IJPSR (2023), Volume 14, Issue 1 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 31 March 2020; received in revised form, 09 November 2020; accepted, 05 November 2022; published 01 January 2023

SYNTHESIS OF (2, 4-DIMETHOXY – 3 - ((3 – PHENYL - 4, 5 – DIHYDROISOXAZOL – 5 - YL) METHOXY) PHENYL) (PHENYL) METHANONE AND THEIR ANTIBACTERIAL ACTIVITY

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Keywords:

2,6-dimethoxy phenol, Aryl (3-hydroxy2, 4-dimethoxyphenyl) methanones, 5- (bromomethyl)-3-phenyl-4,5- dihydroisoxazole, ((2,4-dimethoxy-3- ((3-phenyl-4,5-dihydroisoxazol-5- yl)methoxy) phenyl) (phenyl) methanone, Agar well method, Antibacterial activity

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ABSTRACT: In this study, a series of novel Synthesis of (2,4-dimethoxy-3-((3- phenyl-4, 5- dihydroisoxazol-5-yl) methoxy) phenyl) (phenyl) methanone (8a-p), were synthesized from condensation of an equimolar quantity of aryl (3- hydroxy-2, 4-dimethoxyphenyl) methanones (4a-d) and 5-(bromomethyl)-3- phenyl-4,5-dihydroisoxazole (7a-d) in DMF solvent by employing anhydrous potassium carbonate (K_2CO_3) as a base. The chemical structure of the newly synthesized compounds was characterized by analytical and spectral (^{1}HNMR, ^{13}CNMR and HRMS) techniques. The desired title compounds were screened for qualitative (zone of inhibition) analysis by agar well method, respectively. Among the synthesized compounds in the series, the compounds 8b, 8c, 8f and 8l were found to show major antibacterial activity at a lower concentration, against Gram-positive bacteria such as *Bacillus subtilis*, *Staphylococcus aureus* and Gram-negative bacteria such as *Salmonella typhimurium*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*. The rest of the compounds exhibited ample antibacterial activity compared to Chloramphenicol's standard positive controls.

INTRODUCTION: Benzophenones, like other ketone functionalities, consist of a carbonyl carbon that undergoes intersystem crossing in high yields, making it a robust triplet photosensitizer for use in organic and biological chemistry [1]. Its extensive chemical and physical properties have been studied; however, notable physical and chemical features relevant to this review are discussed here. They are also found in natural products that have broad-spectrum biological effects such as anticancer, antiviral, antimicrobial and anti-inflammatory effects [2].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.14(1).349-56

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.14(1).349-56

However, some research groups continue to explore benzophenone groups in their drug discovery efforts. The interested reader may consult a recent review [3] for further insight into the medicinal properties of benzophenone-containing natural products. The benzophenone analogues have been synthesized by implementing A. Ghinet *et al.,* procedure [4]. Methodologies for synthesizing the core heterocycle linked benzophenones mainly rely upon Friedel craft's acylation, the coupling of hydroxyl benzophenones [5] with 1,2- isoxazolines using potassium carbonate.

This leads us to combine both the bioactive molecules in a single molecular frame to determine the chemical effect towards the antibacterial activity. In recent years, the production of heterocyclic compounds linking multi-structure in a molecule has received significant interest in organic chemistry.

Due to their variable substituents and complex ring systems, many more new benzophenones, especially polyprenylated benzophenones (PPBS), have been identified and reported from higher plants, certain fungi, and some of these reported new compounds have unusually rearranged skeletons with strong antibacterial or anticancer activity [6]. In addition, the strategy to synthesize benzophenones has attracted considerable attention. Heterocycle [7] are well known in all kinds of organic compounds and serves as a key template for various therapeutic agents' development. Researchers have devoted much to finding the optimal synthetic approaches for different heterocyclic compounds [8]. Isoxazolines can be synthesized by the cycloaddition of nitrile oxides derived from respective oximes with alkenes [9]. Cycloaddition reactions are involved in isoxazolines, forming two or more bonds simultaneously and sequentially with a high degree of regioselectivity and stereoselectivity [10]. Cycloaddition is the combination of two or more π systems to form stable cyclic molecules [11] during which sigma bonds are formed between the terminal π systems. The two types of cycloaddition reactions are the Deils-Alder reaction and 1, 3-dipolar cycloaddition reaction [12].

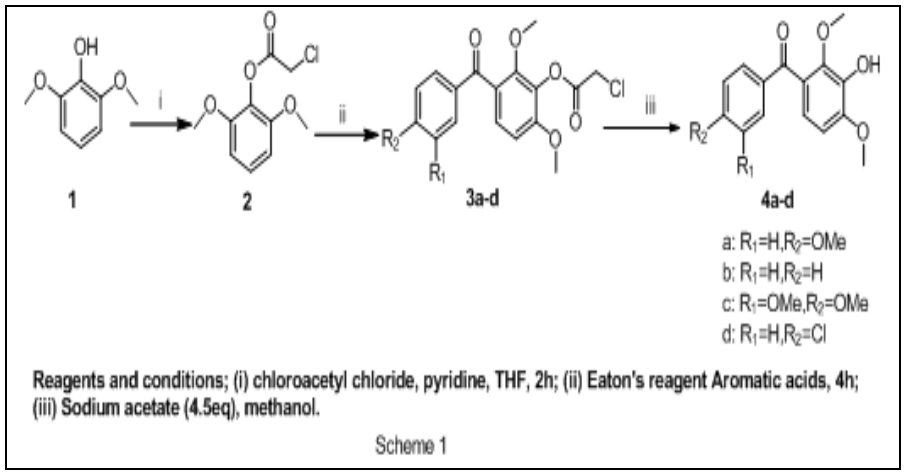
MATERIALSANDMETHODS:

Materials:

Chemistry: The solvents and reagents used were of Analytical Reagent grade and commercially accessible. All melting points were determined by subjecting a compound in melting point apparatus. The 1HNMR spectra were recorded on ShimadzuAMX400-Bruker, 400MHz spectrometer using $CDCl_3$ as a solvent and TMS as internal standard (chemical shift δ in ppm). The Elemental (C,H,N) analyses were achieved on Vario ELIII Elementar. Column chromatography was performed using Merck Silica gel (100-200mesh), and Merck made TLC plates were used for reaction monitoring. Mass spectra were documented on LC-MS Agilent 1100 series with MSD (Iontrap) using 0.1% aqueous TFA in acetonitrile system on C18-BDS Column for 10-minute duration.

Methodology:

General procedure for the synthesis of (2,4-dimethoxy – 3 - ((3 – phenyl - 4, 5-dihydroisoxazol-5-yl) methoxy) phenyl) (phenyl) methanone (8a-p): Individually, the (3-hydroxy-2,4-dimethoxyphenyl) arylmethanone (4a-d) molecules and 5-(bromomethyl)-3-phenyl-4,5-dihydroisoxazole (7a-d) molecules were taken in round bottomed flask and dissolved in DMF solvent and added K_2CO_3. The reaction mixture was refluxed for 4h and the completion of the reaction was examined through thin layer chromatography. The reaction mixture was cooled and cautiously poured into crushed ice and allowed for stirring. The aqueous solution was extracted with diethylether; the organic layer was washed with water, followed by brine solution, dried over sodium sulfate and concentrated under reduced pressure toa cquire the crude product. The crude product was purified by column chromatography using petroleum ether: ethyl acetate as an eluent to afford (2, 4-dimethoxy-3-((3-phenyl-4,5-dihydroisoxazol 5yl) methoxy) phenyl) (phenyl) methanone (8a-p).

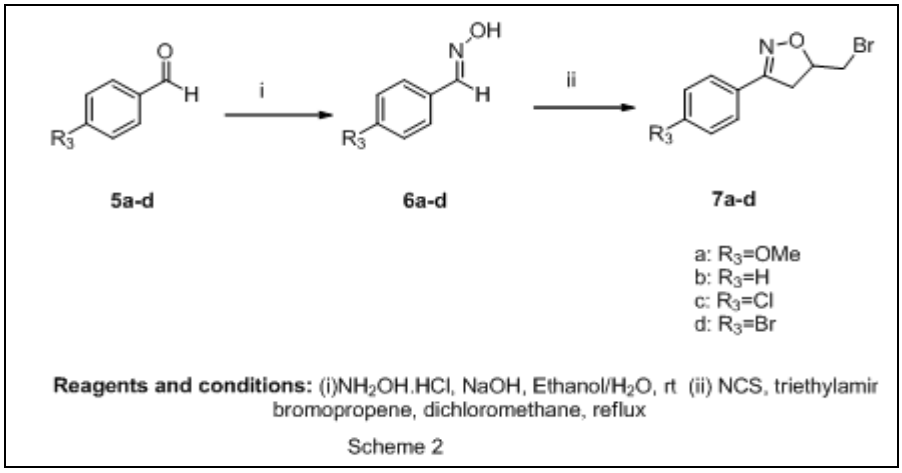


Reagents and conditions; (i) chloroacetyl chloride, pyridine, THF, 2h; (ii) Eaton's reagent Aromatic acids, 4h; (iii) Sodium acetate (4.5eq), methanol.

Scheme 1

A Typical Procedure is Described for the Synthesis of (2,4-dimethoxy-3-((3-phenyl-4,5-dihydroisoxazol-5-yl) methoxy) phenyl) (phenyl) methanone (8f): The aryl (3-hydroxy-2,4-dimethoxyphenyl) (phenyl) methanone (4a) (0.2g,0.0007mol) and 5-(bromomethyl)-3-phenyl-4,5-dihydroisoxazole (7b) (0.14g,0.0007mol) were taken and dissolved in 10ml DMF and added K_2CO_3(0.19g,0.0014mol). The reaction mixture was then refluxed for 3h and concentrated to get the crude product. The reaction progress was monitored through TLC and after the completion of the reaction; the reaction mixture was added to 10 ml of ice cold water. The reaction mixture was extracted with 15ml of diethylether, washed with 15ml of brine, dried over Na_2SO_4 and concentrated under reduced pressure to acquire the crude product. The crude product was purified by column chromatography using silicagel 60:120 and petroleum ether: ethylacetate as an eluent to afford (2,4-dimethoxy-3-((3-phenyl-4, 5-dihydroisoxazol-5-yl) methoxy) phenyl) (phenyl) methanone 8f, as a white solid (0.25g, 85%).

