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Synthesis and Biological Significance of Fluorinated Cyclopropane-carbohydrazide based Benzylidene Derivatives

Khushal Kapadiya[1], Bhavika Joshi[2], Kinjal Chaniyara[2], Bansi Bavarava[2], Kishor Kavadia[2], Jyoti Gohel[2] and Ranjan Khunt[2]*

[1]School of Science, RK. University, Bhavnagar Highway, Rajkot-360020 (Gujarat) India
[2]Chemical Research Laboratory, Department of Chemistry, Saurashtra University, Rajkot-360005 (Gujarat) India
**E-mail: drrckhunt12@yahoo.com*
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Abstract: The present objective deals with the synthesis of a series of *(E)-N'-(substitutedbenzylidene)-2-(3,4-difluorophenyl)cyclopropanecarbohydrazide***(5a-j)**in an economically viable route. The structures of synthesized compounds have been confirmed by spectral analysis, such asMass, IR, ^{1}H *NMR* and ^{13}C*NMR*.All the synthesized compounds were screened for their*in vitro* antibacterial activity against some gram-positive (*Staphylococcus aureus, Streptococcus pyogenes*) and gram-negative (*Escherichia coli*, *Klebsila*) bacterial strains. The various arylidenes of novel cyclopropyl acid may provide valued therapeutic engrossmentin the treatment of microbial diseases, especially against bacterial infections.

Keywords: Cyclopropanecarboxylic acid, Antimicrobial screening, Benzylidene, Carbohydrazide.

INTRODUCTION

Biological activities of clinically approved motifs are the result of a chemical compound's interaction with a human organism after careful consideration of *in vitro* as well *in vivo* studies. Mainly the biological activity is dependent upon the compound's structure and its physical and chemical nature, biologically active entity and its mode of therapeutic treatment in the human structure. Even so, many times chemical compounds reveala spectrum of different types of biological activity. Some of them are useful in the treatment of precise diseases and to lowering its effects, where others may causevarious side effects as well as toxic effects. Activities showed by the chemical compound in biological entities are called the "biological activity spectrum of the substance".

Belongs to the broad area of chemistry, hydrazides, carbohydrazides and other similar compounds are well known as useful building blocks for the synthesis of a variety of heterocyclic rings. A large number ofheterocyclic carbohydrazides and their derivatives are reported to exhibit significant biological activities[1, 2, 3]and the carbohydrazide

function represents an important pharmacophore group in several classes of therapeutically useful substances[1, 3, 4-9].

Carbohydrazide derivatives of schiff bases are the important class of compounds owed to their wide range of pharmacological activities and industrial applications. These compounds are now used to express anticancer[10], anti HIV[11, 12], antitubercular[13], antiviral[14, 15], antimalarial[16], antibacterial[17]. Schiff base/benzylidene of some metal complex and also its derivatives sows analgesic and anti-inflammatory activities[18, 19]also. To manage pathogenic microorganisms a large number of antibacterial agents are available in nature,however, theycould not entirely destroy such organisms, perhapsdue to the pervasive irrational, unscientific and apathetic use of such motifs. In human cycle microorganisms have tended to matchto develop their own defenses. As a result, such drugs gradually lose their effectiveness in action. Repetition and overdose of those drugs often cause severe environmental pollution as well as lose their potency against specific disease. In order to get purge of this kind of situation, it has become a common practice to find out safer, more effective, easy to synthesize and inexpensive new chemical compounds as antibacterial agents.

In this paper, the authors will discuss the biological activity spectrum of various synthesizednovel cyclopropane based derivatives bearing a substituted carbohydrazidegroup at C-1 and a phenyl-substituted group at C-1. Allderivatives were evaluated for their *in vitro* activity against anti-microbial study using various gram positive and gram negative strains.

MATERIAL AND METHODS

Chemicals and solvents were purchased from the Sigma-Aldrich Chemical Co., Merck chemical, Finar and Spectrochem Ltd. The entire chemicals were used without further purification unless otherwise noted. Thin-layer chromatography was accomplished on 0.2 mm precoated plates of Silica gel G60 F254 (Merck). Visualization was made under UV light (254 and 365nm) or with an iodine chamber. IR spectra were recorded on an IR Affinity-1S spectrophotometer (Shimadzu). ^{1}H (400 MHz) and ^{13}C (101.1 MHz) NMR spectra were recorded on a Bruker AVANCE II spectrometer in $CDCl_3$. Chemical shifts are expressed in δ ppms downfield from TMS as an internal standard. Mass spectra were determined using a direct inlet probe on a GCMS-QP 2010 mass spectrometer (Shimadzu). Melting points were measured in open capillaries.

