Synthesis, Characterization and Biological Activity of Some Chalcone Derivatives derived from 1-(2-(benzyloxy)-5-bromo-4-methoxyphenyl)ethanone

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Abstract
Chalcones are a noteworthy part of medicinal chemistry in the 21st century because of their various biological activities due to the presence of α, β-unsaturated carbonyl system. In this study, various novel chalcone derivatives (SCH-1 to SCH-4) were synthesized in the presence of a base catalyzed by Claisen-Schmidt condensation from 1-(2-(benzyloxy)-5-bromo-4-methoxyphenyl)ethanone (S-1) and various benzaldehyde derivatives. These synthesized compounds were characterized by Fourier Transform – Infrared Spectroscopy (FT-IR), Nuclear Magnetic Resonance (^1H NMR and ^{13}C NMR) and Mass spectrometry.

The synthesized products undergo in vitro biological activities like antibacterial and antifungal by the broth dilution method. SCH-1 and SCH-2 exhibit moderate activity against Gram-positive and Gram-negative bacteria, respectively. Moreover, antifungal activity gives different results among which compounds S-1, SCH-1 and SCH-4 show notable antifungal activity.

Keywords: Chalcone, Condensation, Antibacterial, Antifungal, Medicinal Chemistry.

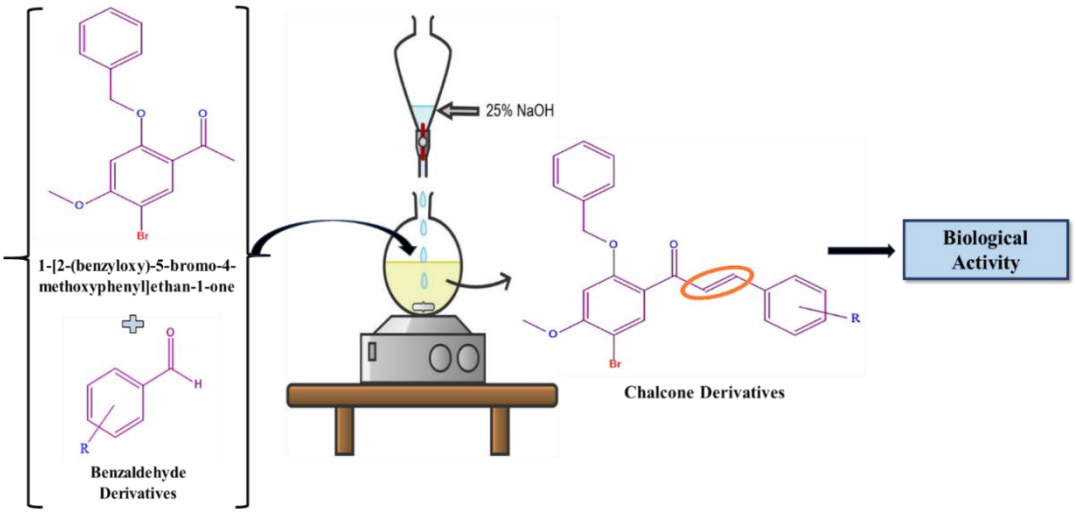
Introduction

Chalcone has a long history of scientific exploration, beginning with its initial synthesis and structural elucidation, resulting in various applications in medicine and industry[24,26]. Due to its biological versatility, the compound has remained at the forefront of research. It is a simple chemical structure composed of many substances that are found in nature. They are naturally abundant in edible plants including vegetables, fruits, spices, tea, and other foodstuffs[13,28].

The term "chalcone" made a significant milestone in the field of chemistry, which has the chemical structure 1,3-diphenyl-2-propen-1-one. It is also referred to as benzylideneacetophenone or benzyl acetophenone[32]. The presence of the reactive keto-ethylenic group (-CO-CH=CH-) contributes to their color and versatile biological activities like antibacterial[2,3,30], anti-inflammatory[1,23], analgesic[6], anticholinergic[17], antiplatelet[10], antiulcer[4,24], antioxidant[25], antimalarial[14,29], antiviral[5], anticancer[15,19], antidiabetic[7], antifungal[16], antileishmanial[18] etc.