^{1}HNMR (400MHz, $CDCl_3$): δ 3.49 (dd,1H, *J*=6.4, 16.8Hz), 3.57(dd,1H, *J*=8.8, 10.8Hz), 3.76(dd, 1H, *J*=10.8, 17.6Hz), 3.83 (s,6H, OCH_3), 4.18 (dd,1H, *J*=4.4, 10.4Hz), 5.04(m,1H), 6.22(s,1H, Ar-H) 6.70(t,1H, *J*=8.60, Ar-H) 6.83(d, 1H, *J*=8.23, Ar-H) 6.92 (m,3H, Ar-H), 7.08 (d,1H, J=7.23, Ar-H), 7.31(m, 1H, Ar-H), 7.53(d,1H, J=7.90, Ar-H), 7.62(d, 1H, J=7.82, Ar-H), 7.70 (d,2H, J=8.24, Ar-H); LCMS: *m/z*= 418.10 $(M+1)^+$; Anal. Calcd for $C_{25}H_{23}NO_5C$, 71.93; H, 5.55; N, 3.36; O, 19.16; Found: C, 70.93; H, 5.35; N, 4.36; O, 19.3.



Scheme 2

(2, 4-dimethoxy-3-((3-(4-methoxyphenyl)-4, 5-dihydroisoxazol-5-yl) methoxy) phenyl) (4-methoxyphenyl) methanone (8a):
^{1}HNMR (400MHz, $CDCl_3$): δ 3.32 (dd,1H, *J*=6.6, 16.6Hz), 3.39(dd,1H, *J*=8.8, 10.8Hz), 3.48(dd, 1H, *J*=10.8, 17.6Hz), 3.77 (s,12H, OCH_3), 4.10(dd,1H, *J*=6.4, 10.4Hz), 4.98-4.99(m,1H), 6.63(d,1H, *J*=8.24Hz, Ar-H), 7.05 (m,5H,Ar-H), 7.62(d,2H, *J*=7.82Hz, Ar-H), 7.69 (d,2H, *J*=8.24, Ar-H); LCMS: *m/z*= 478.10 $(M+1)^+$; Anal. Calcd for $C_{27}H_{27}N0_7$ C, 67.91; H, 5.70; N, 2.93; O, 23.45; Found: C, 68.96; H, 6.80; N, 3.98; O, 22.25.

(2, 4 – dimethoxy – 3 - ((3 – phenyl - 4, 5-dihydroisoxazol-5-yl) methoxy) phenyl) (4-methoxyphenyl) Methanone (8b):
^{1}H NMR (400MHz, $CDCl_3$): δ 3.32 (dd, 1H, J=6.4, 16.6Hz), 3.36 (dd, 1H, J=8.6, 10.4Hz), 3.46 (dd, 1H, J=10.6, 17.2Hz), 3.87 (s, 9H, OCH3), 4.12 (dd, 1H, J=6.2, 10.6Hz), 4.99 (m,1H), 6.64 (d, 1H, J=8.62Hz, Ar-H), 7.06 (d, 3H, J=7.23Hz, Ar-H), 7.54 (d,3H, J=7.90, Ar-H); LCMS: m/z= 448.12 (M+1)+; Anal. Calcd for $C_{26}H_{25}NO_6C$, 69.79; H, 5.63; N, 3.31; O, 21.45; Found: C, 68.59; H, 5.53; N, 4.41; O, 21.65.

(3-((3 - (4 - chlorophenyl) - 4, 5 - dihydroisoxazol – 5 -yl) methoxy)-2, 4-dimethoxyphenyl) (4-methoxyphenyl) methanone (8c):
^{1}HNMR (400MHz, $CDCl_3$): δ 3.41 (dd,1H, *J*=8.4, 16.6Hz), 3.63(dd,1H, *J*=10.4Hz, 10.4Hz), 3.66(dd, 1H, *J*=12.2Hz, 17.2Hz), 3.77 (s,9H, OCH_3), 4.10(dd,1H, *J*=4.4, 10.4Hz), 4.98-4.99(m,1H), 7.05 (d,1H,*J*=8.4Hz, Ar-H), 7.18-7.70(m,9H,Ar-H); LCMS: *m/z*= 482.18 $(M+1)^+$, 484.09 $(M+3)^+$; Anal. Calcd for $C_{26}H_{24}ClNO_6C$, 64.80; H, 5.02; Cl, 7.36; N, 2.91; O, 19.92; Found: C, 65.70; H, 5.12; Cl, 7.50; N, 2.85; O, 19.99.

