skilled in the art that the above description was in respect of preferred embodiments and that various alterations and modifications are possible within the broad scope of the appended claims without departing from the spirit of the invention with the necessary modifications.

Based on the description of disclosed embodiments, persons skilled in the art can implement or apply the present disclosure. Various modifications of the embodiments are apparent to persons skilled in the art, and general principles defined in the specification can be implemented in other embodiments without departing from the spirit or scope of the present disclosure. Therefore, the present disclosure is not limited to the embodiments in the specification but intends to cover the most extensive scope consistent with the principle and the novel features disclosed in the specification.

We Claim:

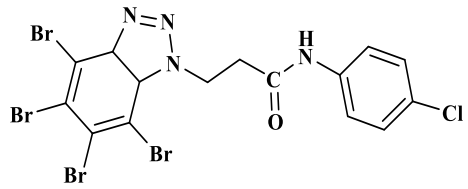
1. A compound of N-(aryl)-3-(perhalo-1*H*-benzo[d][1,2,3] triazol-1-yl) propenamide having formula (4-7) as follows:



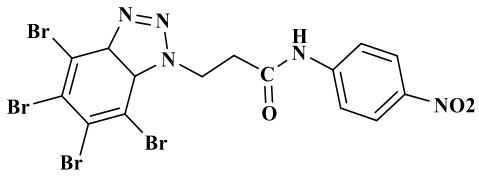
(4-7)

wherein R is Bromine (Br) or Chlorine (Cl) and R1 is Chlorine (Cl) or Nitrogen dioxide (NO2).

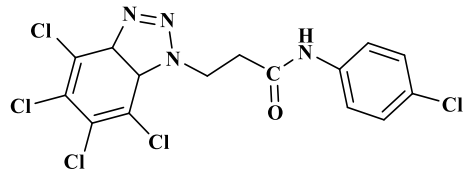
2. The compound as claimed in claim 1, wherein said compound is *N*-(4-chlorophenyl)-3-(perbromo-1*H*-benzo[d][1,2,3] triazol-1-yl) propenamide having the formula (4):



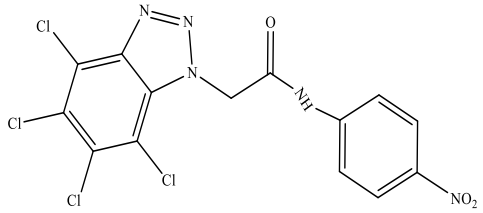
3. The compound as claimed in claim 1, wherein said compound is *N*-(4-nitrophenyl)-3-(perbromo-1*H*-benzo[d][1,2,3] triazol-1-yl) propenamide having the formula (5):



4. The compound as claimed in claim 1, wherein said compound is *N*-(4-chlorophenyl)-3-(perchloro -1*H*-benzo[d][1,2,3] triazol-1-yl) propenamide having the formula (6):



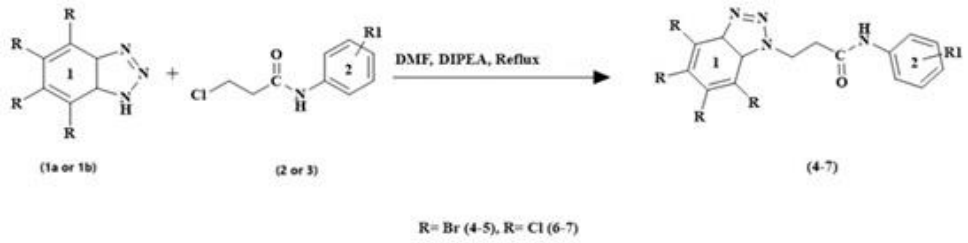
5. The compound as claimed in claim 1, wherein said compound is N-(4-nitrophenyl)-2-(perchloro-1H-benzo[d][1,2,3] triazol-1-yl) propenamide having the formula (7):



6. The compound as claimed in claim 1, wherein said compound of N-(aryl)-2-(perhalo-1*H*-benzo[d][1,2,3] triazol-1-yl)-propenamide of said formula (4-7) is synthesized by reacting a mixture of tetrachloro-benzotriazole and propenamide derivatives in dimethyl methyl formamide (DMF) with N,N-diisopropylethylamine as white powder.