Chalcone is a useful precursor for the synthesis of a wide range of heterocyclic compounds. The inherent reactivity of the α, β-unsaturated carbonyl moiety within the chalcone structure facilitates cyclization reaction, leading to the formation of various heterocyclic rings such as pyrrole, thiazole, pyrazole, oxazole, isoxazoles, pyrazolines, pyridine, cyanopyridines, quinoline etc[8,9,12,27].

Okolo et al[16] synthesized seven chalcone derivatives by Claisen-Schmidt condensation reaction. Some of these compounds show antimicrobial as well as antioxidant activity.



Graphical Abstract

Lagu et al[11] have reported novel trifluoromethyl and trifluoromethoxy-substituted chalcone derivatives and then evaluated the antibacterial and antifungal activity. Furthermore, Prajapati et al[20] have synthesized novel chalcone derivatives from 1-[-4-(benzyloxy)-3-chlorophenyl]ethanone and evaluated *in vitro* antimicrobial as well as antifungal activity. Several compounds exhibited promising potential against fungal and microbial strains.

Globally, it has been observed that the infectious diseases leading to death are due to the spread of antibiotic resistance in patient noncompliance. Antimicrobial resistance is a public health issue that has a big impact on society and the economy. Both naturally occurring and synthetic chalcones have been shown in numerous studies to possess antimicrobial properties, including the ability to combat a range of bacterial and fungal pathogens[21,31].

In the present study, we synthesized 1-(2-(benzyloxy)-5-bromo-4-methoxyphenyl)ethanone (S-1) aromatic ketone compound. Furthermore, various chalcone derivatives such as (E)-1-(2-(benzyloxy)-5-bromo-4-methoxyphenyl)-3-phenylprop-2-en-1-one, (E)-1-(2-(benzyloxy)-5-bromo-4-methoxyphenyl)-3-(p-tolyl)prop-2-en-1-one, (E)-1-(2-(ben zyloxy)-5-bromo-4-methoxyphenyl)-3-(2 methoxyphenyl) prop-2-en-1-one, and (E)-1-(2-(benzyloxy)-5-bromo-4-methoxyphenyl)-3-(4-chlorophenyl)prop-2-en-1-one (SCH-1 to SCH-4) were synthesized through base-catalyzed via Claisen-Schmidt condensation reaction with S-1 and some aromatic aldehydes (benzaldehyde, 4-methylbenzaldehyde, 2-methoxybenzaldehyde and 4-chlorobenzaldehyde).

The structure of these synthesized compounds was characterized by spectral analysis such as Fourier Transform – Infrared Spectroscopy (FT-IR), Nuclear Magnetic Resonance (^{1}H NMR and ^{13}C NMR) and Mass Spectrometry. The progress of the reaction is monitored by thin layer chromatography(TLC). The evaluation of *in vitro* biological activities like antibacterial (Gram-positive and Gram-negative) and antifungal of these synthesized compounds has been conducted by the broth dilution method, which has obtained different results.