General procedure for the preparation of ethyl-2-(3,4-difluorophenyl) cyclopropanecarboxylate (2).

In a 100 ml conical flask equipped with a magnetic stirrer and the septum was charged with a solution of 2-(3,4-difluorophenyl) cyclopropanecarboxylic acid (2.0 mmol) in minutest quantities of ethanol (2.5 ml) and adds 2-3 drops of sulfuric acid (0.05 mmol). The reaction mixture was refluxed at 70 ^{0}C for 2 hrs. Cool the reaction mass and poured into water. The progress of the reaction was monitored by thin layer chromatography. The reaction mixture was filtered, washed with hot methanol and dried over vacuum drier. Compounds were directly used for the next step.

Yield: 94 %; mp 105 ^{o}C ; IR (cm^{-1}): 3039.55 (C-H Stretching), 1750.20 (Esteric carbonyl stretching), 1129.03(C-O bending), 1053.22 (C-F stretching in aldehydic ring), 831.32 (*p*-disubstituted aromatic ring); ^{1}H NMR (400 MHz, $CDCl_3$): 7.09 (m, 1H), 7.03 (m, 2H), 4.17 (q, 2H), 2.93 (m, 2H), 2.26 (m, 1H), 1.57 (m, 1H), 1.37 (t, 3H).;^{13}C NMR (101 MHz, $CDCl_3$) δ 173.51 (Carbonyl carbon), 150.70, 136.11, 121.63, 115.99, 113.95, 61.80, [28.69, 22.18,

14.22: Indicates cyclopropane ring carbons], 14.70 (Esteric methyl carbon).; MS: *m/z*226.1 (M).

General procedure for the preparation of 2-(3,4-difluorophenyl) cyclopropanecarbohydrazide (3).

To a mixture of compounds **(2)** (10 mmol) and hydrazine hydride(20 mmol) were stirred at room temperature for 4.0 hrs. The reaction processwas monitored by thin layer chromatography and after completion of the reaction; the reaction mixture was filtered out and dried in vacuum atmosphere. Isolate the products with the help of diethyl etherby stirring at RT for 10-15 mints. Filterout product and directly used for the next step.

Yield: 88 %; mp 148 ^{o}C ; IR (cm^{-1}): 3346.10 (-NH Stretching of hydrazide), 3029.36 (C-H Stretching), 3042.50 (C-H Stretching), 1698.21 (Amidic carbonyl stretching), 1131.01 (C-O bending), 1050.89 (C-F stretching), 830.45 (*p*-disubstituted aromatic ring); ^{1}H NMR (400 MHz, $CDCl_3$): 7.08 (m, 1H), 7.09 (m, 2H), 6.61 (s, 1H: -NH), 2.92 (m, 2H), 2.32 (s, 2H: -NH_2), 2.20 (m, 1H), 1.46 (m, 1H);^{13}C NMR (101 MHz, $CDCl_3$) δ 172.50 (Carbonyl carbon), 152.50, 139.22, 120.60, 114.88, 112.90, 65.80, [28.44, 21.58, 14.32: Indicates cyclopropane ring carbons], 14.89 (Esteric methyl carbon).; MS: *m/z*212.2 (M).

General procedure for the preparation of (E)-*N*'-(substitutedbenzylidene)-2-(3,4-difluoro phenyl)cyclopropanecarbohydrazide (5a-j).

A mixture of freshly prepared hydrazide intermediate **(3)** (0.01 mmol) and substituted aromatic aldehyde (0.02 mmol, 1.0 eq.) was dissolved in ethanol (3.0 ml) and add glacial acetic acid as a catalytic proportion (0.001 mmol). The reaction mixture was refluxed for 2.0 hrs at 70 ^{o}C temprature. After completion of the reaction, the reaction mixture was cooled at RT and poured into ice cold water. The reaction mixture was filtered out using vacuum and washed with cold water. The product was dried invacuum drier. Crystallization was carried out using ethanol to afford analytically pure products **5a-j**.

Antibacterial Assay

For antibacterial study, a 24 hrs fresh culture was found by inoculation of individual bacteria in double strength nutrient broth-I.P. shadowed by incubation at 37 ± 1 ^{o}C. The prepared stock solution (100 µg/ml) of synthesized various benzylidene hydrazide derivatives was serially diluted in tube[20]containing 1 ml of sterile double strength nutrient broth I.P.[21] to get a concentration of 50–3.125 µg/ml and then inoculated with 100 µl of suspension of the respective organisms in sterile saline (*Staphylococcus aureus, Streptococcus pyogenes and Escherichia coli, Pseudomonas aeruginosa*). The inoculated tubes were incubated at 37 ± 1 ^{o}C for 24 hrs and minimum inhibitory concentrations (MIC) were determined.