7. The compound as claimed in claim 1, wherein said compound exhibits improved anti-HIV and antimicrobial activity.

8. A process for synthesizing compound of N-(aryl)-3-(perhalo-1*H*-benzo[d][1,2,3] triazol-1-yl) propenamide having formula (4-7) under Scheme 1 as follows:



comprising:

reacting 0.01-0.15 moles of precursor benzotriazole with a 0.45-3.15 M halogen source reagent in nitric acid under reflux conditions for 1-48 hours, to obtain a solution A;

filtering the solution A to obtain a precipitate of tetrahalo-benzotriazoles having formula (1a or 1b), wherein R = halogen, preferably Br or Cl;

recrystallizing the precipitate of formula (1a or 1b) in appropriate solvent yielding creamy or white crystals of the tetrahalo-benzotriazole having formula (1a or 1b);

adding 0.033 mole an aromatic amine to 0.21 M glacial acetic acid and stirring under ice-cooled condition to obtain a solution B;

mixing 0.037 M 3-chloropropionyl chloride dropwise to the solution B and stirring the mixture on ice bath for 30-60 minutes and continue stirring for an additional 1-2 hour at room temperature;

pouring the stirred mixture into saline water (pH-7) solution, mixing, and filtering it to obtain another precipitate of acetamide derivative having formula (2 or 3), wherein R1 = Cl or NO_2;

recrystallizing the another precipitate of formula (2 or 3) using a 2:1 mixture of ethanol and water yielding creamy or white crystals of the propenamide derivative having formula (2 or 3);

mixing the derivative having formula (1a or 1b) and the derivative having formula (2 or 3) in equal ratio followed by mixing with 0.25 M dimethylformamide and 0.001 M N,N-diisopropylethylamine and refluxing for 10-20 hours, preferably 15 hours;

cooling the mixture of formula (1a or 1b) and formula (2 or 3) at room temperature to separate a cream-colored crude solid followed by filtering the crude solid to obtain another precipitate of formula (4-7); and

recrystallizing the another precipitate of formula (4-7) using an alcohol to obtain a white powder compound having formula (4-7),

wherein R = halogen, preferably Br or Cl; and R1 = Cl or NO_2,

wherein said process is non-hazardous and involves single reaction for synthesizing the compound of N-(aryl)-3-(perhalo-1*H*-benzo[d][1,2,3] triazol-1-yl) propenamide having formula (4-7).

9. The process as claimed in claim 8, wherein said halogen source reagent includes bromine or hydrochloric acid.

10. The process as claimed in claim 8, wherein said appropriate solvent is selected from acetic acid or nitromethane.

11. The process as claimed in claim 8, wherein said aromatic amine is selected from 4-chloro aniline or 4-nitro aniline.

12. The process as claimed in claim 8, wherein said creamy or white crystals of tetrahalo-benzotriazole having formula (1a or 1b), is tetrabromo-benzotriazole or tetrachloro-benzotriazole.

13. The process as claimed in claim 8, wherein said creamy or white crystals of the propenamide derivative having formula (2 or 3) is 3-chloro-N-(4-chlorophenyl) propenamide (2) or 2-chloro-N-(4-nitroophenyl) propenamide (3).

14. The process as claimed in claim 8, wherein said alcohol is ethanol.

15. The process as claimed in claim 8, wherein said white powder compound having formula (4-7) is *N*-(4-chlorophenyl)-3-(perbromo-1*H*-benzo[d][1,2,3] triazol-1-yl) propenamide (4); *N*-(4-nitrophenyl)-3-(perbromo-1*H*-benzo[d][1,2,3] triazol-1-yl) propenamide (5); *N*-(4-chlorophenyl)-3-(perchloro -1*H*-benzo[d][1,2,3] triazol-1-yl) propenamide (6); or *N*-(4-nitrophenyl)-3-(perchloro -1*H*-benzo[d][1,2,3] triazol-1-yl) propenamide (7).