Material and Methods

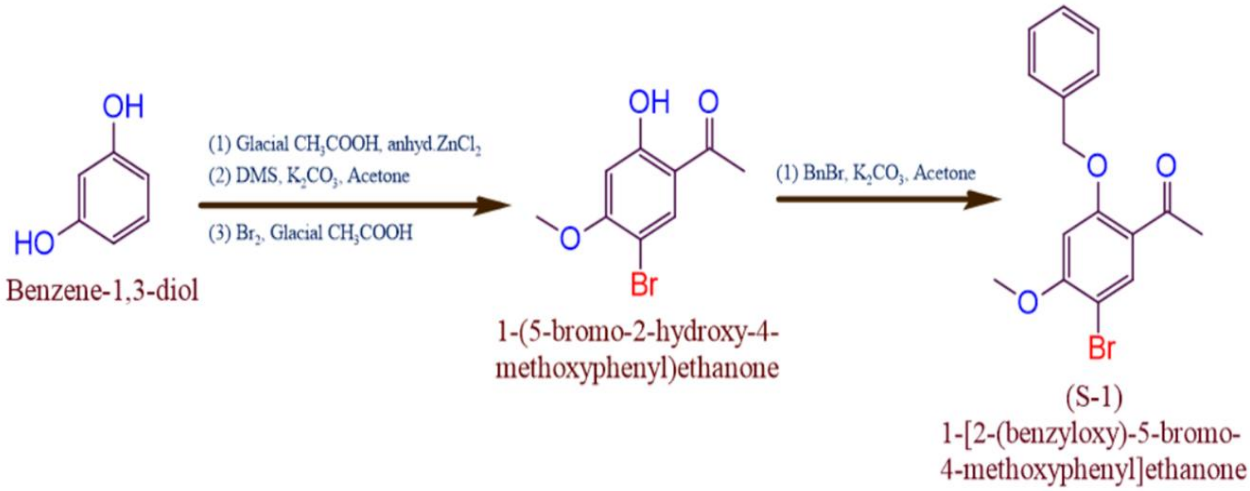
Analytical grade chemicals were used in this experiment. The melting points were determined using the open capillary method. The structure of the compounds was confirmed by Fourier transform infrared (FT-IR) Bruker Tensor 27. The molecular weight of the compounds was determined by Mass Spectrometry (MS). ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker using DMSO as a solvent and TMS was used as the standard reference. To evaluate antibacterial activity, tests were conducted using a broad spectrum of both Gram-positive and Gram-negative bacteria, and for antifungal activity, fungi were tested using the broth dilution method.

Synthesis-

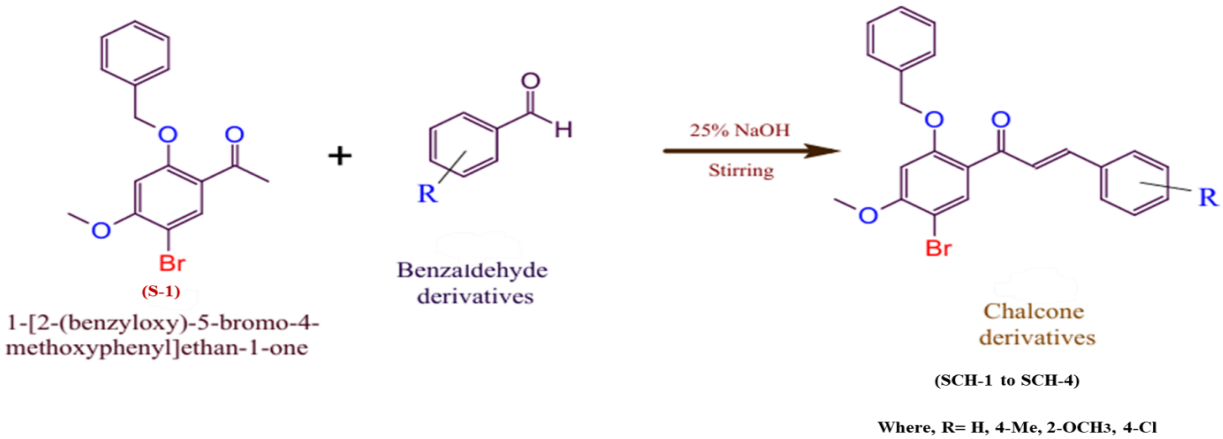
1-(2-(benzyloxy)-5-bromo-4-methoxyphenyl)ethanone (S-1): The compound S-1 was synthesized in multiple steps as given in scheme 1. Initially, benzene-1,3-diol (Resorcinol) is treated with anhydrous $ZnCl_2$ and glacial acetic acid to form 2,4-dihydroxyacetophenone. This was reacted with anhydrous K_2CO_3, dimethyl sulfate (DMS) in acetone to yield 2-hydroxy-4-methoxyacetophenon and further bromination reaction was done with Br_2 in the presence of glacial acetic acid to obtain intermediate 1-(5-bromo-2-hydroxy-4-methoxyphenyl)ethanone.