(3-((3-(4-bromophenyl)-4,5-dihydroisoxazol-5-yl) methoxy) - 2, 4 - dimethoxyphenyl) (4-methoxyphenyl) methanone (8d):
^{1}HNMR (400MHz, CDCl3): δ 3.43 (dd,1H, *J*=8.6, 18.4Hz), 3.62(dd,1H, *J*=10.6Hz, 16.6Hz), 3.65(dd, 1H, *J*=12.2Hz, 18.8Hz), 3.80 (s,9H, OCH_3), 4.12(dd,1H, *J*=4.4, 10.6Hz), 4.99(m,1H), 7.06 (d,1H,*J*=8.4Hz, Ar-H), 7.20-7.70 (m,9H, Ar-H); LCMS: *m/z*= 562.14 $(M+1)^+$, 528.06 $(M+3)^+$; Anal. Calcd for $C_{26}H_{24}BrNO_6C$, 59.33; H, 4.60; Br, 15.18; N, 2.66; O, 18.24; Found: C, 60.43; H, 3.50; Br, 16.18; N, 2.77; O, 17.14.

(2, 4 – dimethoxy – 3 - ((3 - (4 - methoxyphenyl) -4, 5-dihydroisoxazol-5-yl) methoxy) phenyl) (Phenyl) methanone (8e):
^{1}HNMR (400MHz, $CDCl_3$): δ 3.45 (dd, 1H, *J*=8.8, 18.6Hz), 3.58(dd, 1H, *J*=10.4Hz, 16.8Hz), 3.60(dd, 1H, *J*=12.4Hz, 8.6Hz), 3.83 (s,9H, OCH_3), 4.10(dd,1H, *J*=4.6, 10.6Hz), 4.98(m,1H), 7.08(d,1H, *J*=8.63Hz) 7.18-7.68(m,9H, Ar-H); LCMS: *m/z*= 448.13 $(M+1)^+$; Anal. Calcd for $C_{26}H_{25}NO_6$ C, 69.79; H, 5.63; N, 3.13; O, 21.45; Found: C, 20.59; H, 5.63; N, 3.23; O, 20.45.

(3 - ((3 - (4 - chlorophenyl) - 4, 5-dihydroisoxazol -5-yl) methoxy) - 2, 4-dimethoxyphenyl) (phenyl) methanone (8g):
^{1}HNMR (400MHz, $CDCl_3$): δ 3.46 (dd,1H, *J*=8.8, 18.6Hz), 3.64(dd,1H, *J*=10.6Hz, 17.2Hz), 3.68(dd, 1H, *J*=12.8Hz, 8.8Hz), 3.83 (s,6H, OCH_3), 4.11(dd,1H, *J*=4.6, 10.8Hz), 4.99(m,1H), 7.06 (d,1H, *J*=8.3Hz) 7.18(d,1H,*J*=7.6, Ar-H), 7.56(m,5H, Ar-H), 7.64(d,2H, *J*=8.2Hz, Ar-H), 7.72(d,2H,*J*=8.4,Ar-H); LCMS: *m/z*= 452.03 $(M+1)^+$, 454.12 $(M+3)^+$; Anal. Calcd for $C_{25}H_{22}ClNO_5$ C, 66.45; H, 4.91; CL, 7.85; N, 3.10; O, 17.70; Found: C, 64.35; H, 5.81; Cl, 7.95; N, 4.15; O, 17.75.

(3 - ((3 - (4 - bromophenyl) - 4, 5 - dihydroisoxazol-5-yl) methoxy) - 2, 4-dimethoxyphenyl) (Phenyl) methanone (8h):
^{1}HNMR(400MHz, $CDCl_3$): δ 3.42 (dd,1H, *J*=8.6, 18.4Hz), 3.63(dd,1H, *J*=10.4Hz, 16.4Hz), 3.66(dd,1H,*J*=12.4Hz, 18.6Hz), 3.83 (s,6H, OCH_3), 4.11(dd,1H, *J*=4.6, 10.8Hz), 4.99(m,1H), 7.04 (d, 1H, *J*=8.0Hz,Ar-H) 7.20(d,1H,*J*=8.4Hz,Ar-H), 7.54(m,5H, Ar-H), 7.63(d, 2H, *J*=8.2Hz, Ar-H), 7.70(d,2H, *J*=8.2Hz,Ar-H); LCMS: *m/z*= 496.00 $(M+1)^+$, 498.02 $(M+3)^+$; Anal. Calcd for $C_{24}H_{22}BrNO_5$ C, 60.50; H, 4.47; Br, 16.10; N, 2.82; O, 16.12; Found: C, 61.45; H, 4.51; Br, 15.20; N, 3.62; O, 15.22

(2, 4-dimethoxy – 3 - ((3 - (4 - methoxyphenyl)-4, 5-dihydroisoxazol-5-yl) methoxy) phenyl) (3, 4-dimethoxyphenyl) methanone (8i):
^{1}HNMR (400MHz, $CDCl_3$): δ 3.45 (dd,1H, *J*=8.8, 18.6Hz), 3.54(dd,1H, *J*=10.4Hz, 16.8Hz), 3.57(dd, 1H, *J*=10.6Hz, 8.8Hz), 3.76 (s,5H, OCH_3), 3.85(s,2H,OCH_3), 3.93(s,8H,OCH_3) 4.18(dd,1H, *J*=5.2,10.8Hz), 5.04(m,1H), 6.69 (t,1H,*J*=8.3Hz) 6.15(m,4H, Ar-H), 7.31(m,2H,Ar-H), 7.72(d,2H, *J*=8.6Hz,Ar-H); LCMS: *m/z*= 508.10 $(M+1)^+$; Anal. Calcd for $C_{28}H_{29}NO_8$ C, 66.26; H, 5.76; N, 2.76; O, 25.22; Found: C, 65.46; H, 6.56; N, 3.46; O, 24.32.