Spectral Discussion

(E)-*N*'-(4-Chlorobenzylidene)-2-(3,4-difluorophenyl) cyclopropanecarbohydrazide (5a).

IR (cm^{-1}): 3210.50 (N-H stretching broad), 3030 (aromatic stretching), 2924.09 (C-H stretching), 1651.07 (C=O stretching of amide), 1612.07 (C=N stretching), 1519,1458,1365 (Aromatic ring skeleton), 1404.18 (C-H bending), 1118.70 (N-H bending), 810.10 (Aromatic *p*- disubstitution), 771.53(C-F stretching), 666.30(C-Cl stretching);^{1}HNMR (400 MHz, $CDCl_3$) δppm:11.59 (s, 1H), 7.86 (m, 2H), 7.54 (m, 3H), 7.26 (m, 1H), 7.10 (m, 1H), 6.76 (m, 1H), 2.74 (m, 1H), 2.45 (dt, 1H), 1.74 (m, 1H), 1.14 (dt, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ

172.32, 152.00, 151.79, 150.85, 150.65, 149.81, 149.48, 149.27, 148.33, 148.13, 136.54, 136.51, 136.46, 136.43, 134.39, 133.54, 128.60, 128.50, 124.36, 124.33, 124.28, 124.24, 114.08, 114.00, 113.88, 113.80, 113.14, 113.06, 112.94, 112.86, 27.04, 26.99, 23.45, 15.98.

(E)-*N*'-(4-Ethoxybenzylidene)-2-(3,4-difluorophenyl) cyclopropanecarbohydrazide (5b).

IR (cm^{-1}): 3209.55 (N-H stretching broad), 3030(aromatic stretching), 2978.09 (C-H stretching), 1651.07 (C=O stretching of amide), 1604.77 (C=N stretching), 1512,1458,1390 (Aromatic ring skeleton), 1396.46 (C-H bending),1242.16 (C-O stretching), 1111.70 (N-H bending), 817.82 (*p*- disubstitution), 771.53 (C-F stretching);^{1}HNMR (400 MHz, $CDCl_3$) δppm:11.21 (s, 1H), 7.89 (m, 2H), 7.49 (m, 1H), 7.21 (m, 1H), 7.04 (m, 3H), 6.71 (m, 1H), 4.05 (q, 2H), 2.68 (m, 1H), 2.39 (dt, 1H), 1.69 (m, 1H), 1.34 (t, 3H), 1.08 (dt, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ175.02, 160.10, 155.15, 152.70, 152.01, 149.96, 148.60, 148.45, 148.02, 137.50, 136.50, 136.00, 135.20, 128.55, 127.65, 124.91, 124.53, 124.29, 124.09, 119.04, 116.01, 115.50, 114.80, 114.22, 113.15, 113.10, 112.54, 112.06, 65.30, 29.55, 26.98, 23.41, 19.20, 15.50.

(E)-*N*'-(3-Bromobenzylidene)-2-(3,4-difluorophenyl) cyclopropanecarbohydrazide (5c).

IR (cm^{-1}):3217.27 (N-H stretching broad), 3030(Aromatic stretching), 2978.09 (C-H stretching), 1651.07 (C=O Stretching of amide), 1604.77 (C=N stretching), 1512,1458,1390 (Aromatic ring skeleton), 1396.46 (C-H bending),1249.87 (C-O stretching), 1111.00 (N-H bending), 771 (C-F stretching), 779.24 (Aromatic *m*- disubstitution), 671.23(C-Br stretching);^{1}H NMR (400 MHz, $CDCl_3$) δppm:11.54 (s, 1H), 7.87 (td, 3H), 7.60 (m, 9H), 7.42 (t, 3H), 7.21 (m, 3H), 7.05 (m, 3H), 6.71 (m, 3H), 2.67 (qt, 3H), 2.39 (dt, 3H), 1.08 (dt, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.30, 155.05, 154.70, 152.80, 151.45, 151.08, 149.69, 148.27, 147.03, 146.10, 139.70, 137.59, 136.91, 136.46, 135.92, 133.52, 132.98, 130.07, 129.03, 125.55, 124.58, 124.08, 123.87, 121.03, 119.55, 115.69, 114.28, 113.55, 113.24, 113.16, 112.98, 29.34, 27.99, 24.40, 19.90.

(E)-*N*'-(2-Hydroxybenzylidene)-2-(3,4-difluorophenyl) cyclopropanecarbohydrazide (5d).