Dated this the 5th day of March, 2025



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TETRAHALO-BENZOTRIAZOLE DERIVATIVES AND PROCESS THEREOF FOR ANTIMICROBIAL APPLICATIONS

ABSTRACT OF THE INVENTION

Disclosed herein is a simple and non-hazardous process for synthesizing tetrahalo-benzotriazole derivatives. It involves reacting tetrahalo-benzotriazole with respective propanamide derivatives, leading to various *N*-(aryl)-2-(perhalo-1H-benzo[d][1,2,3] triazol-1-yl)-amides. The structures of synthesized compounds exhibiting significant antimicrobial activity against HIV-virus, gram-positive, gram-negative bacteria, mycobacteria, and fungi, are confirmed via NMR and LC-MS analysis. Furthermore, non-toxic properties of the synthesized compounds are determined, with no adverse effects at doses up to 2000 mg/kg body weight.

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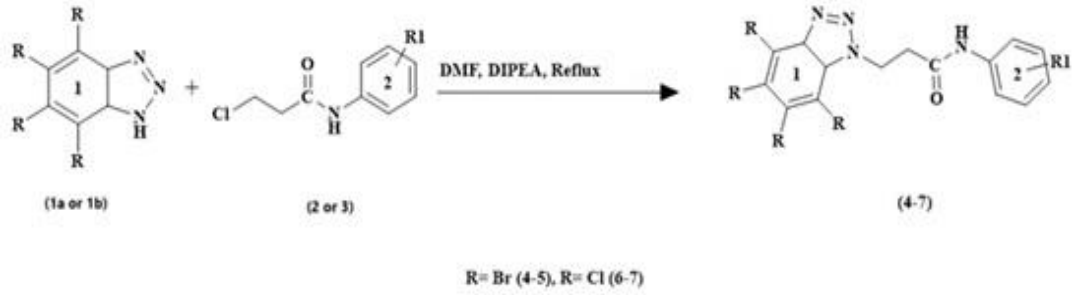
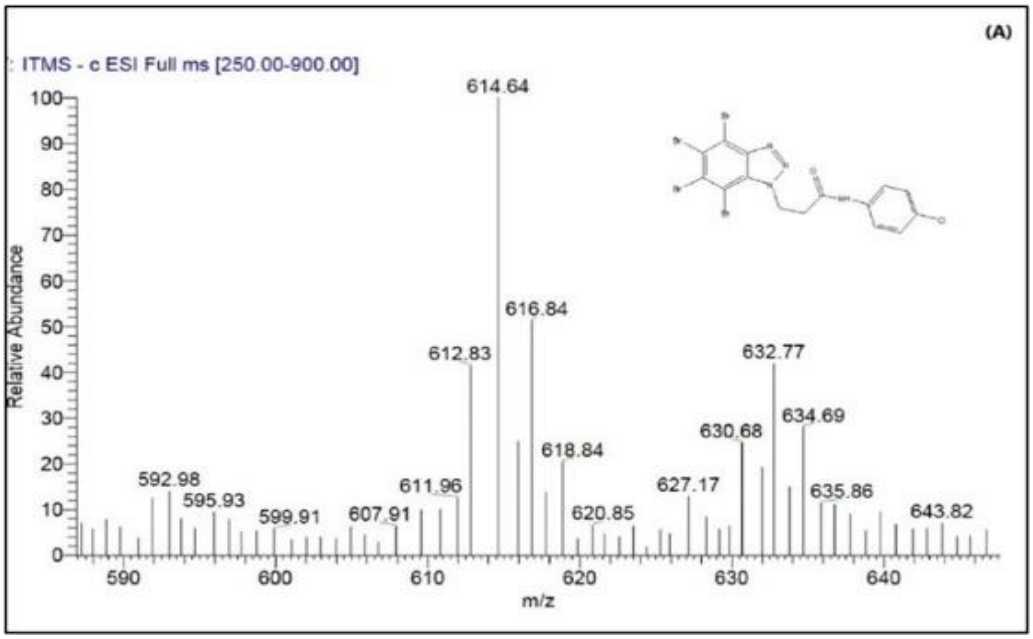