A mixture of 0.01 mole of intermediate, 0.01 mole of benzyl bromide (BnBr), and 0.01 mole of potassium carbonate in 100 ml dry acetone was stirred at 60-70°C temperature for 7-8 hours. Then, this reaction mixture was allowed to cool at room temperature and quenched with 400 ml of water. The product S-1 was filtered, washed with water, and recrystallized in ethanol.

General procedure for substituted chalcone derivatives (SCH-1 to SCH-4): 0.01 mole of S-1 and 0.01 mole of benzaldehyde derivatives were dissolved in 25 ml of ethanol.



Scheme 1: Preparation of 1-(2-(benzyloxy)-5-bromo-4-methoxyphenyl)ethanone (S-1)



Scheme 2: Preparation of Substituted Chalcone Derivatives SCH-1 to SCH-4

In this mixture, 25% sodium hydroxide (NaOH) solution is added dropwise with continuous stirring. This reaction mixture was stirred at room temperature for 24 hours which was monitored by TLC (Hexane: Ethyl Acetate = 7:3). After 24 hours, the reaction mixture was poured into 400 ml of cold water and neutralized with 10% hydrochloric acid (HCl). The precipitate formed was filtered, washed, and recrystallized in ethanol.

1-(2-(benzyloxy)-5-bromo-4-methoxyphenyl)ethanone (S-1):
Molecular formula: $C_{16}H_{15}BrO_3$ (Mol. Wt. = 335.19 gm/mol); Off-white; M.P. 124-126°C; Yield: 72%
IR (KBr, cm^{-1}): 3059, 3029(Aromatic C-H str.), 2939(C-H str.), 1645(-C=O), 1588(C=C str.), 1273(C-O-C sym.), 1054(C-O-C asym.), 632(C-Br)
^{1}H NMR (400 MHz, DMSO) δppm: 6.96 – 7.82 (m, 7H, Ar-H), 5.33(s, 2H, -OCH_2-), 3.95(s, 3H, -OCH_3), 2.45(s, 3H, -$COCH_3$)
^{13}C NMR (100 MHz, DMSO) δppm: 195.65, 160.09, 159.86, 136.49, 134.12, 129.06, 128.70, 128.61, 121.65, 102.18, 99.45, 57.33,71.29, 32.21
ESI-Mass: 335.3 $[M]^+$, 337.3$[M+2]^+$

(E)-1-(2-(benzyloxy)-5-bromo-4-methoxyphenyl)-3-phenylprop-2-en-1-one (SCH-1):
Molecular formula: $C_{23}H_{19}BrO_3$ (Mol. Wt.= 423.30 gm/mol); Light Yellow; M. P. 98-100°C; Yield: 75%
IR (KBr, cm^{-1}): 3062, 3025(Aromatic C-H str.), 2987, 2922, 2853(C-H str.), 1648(-C=O) 1582(C=C str.), 1259(C-O-C sym.), 1055(C-O-C asym.), 971(CH=CH bend.), 688(C-Br)
^{1}H NMR (400 MHz, DMSO) δppm: 7.60-7.87(d, 2H, -CH=CH-), 6.96-7.56(m, 11H, Ar-H), 5.32(s, 2H, -OCH_2), 3.95-4.01(s, 3H, -OCH_3)
^{13}C NMR (100 MHz, DMSO): 187.84, 160.13, 159.66,142.26, 136.33, 135.10, 134.66, 130.72, 129.29, 129.06, 128.93, 128.77, 128.63, 128.45, 127.12, 122.15, 102.41, 99.35, 77.50, 57.43
ESI-Mass: 423.4 $[M]^+$, 425.4 $[M+2]^+$