IR (cm^{-1}); 3634.19 (-OH stretching), 3209.55 (N-H stretching broad), 3030 (Aromatic stretching), 2924.09 (C-H stretching),1651.07 (C=O stretching of amide), 1612.07 (C=N stretching), 1519,1458,1365(ring skeleton), 1404.18 (C-H bending), 1118.70 (N-H bending), 1041.56 (-OH bending), 771.53 (C-F stretching), 717.52 (Aromatic *o*- disubstitution); ^{1}HNMR (400 MHz, $CDCl_3$) δppm:10.98 (s, 1H), 8.22 (s, 1H), 7.66 (d, 1H), 7.51 (m, 1H), 7.32 (td, 1H), 7.20 (m, 1H), 7.05 (m, 1H), 6.92 (m, 2H), 6.69 (m, 1H), 2.67 (qt, 1H), 2.39 (dt, 1H), 1.69 (m, 1H), 1.08 (dt, 1H);^{13}C NMR (101 MHz, $CDCl_3$) δ174.66, 159.90, 152.89, 151.75, 150.75, 150.48, 149.87, 149.15, 148.30, 148.56, 139.55, 138.98, 137.68, 136.96, 136.13, 135.10, 134.55, 133.55, 129.56, 126.55, 125.66, 124.88, 124.64, 122.57, 120.55, 118.59, 115.98, 114.57, 113.69, 113.26, 112.97, 112.70, 29.56, 27.82, 25.61, 17.82.

(E)-*N*'-(3,4-Dimethoxybenzylidene)-2-(3,4-difluorophenyl) cyclopropanecarbohydrazide(5e).

IR (cm^{-1}); 3201.83 (N-H stretching broad), 3030(Aromatic stretching), 2924.09 (C-H stretching), 1651.07 (C=O stretching of amide), 1612.07 (C=N stretching), 1512,1458,1334 (Aromatic ring skeleton), 1419.61 (C-H bending),1226.73 (C-O stretching), 1141.86

(N-H bending), 810.10 (Aromatic *p*-disubstitution), 771.53(C-F stretching);^{1}HNMR (400 MHz, $CDCl_3$) δppm:11.33 (s, 1H), 7.57 (m, 2H), 7.22 (m, 2H), 7.02 (m, 2H), 6.72 (m, 1H), 3.85 (d, 6H), 2.67 (m, 1H), 2.39 (dt, 1H), 1.69 (m, 1H), 1.08 (dt, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ174.56, 155.08, 154.70, 153.80, 152.95, 151.82, 150.18, 149.97, 149.23, 148.55, 139.70, 137.69, 137.29, 136.95, 136.35, 134.02, 133.68, 131.64, 129.29, 127.49, 125.88, 125.06, 124.95, 120.10, 117.29, 115.08, 114.29, 113.87, 113.54, 113.26, 112.94, 112.59, 29.68, 27.85, 25.86, 19.59.

(E)-*N*'-(3,4,5-Trimethoxybenzylidene)-2-(3,4-difluorophenyl) cyclopropanecarbohydrazide(5f).

IR (cm^{-1}); 3201.83(N-H stretching broad), 3030(Aromatic stretching), 2924.09 (C-H stretching), 1651.07 (C=O stretching of amide), 1612.07 (C=N stretching), 1512,1458,1334 (Aromatic ring skeleton), 1411.89 (C-H bending),1226.73 (C-O stretching), 1126.43 (N-H bending), 810.10 (Aromatic *p*-disubstitution), 771.53(C-F stretching);^{1}HNMR (400 MHz, $CDCl_3$) δppm:11.23 (s, 1H), 7.56 (t, 1H), 7.21 (m, 3H), 7.05 (m, 1H), 6.71 (m, 1H), 3.85 (s, 6H), 3.75 (s, 3H), 2.68 (m, 1H), 2.39 (dt, 1H), 1.69 (m, 1H), 1.09 (dt, 1H);^{13}C NMR (101 MHz, $CDCl_3$) δ174.30, 157.80, 155.59, 154.78, 153.77, 152.60, 151.59, 150.49, 149.55, 148.94, 145.29, 139.93, 137.26, 136.59, 136.23, 132.29, 130.31, 129.35, 127.34, 126.20, 119.19, 115.29, 114.24, 113.68, 113.19, 113.01, 112.59, 112.05, 110.84, 63.50, 59.19, 29.01, 26.53, 24.91, 19.90.

(E)-*N*'-(2,5-Dimethylbenzylidene)-2-(3,4-difluorophenyl) cyclopropanecarbohydrazide(5g).