Figure 1

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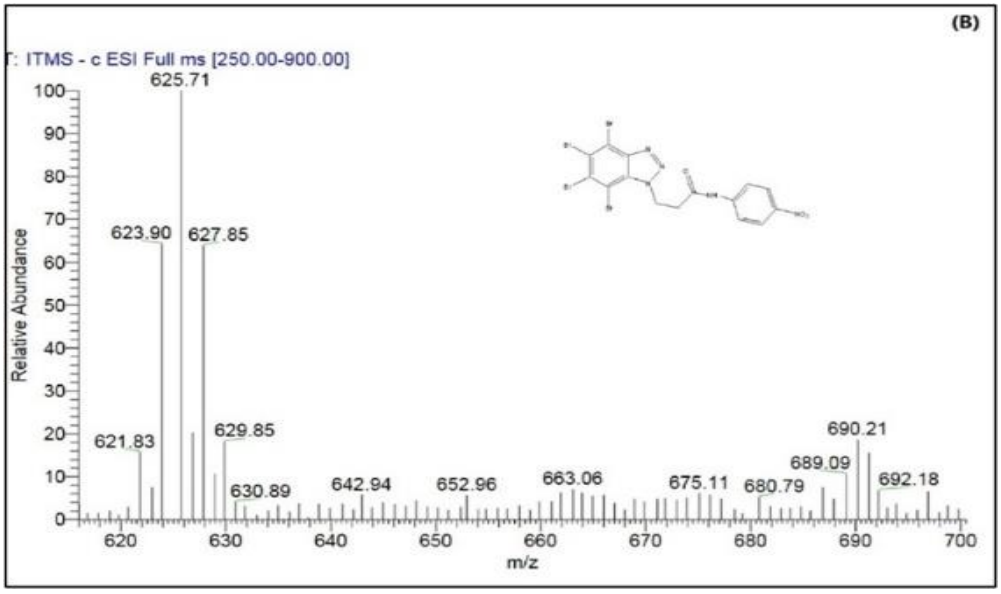


Figure 2 (A-B)