(E)-1-(2-(benzyloxy)-5-bromo-4-methoxyphenyl)-3-(p-tolyl)prop-2-en-1-one (SCH-2):
Molecular formula: $C_{24}H_{21}BrO_3$(Mol. Wt. = 437.33 gm/mol); Light Yellow; M.P. 76-78°C, Yield: 76%
IR (KBr, cm^{-1}): 3050(Aromatic C-H str.), 2942, 2915, 2851(C-H str.), 1648(-C=O str.), 1590(C=C str.), 1270(C-O-C sym.), 1171(C-O-C asym.), 975(CH=CH bend.), 689(C-Br)
^{1}H NMR (400 MHz, DMSO): 7.58-7.85(d, 2H, -CH=CH-), 7.04-7.55(m, 11H, Ar-H), 5.33(s, 2H, -OCH_2), 3.96-4.01(s, 3H, -OCH3), 2.28(s, 3H, -CH_3)
^{13}C NMR (100 MHz, DMSO): 188.06,160.04, 159.53, 142.51, 138.51, 136.39, 135.00, 134.59, 131.51, 129.41, 129.20, 129.00, 128.71, 126.89, 125.96, 122.35, 102.37, 99.40, 71.40, 57.43, 21.35
ESI-Mass(m/z): 437.31$[M]^+$, 439.30$[M+2]^+$

(E)-1-(2-(benzyloxy)-5-bromo-4-methoxyphenyl)-3-(2-methoxyphenyl)prop-2-en-1-one (SCH-3):
Molecular formula: $C_{24}H_{21}BrO_4$(Mol. Wt. = 453.33 gm/mol); Yellow; M.P. 125-126°C; Yield: 69%
IR (KBr, cm^{-1}): 3070(Aromatic C-H str.), 2916, 2846 (C-H str.), 1639(-C=O), 1588(C=C str.), 1242(C-O-C sym.), 1044(C-O-C asym.), 993 (CH=CH bend.), 681(C-Br bend.)
^{1}H NMR (400 MHz, DMSO) δppm: 7.57-7.87 (d, 2H, -CH=CH), 6.85-7.83(m, 11H), 5.32(s, 2H, -OCH_2), 3.80-4.00(s, 6H, -OCH_3),
^{13}C NMR (100 MHz, DMSO): 188.12, 159.98, 159.84, 158.47, 136.77, 136.38, 134.63, 132.37, 129.00, 128.74, 128.68, 128.08, 127.00, 123.42, 122.43, 121.08, 112.10, 102.37, 99.34, 71.39, 56.04 - 57.38
ESI-Mass: 453.3$[M]^+$, 455.18$[M+2]^+$

(E)-1-(2-(benzyloxy)-5-bromo-4-methoxyphenyl)-3-(4-chlorophenyl)prop-2-en-1-one (SCH-4):
Molecular formula: $C_{23}H_{18}BrClO_3$(Mol. Wt. = 457.74 gm/mol); Yellow; M.P. 104-105°C, Yield: 70%
IR (KBr, cm^{-1}): 3101, 3053(Aromatic C-H str.), 2913,2846(C-H str.), 1644(-C=O), 1582(C=C str.), 1242(C-O-C sym.), 1201(C-O-C asym.), 995(CH=CH bend.), 673(C-Br)
^{1}H NMR(500 MHz, $CDCl_3$) δppm: 7.57-8.06(d, 2H, -CH=CH), 6.66-7.55(m, 11H, Ar-H), 5.31(s, 2H, -OCH_2), 3.96-4.01(s, 3H, -OCH_3)

^{13}C NMR (100 MHz, DMSO): 187.71,160.21, 159.71, 140.65, 136.32, 135.13, 134.64, 134.09, 130.37, 129.28, 129.09, 128.95, 128.81, 127.82, 122.04, 102.43, 99.32, 71.52, 57.44
ESI-Mass: 457.3$[M]^+$, 459.3$[M+2]^+$