(2, 4-dimethoxy – 3 - ((3 – phenyl - 4, 5-dihydroisoxazol-5-yl)methoxy) phenyl) (3, 4-dimethoxyphenyl) methanone (9j):
^{1}HNMR (400MHz, $CDCl_3$): δ 3.46 (dd,1H, *J*=8.8, 18.8Hz), 3.56(dd,1H, *J*=10.6Hz, 16.2Hz), 3.57(dd,1H, *J*=12.6Hz,8.8Hz), 3.76(s,3H,OCH_3), 3.85(s,2H,OCH_3), 3.93(s,8H,OCH_3) 4.11(dd,1H, *J*=5.4Hz,10.8Hz), 5.03(m,1H), 6.70 (t,1H,*J*=8.4Hz) 6.17(m,4H, Ar-H), 7.30(m,2H,Ar-H), 7.70(d,2H, *J*=8.4Hz,Ar-H); LCMS: *m/z*= 478.10 $(M+1)^+$; Anal. Calcd for $C_{27}H_{27}NO_7$ C, 67.91; H, 5.70; N, 2.93; O, 23.45; Found: C, 69.71; H, 5.80; N, 2.93; O, 22.55.

(3 - ((3 - (4 - chlorophenyl)-4, 5-dihydroisoxazol-5-yl) methoxy) - 2, 4 - dimethoxyphenyl) (3, 4 - dimethoxyphenyl) methanone (8k)
^{1}HNMR (400MHz, $CDCl_3$): δ 3.46 (dd,1H, *J*=8.6, 18.4Hz), 3.53(dd,1H, *J*=10.2Hz, 16.6Hz), 3.57(dd, 1H, *J*=12.6Hz, 18.6Hz), 3.86 (s,4H, OCH_3), 3.93(s,8H,OCH_3) 4.10(dd,1H, *J*=4.6,10.6Hz), 5.09(m,1H), 6.94 (m,3H,Ar-H), 7.30(m,2H,Ar-H), 7.54(t,2H,*J*=6.72Hz,Ar-H), 7.64(d,2H,*J*=8.0Hz,Ar-H); LCMS: *m/z*= 512.04 $(M+1)^+$, 514.08 $(M+3)^+$; Anal. Calcd for $C_{27}H_{26}ClNO_7$ C, 63.34; H, 5.12; Cl, 6.93; N, 2.74; O, 21.88; Found: C, 62.24; H, 5.22; Cl, 7.93; N, 3.84; O, 20.78.

(3 - ((3 - (4 - bromophenyl) -4,5-dihydroisoxazol-5-yl)methoxy)-2, 4-dimethoxyphenyl) (3,4-dimethoxyphenyl) methanone (8l):
^{1}HNMR (400MHz, $CDCl_3$): δ 3.45 (dd,1H, *J*=8.8, 18.6Hz), 3.53(dd,1H, *J*=10.2Hz, 16.6Hz), 3.57(dd,

^{1}H, *J*=12.6Hz, 18.6Hz), 3.86 (s,4H,OCH_3), 3.93(s, 8H,OCH_3), 4.11(dd,1H, *J*=4.8,10.6Hz), 5.09 (m,1H), 6.94 (m,3H, Ar-H), 7.31(m,2H,Ar-H), 7.54(t,2H,*J*=6.72Hz,Ar-H), 7.64(d,2H,*J*=8.0Hz,Ar-H); LCMS: *m/z*= 566.00 $(M+1)^+$, 558.01 $(M+3)^+$; Anal. Calcd for $C_{27}H_{26}BrNO_7$ C, 58.27; H, 4.71; Br, 14.36; N, 2.52; O, 20.13; Found: C, 57.17; H, 4.81; Br, 15.26; N, 2.72; O, 20.03.

(4-chlorophenyl) (2, 4-dimethoxy-3-((3-phenyl-4,5-dihydroisoxazol-5-yl) methoxy) phenyl) methanone (8m):

^{1}HNMR(400MHz, $CDCl_3$): δ 3.46 (dd,1H, *J*=8.8, 18.6Hz), 3.64(dd,1H, *J*=10.6Hz, 17.2Hz), 3.68(dd, 1H, *J*=12.8Hz, 8.8Hz), 3.83 (s,6H, OCH_3), 4.11(dd,1H, *J*=4.6, 10.8Hz), 4.99(m,1H), 7.06 (d,1H, *J*=8.3Hz) 7.18(d,1H,*J*=7.6, Ar-H), 7.56(m,5H, Ar-H), 7.64(d,2H, *J*=8.2Hz,Ar-H), 7.72(d,2H,*J*=8.4,Ar-H); LCMS: *m/z* = 452.10 $(M+1)^+$, 454.06 (M+3); Anal. Calcd for $C_{25}H_{22}ClNO_5$ C, 66.45; H, 4.91; Cl, 7.85; N, 3.10; O, 17.70; Found: C, 66.25; H, 4.81; Cl, 7.95; N, 4.20; O, 16.80.