IR (cm^{-1}); 3201.83(N-H stretching broad),3030(Aromatic stretching), 2924.09 (C-H stretching), 1651.07 (C=O stretching of amide), 1612.07 (C=N stretching), 1604.77(C-C stretching), 1519,1458,1365(Aromatic ring skeleton), 1404.18 (C-H bending), 1141.86 (N-H bending), 771.53(C-F stretching), 717.52 (Aromatic *o*- disubstitution);^{1}HNMR (400 MHz, $CDCl_3$) δppm:11.44 (s, 1H), 7.49 (d, 1H), 7.22 (m, 2H), 7.01 (m, 1H), 6.81 (m, 1H), 6.63 (m, 1H), 2.58 (m, 1H), 2.39 (m, 7H), 1.68 (m, 1H), 0.99 (dt, 1H);^{13}C NMR (101 MHz, $CDCl_3$) δ174.56, 159.81, 157.59, 155.70, 154.29, 153.56, 152.58, 150.20, 149.31, 148.69, 145.46, 139.50, 137.29, 136.86, 136.12, 133.49, 129.59, 126.29, 125.79, 124.94, 119.29, 116.67, 115.22, 114.83, 113.19, 112.94, 112.23, 111.80, 69.50, 59.24, 29.22, 28.19, 24.79, 17.90.

(E)-*N*'-(3,4-Bis(cyclopropylmethoxy) benzylidene)-2-(3,4-difluorophenyl) cyclopropanecarbo-hydrazide (5h).

IR (cm^{-1}); 3209.55 (N-H stretching broad),3030(Aromatic stretching), 2924.09 (C-H stretching), 1674.07 (C=O stretching of amide), 1612.07 (C=N stretching), 1519,1458,1365 (Aromatic ring skeleton), 1404.18 (C-H bending),1219.01 (C-O stretching), 1111.00 (N-H bending), 810.10 (Aromatic *p*- disubstitution), 763.81(C-F stretching);^{1}HNMR (400 MHz, $CDCl_3$) δppm: 11.20 (s, 1H),7.79 (d, 1H), 7.37 (q, 1H), 7.22 (m, 2H), 7.01 (m, 1H), 6.85 (m, 1H), 3.96 (d, 4H), 2.65 (qt, 1H), 2.43 (m, 1H), 1.91 (m, 1H), 1.32 (m, 2H), 1.06 (dt, 1H), 0.66 (m, 4H), 0.41 (m, 4H);^{13}C NMR (101 MHz, $CDCl_3$) δ174.00, 155.46, 154.89, 153.56, 152.60, 151.59, 150.79, 149.89, 149.59, 148.86, 148.68, 148.06, 139.50, 137.69, 136.19, 135.59, 129.41, 127.59, 126.86, 125.26, 125.08, 124.89, 119.57, 117.28, 115.95, 115.79, 114.22, 113.73, 112.94, 112.81, 79.59, 29.49, 28.29, 25.87, 19.28, 15.71, 14.28.

(E)-*N*'-(4-Methylbenzylidene)-2-(3,4-difluorophenyl) cyclopropanecarbohydrazide(5i).

IR (cm^{-1}); 3209.55 (N-H stretching broad), 3070 (Aromatic stretching), 2924.09 (C-H stretching), 1651.07 (C=O stretching of amide), 1612.07 (C=N stretching),1604.77(C-C stretching), 1519,1424,1357 (Aromatic ring skeleton), 1404.18 (C-H bending), 1111.00 (N-H bending), 810.10 (Aromatic*p*- disubstitution), 771.53(C-F stretching);^{1}HNMR (400 MHz, $CDCl_3$) δppm:11.10 (s, 1H), 7.91 (m, 2H), 7.77 (d, 1H), 7.40 (dq, 2H), 7.20 (m, 1H), 6.87 (m, 2H), 2.62 (m, 1H), 1.93 (dt, 1H), 1.05 (dt, MHz,$CDCl_3$):174.60,151.9,150.37,149.13,147.80,144.69,140.52,137.85,131.07,129.51,127.16,122.71,117.23,115.29,29.72,25.57,21.52,17.12.