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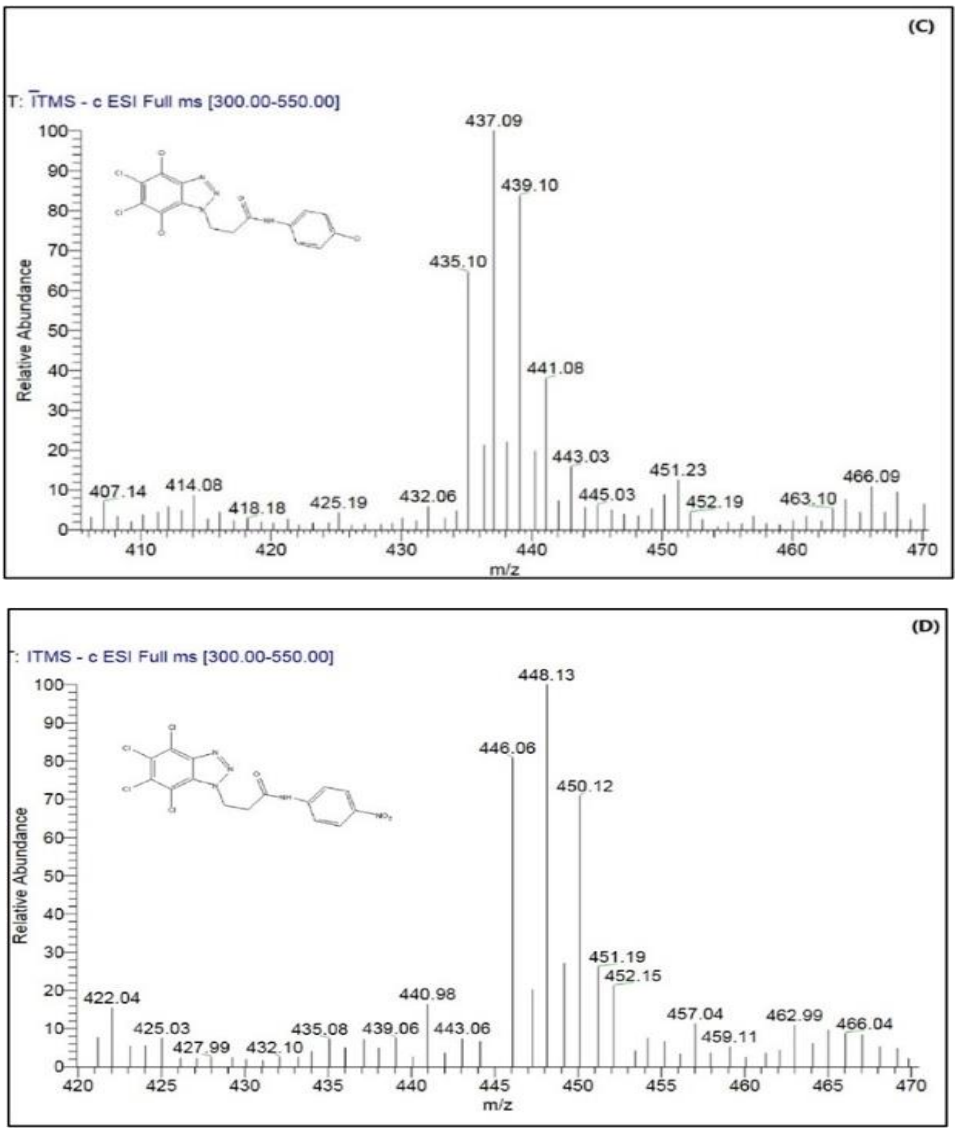
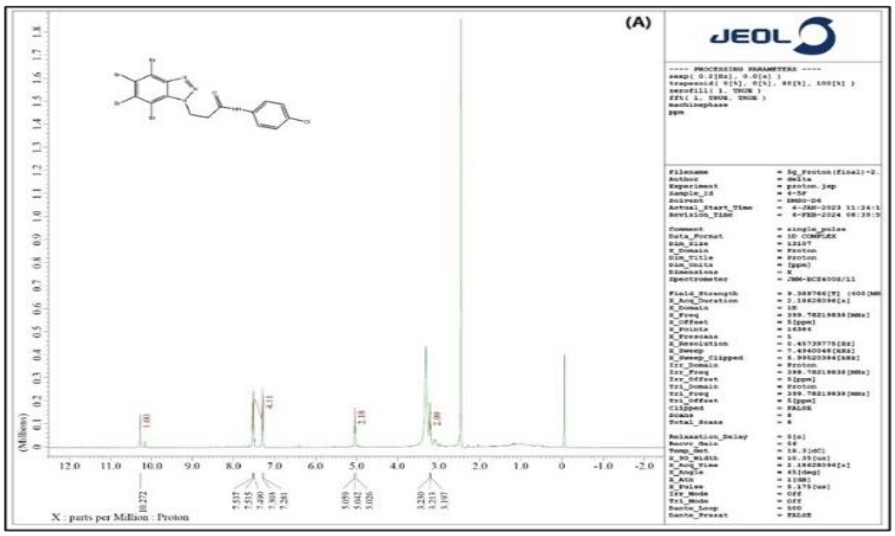


Figure 2 (C-D)