Biological Activity
Antibacterial and Antifungal activity: "*In vitro*" biological activity was assessed for all the synthesized compounds through the broth dilution method[22]. Antimicrobial activities were screened against gram-positive *Staphylococcus aureus* and Gram-negative *Escherichia coli.* microorganisms. Antifungal activity was screened against *Candida albicans*. To get an appropriate drug concentration for testing on a common bacterial strain, DMSO was used as a diluent. For both primary and secondary screening, serial dilutions were made. Before injections, a loopful of medium from the antibiotic-free control tube was distributed across a quarter of a plate suitable for the test organism's development. The plate was incubated at 37°C overnight. The minimum inhibition concentration (MIC) of control organisms was measured to ensure accurate medication concentration. MIC is the lowest concentration that prevents the organism's growth. Growth from the control tube before incubation (which represents the original inoculum) is compared. A stock solution of 2000 µg/ml of each synthesized product was prepared, from which it was diluted to various concentrations of 1000, 500, and 250 µg/ml used in the primary screening. The active synthetic compounds discovered in this primary screening were tested against all types of microbes in a secondary screening. The compounds identified as effective in the primary screening were similarly diluted to various concentrations (µg/ml) of 200, 100, 50, 25, 12.5, 6.25, and many other concentrations. MIC was determined as the highest dilution that showed at least 99% inhibition.

Results and Discussion

Antibacterial Activity: The synthesized compounds exhibit varying MIC values against Gram-positive (*S. aureus* MTCC96) and Gram-negative (*E. coli* MTCC443) microorganisms. Notably, compound SCH-1 shows moderate activity against *S. Aureus* MTCC96 with a value of 62.5 µg/ml compared to those of standard drugs chloramphenicol and ciprofloxacin (MIC 50 µg/ml), while the other compounds had poor activities. SCH-2 (MIC 62.5 µg/ml) exhibits moderate activity against *E. coli* compared to the standard drug chloramphenicol.

Table 1
Antibacterial and Antifungal activity of S-1 and newly synthesized SCH-1 to SCH-4

S.N.	Compounds	E. coli (MTCC443)	S. aureus (MTCC96)	C. albicans (MTCC227)
1	S-1	100	200	500
2	SCH-1	200	62.5	500
3	SCH-2	62.5	100	1000
4	SCH-3	200	125	>1000
5	SCH-4	100	100	500
Standard Drugs	CHLORAMPHENICOL	50	50	-
	CIPROFLOXACIN	25	50	-
	GRISEOFULVIN	-	-	500