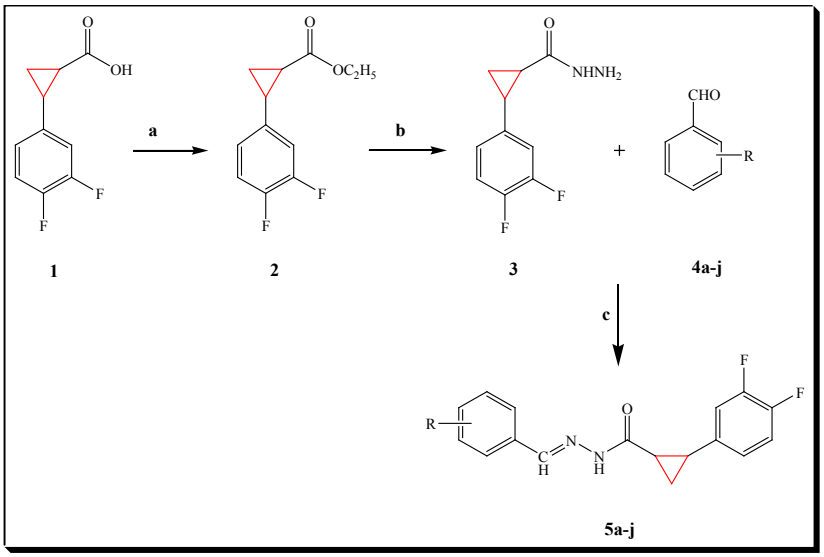
(E)-*N*'-(4-Fluorobenzylidene)-2-(3,4-difluorophenyl) cyclopropanecarbohydrazide(5j).

IR (cm^{-1}); 3201.83 (N-H stretching broad), 3030(Aromatic stretching), 2970.38 (C-H stretching), 1658.78 (C=O stretching of amide), 1604.77 (C=N stretching), 1519,1404,1350 (Aromatic ring skeleton), 1411.89 (C-H bending), 1110.00 (N-H bending), 840.10 (Aromatic *p*- disubstitution), 763.81(C-F stretching);^{1}HNMR (400 MHz, $CDCl_3$) δppm:11.23 (s, 1H), 7.79 (m, 2H), 7.51 (m, 1H), 7.23 (m, 3H), 7.05 (m, 1H), 6.71 (m, 1H), 2.67 (m, 1H), 2.39 (dt, 1H), 1.07 (dt, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ176.00, 169.85, 165.22, 159.19, 152.70, 151.59, 150.94, 150.19, 149.98, 149.07, 148.35, 148.14, 139.50, 137.15, 136.66, 136.29, 132.56, 131.88, 130.97, 129.97, 128.30, 126.34, 125.88, 127.58, 119.54, 116.64, 115.89, 114.82, 113.81, 113.12, 113.02, 112.58, 112.05, 29.87, 27.81, 25.40, 19.69.

RESULTS AND DISCUSSION

Chemistry

The synthesis of the target scaffold and its various derivatives **(5a-j)** was performed according to reactions outlined in **Reaction Scheme 1**. The 2-(3,4-difluorophenyl)cyclopropanecarboxylic acid **(1)** was refluxed with ethanol in the presence of catalytic amount of sulfuric acid to yield the ethyl ester **(2)**. The ethyl ester **(2)** was refluxed with hydrazine hydrate to yield the acid hydrazide **(3)**, which was then condensed with



Reaction and Conditions: **(a)** Ethanol, Sulfuric acid, 70 °C, 2.0 hrs; **(b)** Hydrazine hydrate, RT, 4.0 hrs; **(c)** Glacial acetic acid, Ethanol, 70 °C, 2.0 hrs.

Reaction Scheme 1: Synthesis of various derivatives of (E)-*N*'-benzylidene-2-(3,4-difluorophenyl)cyclopropanecarbohydrazide

corresponding aromatic aldehydes **(4a-j)** to yield the target substituted cyclopropanecarboxylic acid benzylidene hydrazide derivatives. The physicochemical characteristics of synthesized compounds **(5a-j)** are presented in **Table 1**.

IR, ^{1}H NMR and mass spectra of the synthesized compounds are in agreement with the assigned structures. The IR spectra of all synthesized compounds showed some characteristic peaks indicating the presence of particular groups in the adducts. Formation of the final compounds was confirmed by the absence of the absorption peak of the aldehydic carbonyl group and 1038–1055 cm^{-1} in IR due to the presence of C-O and C-O-C stretching respectively.