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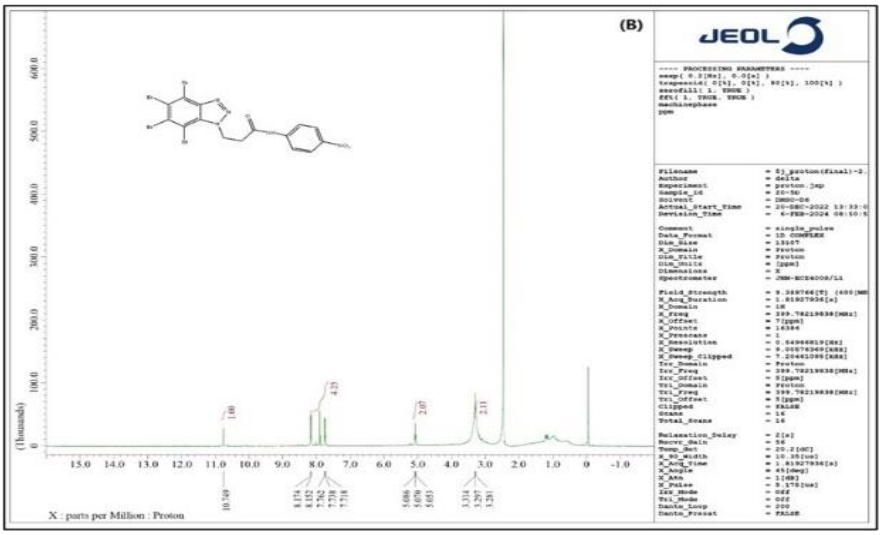
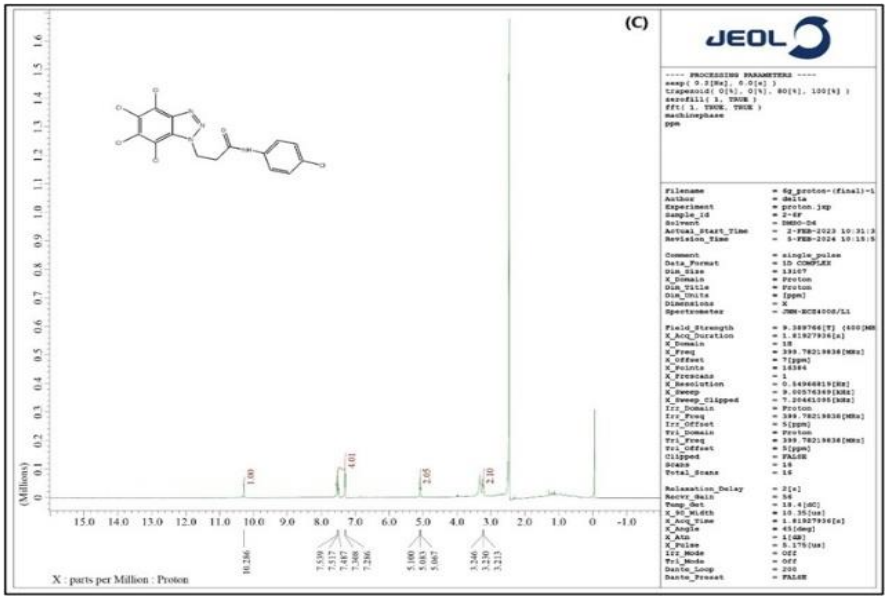


Figure 3 (A-B)