(4-chlorophenyl) (3-((3-(4-chlorophenyl)-4, 5-dihydroisoxazol – 5 - yl) methoxy)-2, 4-dimethoxyphenyl) methanone (8n):

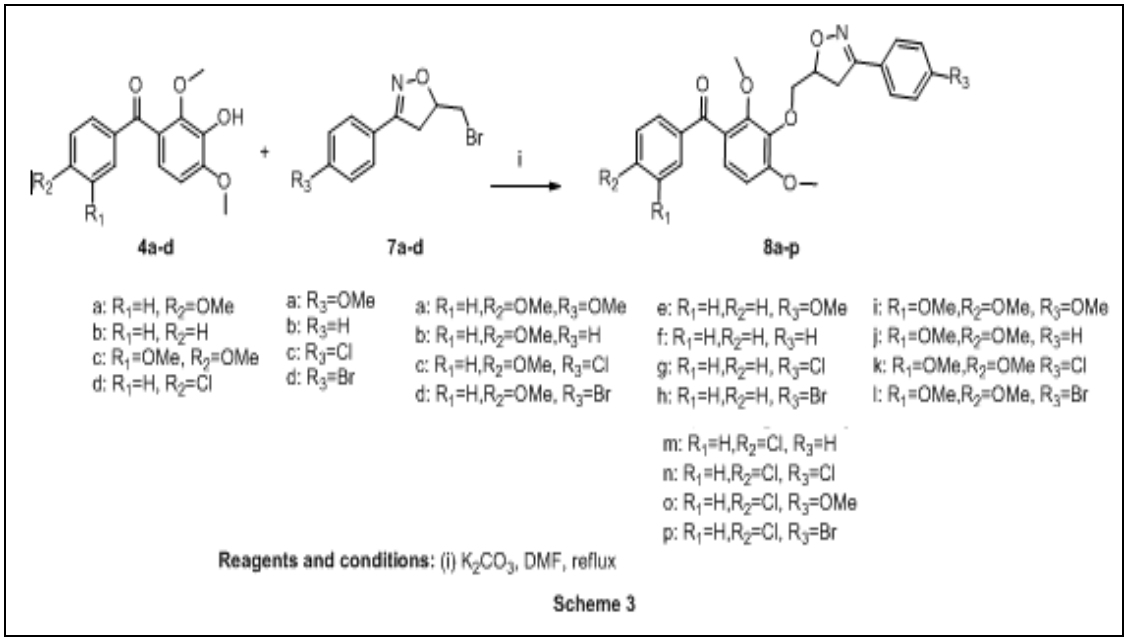
^{1}HNMR (400MHz, CDCl3): δ 3.45 (dd,1H, *J*=8.6, 18.4Hz), 3.65(dd,1H, *J*=10.8Hz, 17.4Hz), 3.65(dd, 1H, *J*=10.8Hz, 18.2Hz), 3.83 (s,6H, OCH_3), 4.10(dd,1H, *J*=4.6, 10.8Hz), 4.99(m,1H), 7.06 (d,1H, *J*=8.3Hz) 7.18(d,1H,*J*=7.6, Ar-H), 7.56(m,5H, Ar-H), 7.64(d,2H, *J*=8.2Hz, Ar-H), 7.72(d,2H,*J*=8.4,Ar-H); LCMS: *m/z*= 486.00 $(M+1)^+$, 488.02 $(M+3)^+$, 490.00 $(M+5)^+$; N Anal. Calcd for $C_{25}H_{21}Cl_2NO_5$ C, 61.74; H, 4.35; Cl, 14.58; N, 2.88; O, 16.45; Found: C, 60.54; H, 4.45; Cl, 15.58; N, 2.78; O, 16.65.

(4-chlorophenyl) (2, 4-dimethoxy - 3 - ((3 - (4-methoxyphenyl) - 4, 5-dihydroisoxazol – 5 - yl) methoxy) phenyl) methanone (8o):

^{1}HNMR (400MHz, CDCl3): δ 3.41 (dd,1H, *J*=8.4, 16.6Hz), 3.63(dd,1H, *J*=10.4Hz, 10.4Hz), 3.66(dd, 1H, *J*=12.2Hz, 17.2Hz), 3.77 (s,9H, OCH_3), 4.10(dd,1H, *J*=4.4, 10.4Hz), 4.98-4.99(m,1H), 7.05 (d,1H,*J*=8.4Hz, Ar-H), 7.18-7.70(m,9H,Ar-H); LCMS: *m/z*= 482.04 $(M+1)^+$, 484.10 $(M+3)^+$; Anal. Calcd for $C_{26}H_{24}ClNO_6$ C, 64.80; H, 5.02; Cl, 7.36; N, 2.91; O, 19.92; Found: C, 65.75; H, 5.12; Cl, 7.46; N, 2.96; O, 18.72.