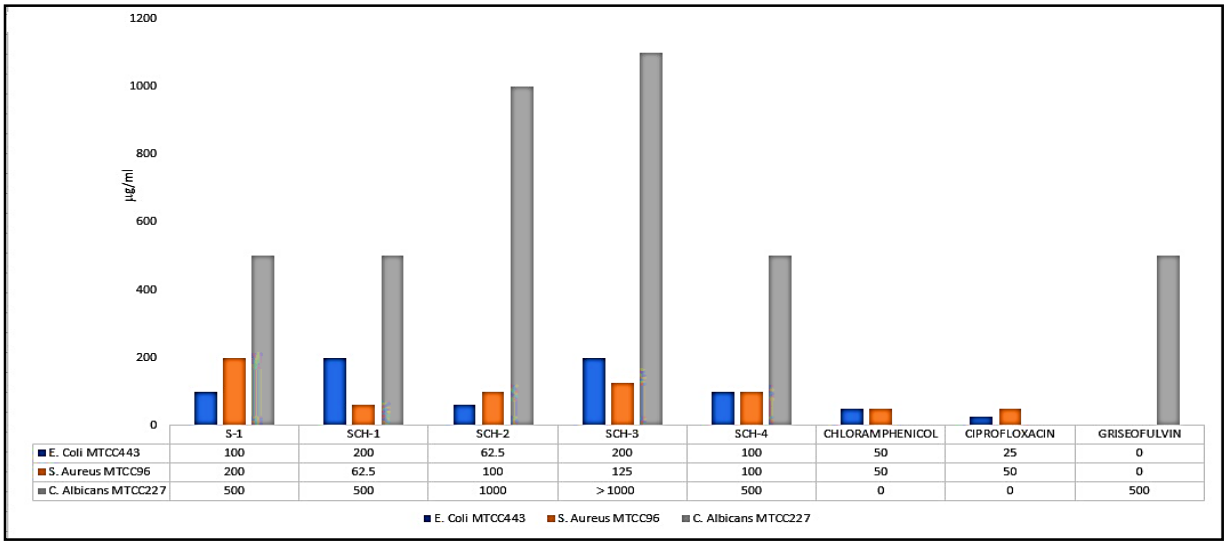


Fig. 1: The graphical representation of antimicrobial and antifungal activities of synthesized compounds