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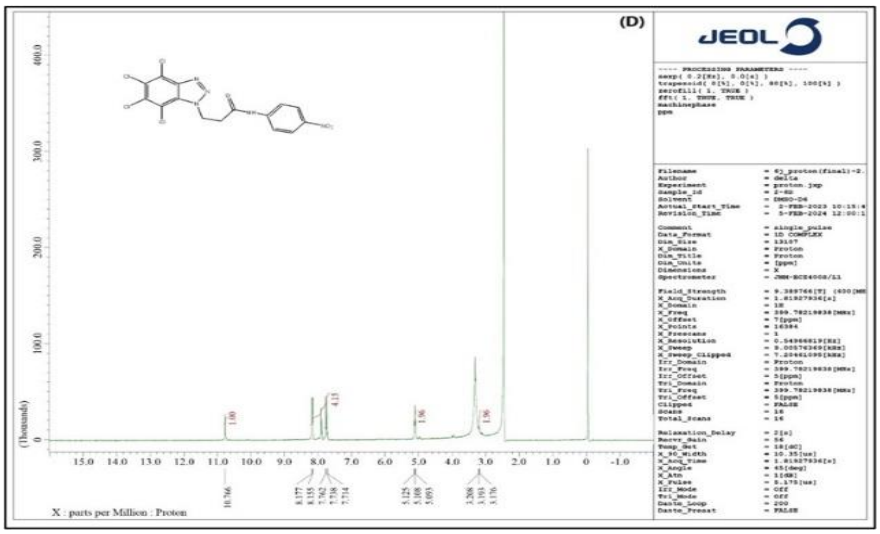
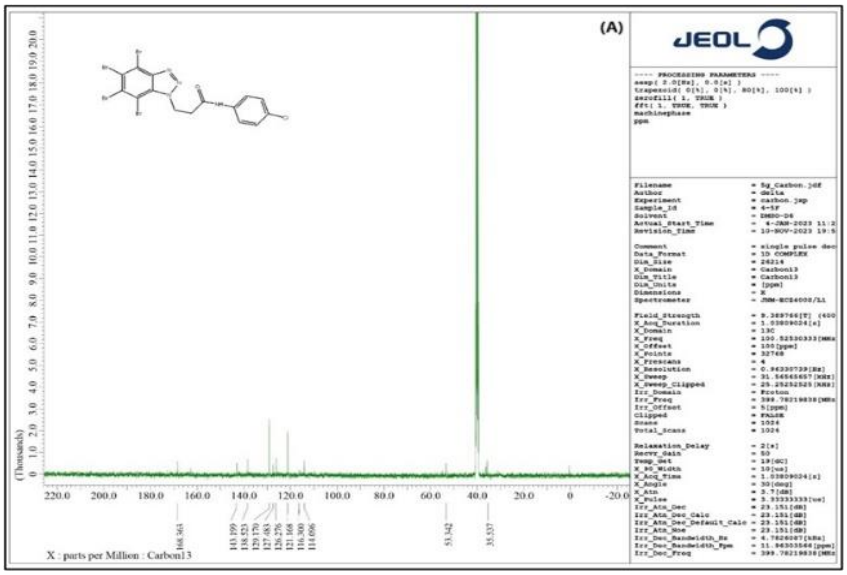


Figure 3 (C-D)

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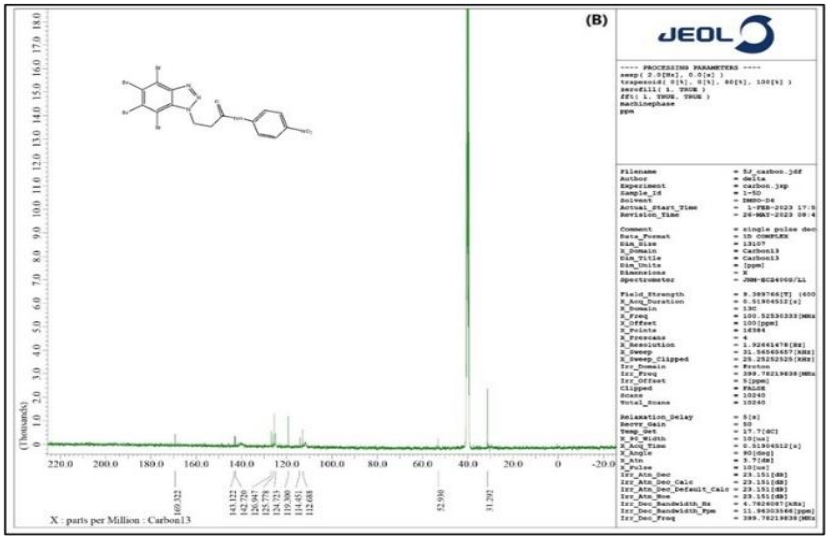