(3-((3 - (4 - bromophenyl) - 4, 5-dihydroisoxazol-5-yl) methoxy)-2, 4-dimethoxyphenyl) (4-chlorophenyl) methanone (8p):

^{1}HNMR (400MHz, CDCl3): δ 3.45 (dd,1H, *J*=8.6, 16.8Hz), 3.64(dd,1H, *J*=8.4Hz, 10.6Hz), 3.65(dd, 1H, *J*=12.0Hz, 17.4Hz), 3.83 (s,6H,OCH_3), 4.11(dd,1H,*J*=4.4, 10.4Hz), 4.98-4.99(m,1H), 7.06 (d,2H,*J*=8.6Hz, Ar-H), 7.18-7.70(m,9H,Ar-H); LCMS: *m/z*= 530.00 $(M+1)^+$, 532.01 $(M+3)^+$, 534.00 (M+5)+; Anal. Calcd for $C_{25}H_{21}BrClNO_5$ C, 56.57; H, 3.99; Br, 15.05; Cl, 6.68; N, 2.64; O, 15.07; Found: C, 55.47; H, 3.89; Br, 15.15; Cl, 6.78; N, 2.54; O, 15.17.



Scheme 3

Antibacterial Activity by Well Diffusion Technique *(*determination of zone of inhibition) The antibacterial activity of the synthesized novel (2,4-dimethoxy-3-((3-phenyl-4, 5-dihydroisoxazol-5-yl) methoxy) phenyl) (phenyl) methanone (8a-p) series were examined by following the well diffusion technique of Odeyemi and Fagbohun, 2 005. Sterile solidified nutrient agar plates were prepared and immunized with different test bacterial strain by spread plate method. 6mm wells were made in the nutrient agar plates and were filled with the preset concentration of different test samples (10µg). The loaded plates were then kept for incubation at 37oC for 24 hrs. Antibacterial activities of all the synthesized novel compounds (8a-p) were estimated by measuring the zone of inhibition against the test microorganisms. DMF (Dimethyl formamide) was used as negative control and 10µg chloramphenicol was used as a positive control. After incubation, the inhibition zone formed around the wells was measured in millimeters. The study was achieved in triplicate.

RESULTS AND DISCUSSION:

Chemistry: *In-vitro* antibacterial activity of synthesized compounds (8a-p) was performed against a panel of Gram-positive and Gram-negative human phytopathogenic bacteria by agar well diffusion method using chloramphenicol along with 20% dimethyl formamide (DMF) as positive and negative controls respectively.

The final coupled compounds (8a-p) were synthesized as outlined in Scheme 3. Compounds (8a-p) were obtained by condensing (4a-d) with (7a-d) in the presence of potassium carbonate as a base and DMF as solvent. The intermediates (4a-d) and (7a-d) were obtained by a synthetic route represented in schemes 2 and scheme3, respectively. The desired 3-hydroxy-2, 4-dimethoxybenzophenones (4a-d) were synthesized from 2, 6-dimethoxyphenyl2-chloroacetate (2) and aromatic benzoic acids in Eaton's reagent ($(MeSO_3H/P_2O_5)$ at 80°C. After the completion of the reaction, the reaction mixture was cooled and diluted with dichloromethane and carefully poured in to a beaker containing 10% $NaHCO_3$, allowed for stirring, the aqueous solution was extracted with CH_2Cl_2 and the combined organic layers were washed with water, brine solution, dried over sodium sulfate and concentrated under reduced pressure to produce a brownish oil as crude product. This crude product was purified by column chromatography on silica gel to give 3-benzoyl-2,6-dimethoxyphenyl2-chloroacetate (3a-d). The (3a-d) compounds and sodium acetate were taken in a round-bottomed flask, followed by dissolving in methanol and refluxed for 4h; then their action mixture was extracted with ethyl acetate, the organic layer then washed with water, brine solution, dried over sodium sulfate and concentrated with reduced pressure to get the crude product. This crude product was recrystallized, taking methanol to obtain pure white crystalline solid (3-hydroxy-2,4-dimethoxyphenyl) (phenyl) methanones (4a-d) in excellent yield.

The compounds **(**7a-d) were synthesized as shown in the scheme 2. Substituted aromatic aldehydes (5a-d) were converted into amidoxime (6a-d) by refluxing them with hydroxylamine hydrochloride and sodium carbonate in water. The amidoximes (6a-d) were treated with 3-bromopropene in dichloromethane, followed by reflux to obtain 5-(bromomethyl)-3-phenyl-4,5-dihydroisoxazole (7a-d). In scheme 1, the formation of 4a-d was confirmed by ^{1}HNMR, ^{13}CNMR, Mass spectroscopy, and elemental analysis. In ^{1}HNMR, the para proton of the 2,6-dimethoxy phenoxy group appeared as a triplet at δ7.20 -7.35, whereas the meta proton was Adoubl *et at* δ6.65-7.00. After friedel craft's acylation, para and meta protons appeared as doublet at δ 7.28 and 6.70, respectively, corresponding to the hydroxy proton in (4a-d). 1HNMR confirmed the formation of the compounds 7a-d. The isoxazoline protons and aromatic proton appeared in the range δ 3.25-5.01 and 7.35-7.59, respectively.