Code	R	M.F.	M.W. (gm/mol)	Yield (%)	mp (°C)	Rf[a]
5a	4-Cl	$C_{17}H_{13}ClF_2N_2O$	334.07	78	154	0.31
5b	4-OC_2H_5	$C_{19}H_{18}F_2N_2O_2$	344.13	84	162	0.34
5c	3-Br	$C_{17}H_{13}BrF_2N_2O$	378.02	76	176	0.42
5d	4-OH	$C_{17}H_{14}F_2N_2O_2$	316.1	81	166	0.45
5e	2,5-di OCH_3	$C_{19}H_{18}F_2N_2O_3$	360.35	87	204	0.39
5f	3,4,5-tri OCH_3	$C_{20}H_{20}F_2N_2O_4$	390	76	154	0.38
5g	2,5-diCH_3	$C_{19}H_{18}F_2N_2O$	328	87	158	0.30
5h	3,4-diCP[¶]	$C_{25}H_{26}F_2N_2O_3$	440	70	170	0.32
5i	4-CH_3	$C_{18}H_{16}F_2N_2O$	314	89	145	0.36
5j	4-F	$C_{17}H_{13}F_3N_2O$	318	76	150	0.40

[¶] **CP=** Cyclopropyl methoxy group; [a]Mobile phase:**hexane: ethyl acetate** (3:7)

Table 1: Physical parameters of synthesized compounds (**5a-j**).

The formation of intermediate compound **3** was confirmed by the absence of absorption bands around 1050 cm^{-1} corresponds to C–O–C stretches and appearance of peak around 3400 cm^{-1} in IR agrees to N–H stretching of NH_2. The appearance of a singlet around d 3.85 ppm for two protons in its ^{1}H NMR spectra which might be assigned to NH_2 group also confirms the formation of compound **3**. In ^{1}H NMR spectra appearance of a single proton in -CONH of compound **5a-5j** was confirmed by the appearance of a singlet at 9.85–9.97 ppm. The IR spectrumof title compound shows absorption bands at 3346– 3387 cm^{-1}, 1721–1738 cm^{-1}, and weak bands at 1612– 1647 cm^{-1}, which can be flexible to NH, C-O, and C-N vibrations respectively. IR spectrum of compounds **5a-5j** shows a specific IR frequency related to cyclopropane ring, which also confirmed that there is no **Bayers strain theory** apply and no opening of cyclopropane ring was taken place. In addition the presence of chlorine and bromine in compounds 5a and 5crespectively, was confirmed by the appearance of M+2 and M+1 peak in the mass spectrum with 3:1 and 1:1 abundance ratio. The proton magnetic resonance spectra of synthesized compounds were recorded in $CDCl_3$ solvent. The following inferences can be derived by comparing the ^{1}HNMR spectra of final compounds:

- A singlet at 2.19–2.54 ppm for one proton of methine carbon
- A multiplet at 6.86–8.22 ppm for Ar–CH,
- A singlet at ~6.70 ppm for –NH proton of -CONH group, moreover cyclopropane ring proton was also are in great agreement with desired motifs.

Biological Assessment

All the synthesized compounds were screened for their antibacterial activity against Gram-positive *(S. aureus, S. pyogenes)* and Gram negative *(E. coli, P. aeruginosa)* bacteria, using ciprofloxacin and chloramphenicol as the referral antibacterial agent. Results were expressed in **minimum inhibition concentration (MIC) (Table 2)**.

Compounds and standard drugs	Antibacterial activity			
	Minimum inhibitory concentration µg/ml			
	Gram +Ve Bacteria		Gram -Ve Bacteria	
	S. aureus	*S. pyogenes*	*E. coli*	*P. aeruginosa*
Ciprofloxacin	8.0	8.0	15.0	15.0
Chloramphenicol	8.0	8.0	15.0	8.0
5a	**8.90**	9.3	**15.20**	**15.31**
5b	9.9	14.0	18.50	**8.80**
5c	11.70	30.22	31.40	30.10
5d	**8.85**	**8.51**	31.50	42.00
5e	15.10	17.20	17.22	20.22
5f*	21.20	25.00	30.20	35.24
5g	15.70	15.50	17.60	20.25
5h	10.80	12.20	11.50	22.50
5i	**8.62**	11.25	**15.85**	**15.75**
5j	**9.1**	**9.03**	31.50	22.70

Table 2: Antimicrobial screening of compounds as a MIC **(5a-j)**
*Compounds show lowest activity

As shown in **Table2,** five compounds showed comparable activities with the standard against used various strains, compounds **5b** and **5i** showed the nearly same activity against *S. aureus,E. coli,*and *P. aeruginosa*, while the same were not showed markeble activity against *S. pyogenes* Moreover **5b** demonstrated better activity (MIC: **8.80** µg/ml) than Chloramphenicol against *P. aeruginosa*. Compounds **5d** showed the nearly same activity (MIC: **8.85 and 8.51** µg/ml respectively) against *S. aureus, S. pyogenes*, while none of the other synthesized compounds exhibited activity against both of these strains except compounds **5j**, which are active against both of these strains but in lower than the **5d**. Activities showed by above compounds **(5a, 5b, 5d, 5i)** is due to the presence of electron donating and withdrawing group at para position, compounds 5f was not showed activities against any of the used strains, may be due to more substitutions presence in compounds *i.e.***Trimethoxy group** in aldehydic ring.