Figure 4 (A-B)

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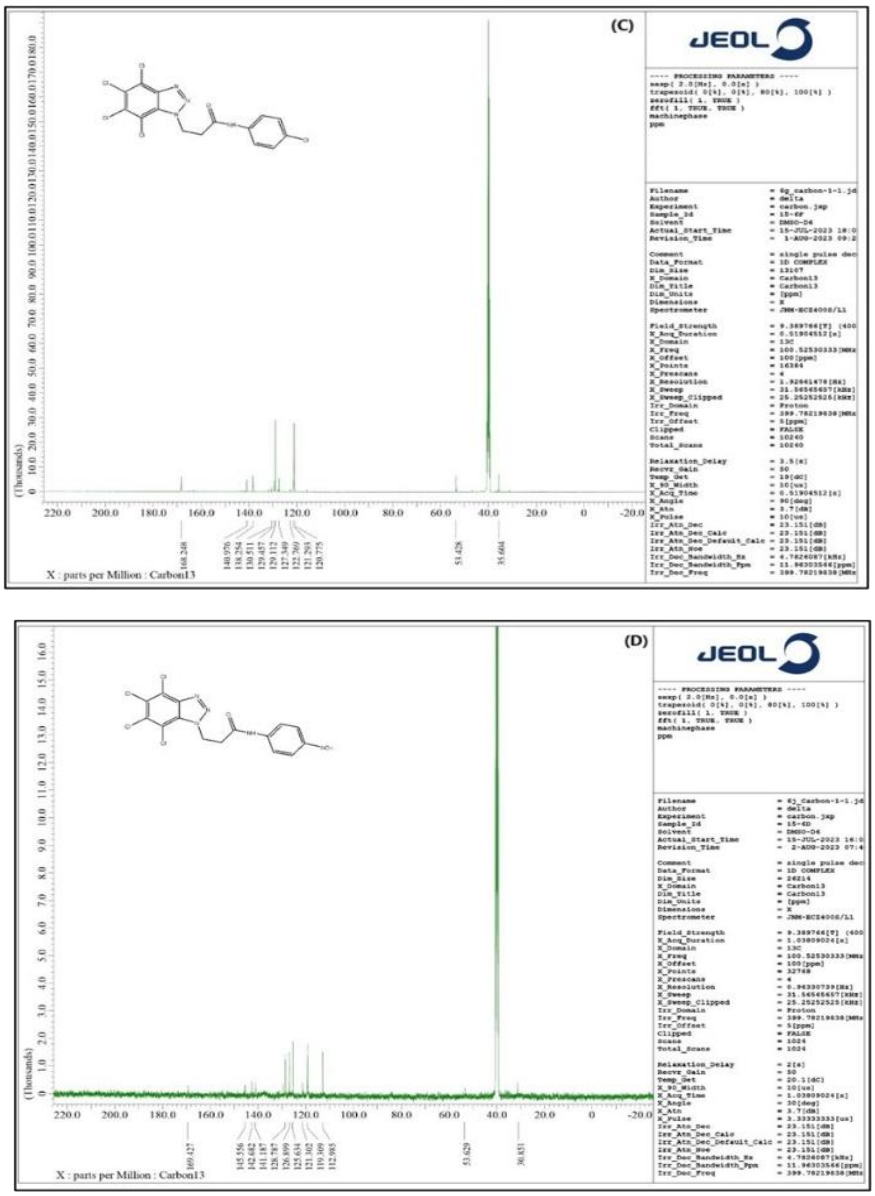


Figure 4 (C-D)

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