The formation of title compounds (8a-p) was confirmed by 1HNMR and Mass spectroscopy. The methylene proton and methoxy protons appeared in the range δ 5.28 and 3.75- 3.92, respectively.

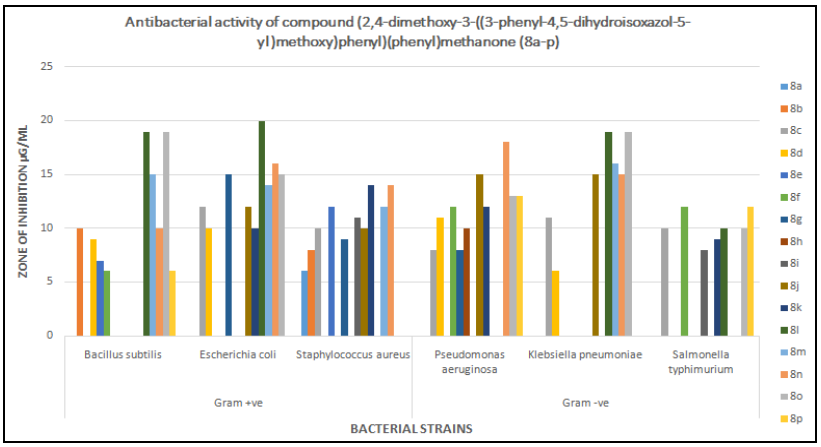
Biology: *In-vitro* antibacterial activity data of compounds (8a-p) against tested organisms exhibited varying antibacterial activity against used test cultures. Sample 8c, 8d, 8g, 8l, 8o –displayed bacteriostatic activity, whereas 8m and 8n displayed strong bactericidal activity against *Bacillus subtilis*, 8n was more potent than the positive control used.

In Escherichia coli, only 8b, 8d, 8l, 8m and 8o were active and 8n was stronger than the positive control. Whereas *Klebsiella pneumonae* displayed the resistance against used test sample (2,4-dimethoxy-3-((3-phenyl-4,5-dihydroisoxazol-5-yl) methoxy) phenyl) (phenyl) methanone (8a-p) series. Overall, among the 8a-p series sample tested for their antibacterial activity against different bacterial strains, 8m, and 8n were potent and followed by 8c, 8k, 8j, 8l and 80. And the present work concludes that samples 8m and 8n can be used to replace the positive control against respective test cultures.

TABLE 1: ANTIBACTERIAL ACTIVITY DATA OF (2, 4 – DIMETHOXY – 3 - ((3 – PHENYL - 4, 5-DIHYDROISOXAZOL - 5 -YL) METHOXY) PHENYL) (PHENYL) METHANONE (8A-P) ZONE OF INHIBITION IN MM

	Bacterial Strains	8a	8b	8c	8d	8e	8f	8g	8h	8i	8j	8k	8l	8m	8n	8o	8p	+ve control Chloramphenicol
Gram +ve	*Bacillus subtilis*	–	10	–	9	7	6	–	–	–	–	–	19	15	10	19	6	15
	Escherichia coli	–	–	12	10	–	–	15	–	–	12	10	20	14	16	15	–	19
	Staphylococcus aureus	6	8	10	–	12	–	9	–	11	10	14	–	12	14	–	–	20
Gram -ve	*Pseudomonas aeruginosa*	–	–	8	11	–	12	8	10	–	15	12	–	–	18	13	13	22
	Klebsiella pneumonia	_	_	11	6	–	–	–	–	–	15	–	19	16	15	19	–	23
	Salmonella typhimurium	–	–	10	–	–	12	–	–	8	–	9	10	–	–	10	12	25

Values are zones of inhibition in mm, "-" – Not sensitive



CONCLUSION: In conclusion, we have reported a facile route for the rapid synthesis of novel (2,4-dimethoxy-3-((3-phenyl-4,5-dihydroisoxazol-5-yl) methoxy) phenyl) (phenyl) methanone (8a-p) from 5-(bromomethyl)-3-phenyl-4, 5-dihydroisoxazole (7a-d) with aryl (3-hydroxy-2,4-dimethoxy-phenyl-methanones (4a-d) using K_2CO_3. The new molecular framework has displayed broad-spectrum antibacterial activity, which is validated by the presence of hydroxyl, carbonyl group and electronegative atoms among the synthesized compounds (8a-p), molecules 8m and 8n bearing electronegative atoms, respectively in the molecular framework have exhibited potent antibacterial activity when compared to the standard positive controls.

ACKNOWLEDGEMENTS: The authors thank the Institution of Excellence (IOE) for providing financial support for the synthetic work. The authors also thank the University of Mysore, Mysore, for providing laboratory facilities.

CONFLICTS OF INTEREST: Nil

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How to cite this article:
Manasa HS and Shashikanth S: Synthesis of (2, 4-dimethoxy – 3 - ((3 – phenyl - 4, 5 – dihydroisoxazol – 5 - yl) methoxy) phenyl) (phenyl) methanone and their antibacterial activity. Int J Pharm Sci & Res 2023; 14(1): 349-56. doi: 10.13040/IJPSR.0975-8232.14(1). 349-56.