Overall study shows that, there is necessary step should be taken to modified the synthesized scaffold to increase its potency in the area of antimicrobial agents.

CONCLUSION

A series of compounds *(E)-N'-(substitutedbenzylidene)-2-(3,4-difluorophenyl) cyclopropanecarbohydrazide* **(5a-j)** containing hydrazide as a core, were synthesized from 2-(3,4-difluorophenyl)cyclopropanecarboxylic acid. The screening of antimicrobial activity of the synthesized compounds has revealed

that some of the compounds are active against Gram-positive *(S. aureus, S. pyogenes)* and Gram negative *(E. coli, P. aeruginosa)* bacteria at comparable concentrations as compared to used standard drugs. The antimycobacterial activity results showed that the presence of electron-withdrawing halogen groups (viz. chloro, bromo, and fluoro) and electron donating groups (viz. Me, Et, Hydroxyls) at ***para*** position of the phenyl ring, which exhibited minimum sterically repulsion **(5a, 5d, 5i, 5j)**improved the antibacterial activity as compared to more substituted group **(5f)**.

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REFERNCES

1. A. K. Mansour, M. M. Eid, N. S. Khalil, Molecules, **2003**, 8, 744-755.
2. K. A. Metwally, L. M. Abdel-Aziz, E. S. M. Lashine, M. I. Husseiny, R.H. Badawy, Bioorg. Med. Chem.,**2006**, 14, 8675-8682.
3. P. Bharath Kumar, S.Subramaniyan, K.Yamini, Rasayan J. of chemistry, **2011**, 4, 2, 400-404.
4. C. Ghiglieri-Bertez, C. Coquelet, A. Alazet, C. Bonne, Eur. J. Med. Chem.,**1987**, 22, 147-152.
5. D. W. Combs, M. S. Rampulla, J. P. Demers, R. Falotico, J. B. Moore, J. Med. Chem.,**1992**, 35, 172-176.
6. M. L. C. Montanari, C. A. Montanari, Quím. Nova,**2002**,25, 231-240.
7. A. R. Farghaly, J. Chin. Chem. Soc.,**2004**, 51, 147-156.
8. B. Sapijanskaite, V. Mickevièius, Chem. Heterocycl. Compd.,**2008**, 44, 807-814.
9. Y. Xia, X. D. Fan, B. X. Zhao, J. Zhao, D. S. Shin, J. Y. Miao, Eur. J. Med. Chem.,**2008**, 43, 2347-2353.
10. M. M. Ali, M. Jesmin, M. K. Islam, M. A. K Azad, Med. J. Isl. W. Acad. Sci.,**2013**, 21(3), 47-104.
11. W.W.Wardakhan, S. N. Nasser Eid, R. M.Mohareb, Acta Pharmaceutica.,**2013**, 63,1, 45–57.
12. S. N. Pandeya, G. Nath, E. DeClecq, Euro. J. Pharm.,**1999**, 9(1), 25-31.
13. M. R. Islam, A. H. Mirza, Q. M. N. Huda, B. R. Khan, J. Bang. Chem. Soc.,**1989**, 2, 87-95.
14. C. Jr. Shipman, S. H. Smith, J. C. Drach, D. L. Klayman, Antiviral Res.,**1986**, 6(4) 197-22.
15. Y. Li, Z. S. Yang, H. Zhang, B. J. Caw, F. D. Wang, Bio Org. & Med. Chem.,**2003**, 11, 4363-4368.
16. M. N. Islam, S. M. S. Shahriar, M. K. Islam, M. Jesmin, M. M. Ali, J. A. Khanam, International Letters of Chemistry, Physics and Astronomy,**2013**, 5, 12-20.
17. B. Prabhakaran, N. Santhi, M. Emayavaramban, International Letters of Chemistry, Physics and Astronomy,**2013**, 3, 53-66.
18. J. Mele, M. Islam, S. Mohsin Ali, International Letters of Chemistry, Physics and Astronomy,**2014**, 8, 64-72.
19. A. Kajal, S. Bala, S. Kamboj, V. Saini, Medicinal Chemistry Research, **2014**, 23, 5, 2676-2689.
20. J. G. Cappucino, N. Sherman, Microbiology—a laboratory manual. Addison Wesley Longman Inc., Redwood City, **1999**, 263.
21. Pharmacopoeia of India, Controller of Publications, vol I. Ministry of Health Department, Govt. of India, New Delhi, **2007**, 37.