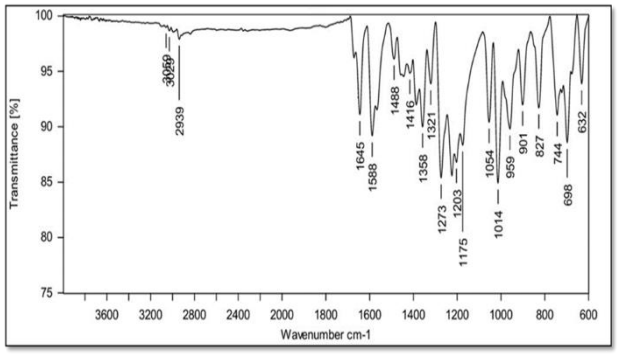


Fig. S1: IR of S-1

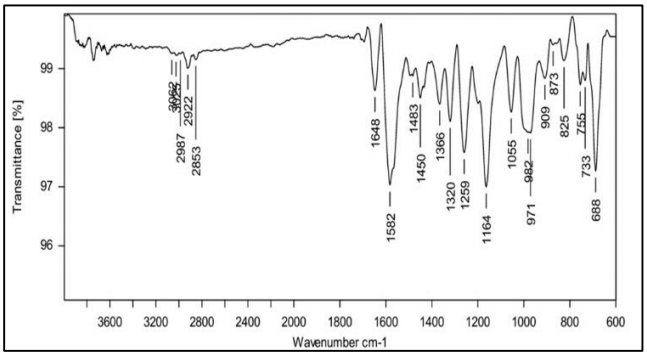


Fig. S2: IR of SCH-1

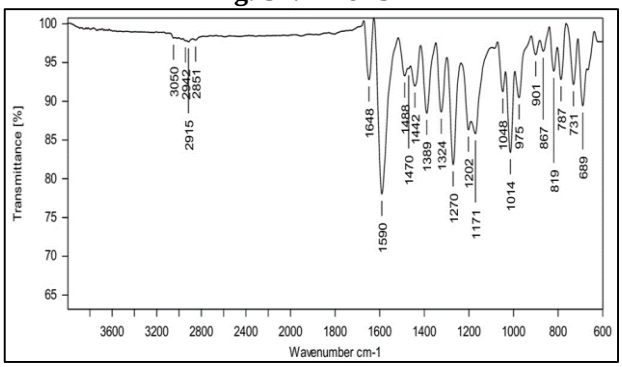


Fig. S3: IR of SCH-2

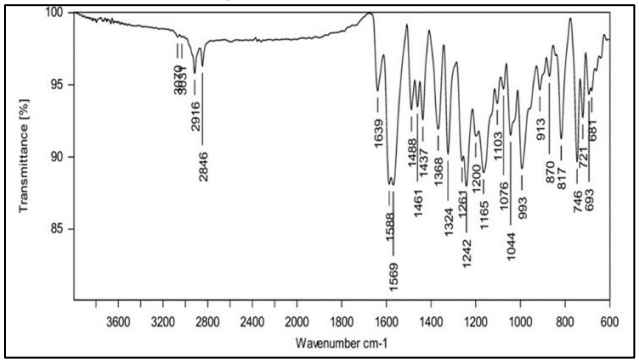


Fig. S4: IR of SCH-3

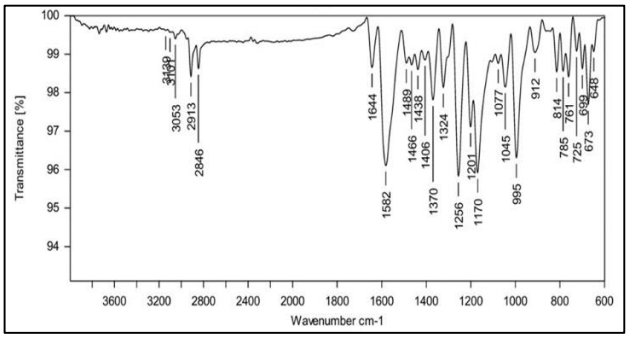


Fig. S5: IR of SCH-4

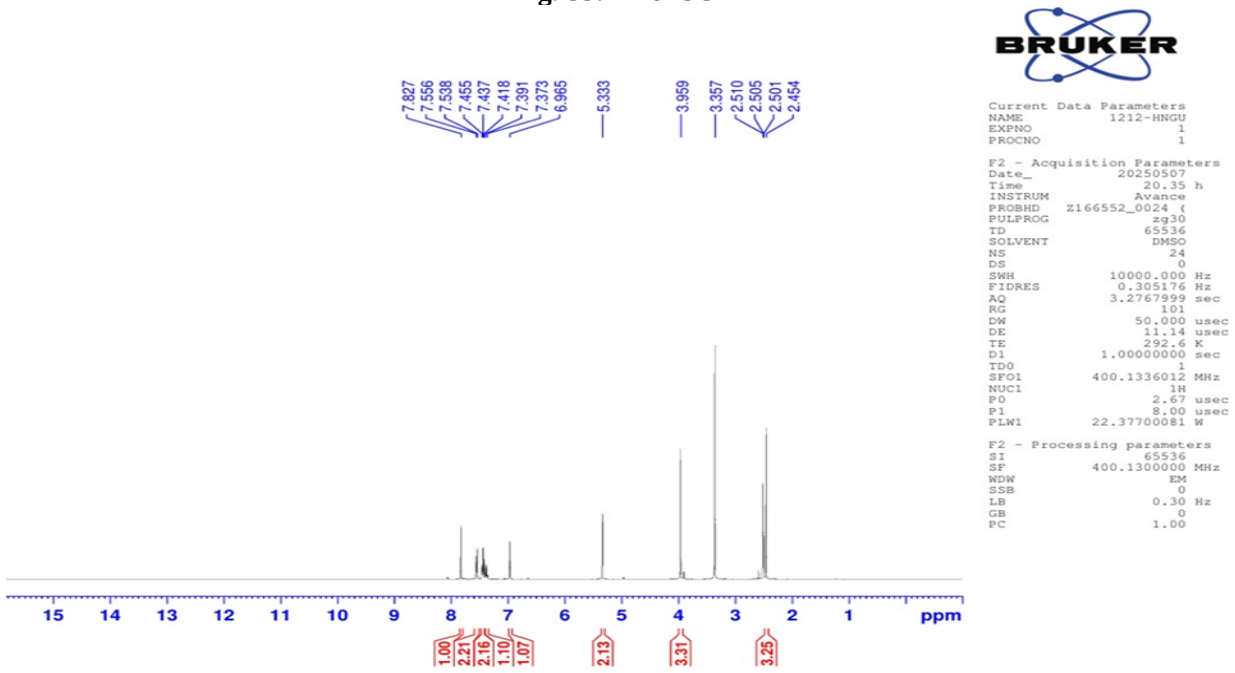


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Fig. S6: ^{1}H of NMR of S-1

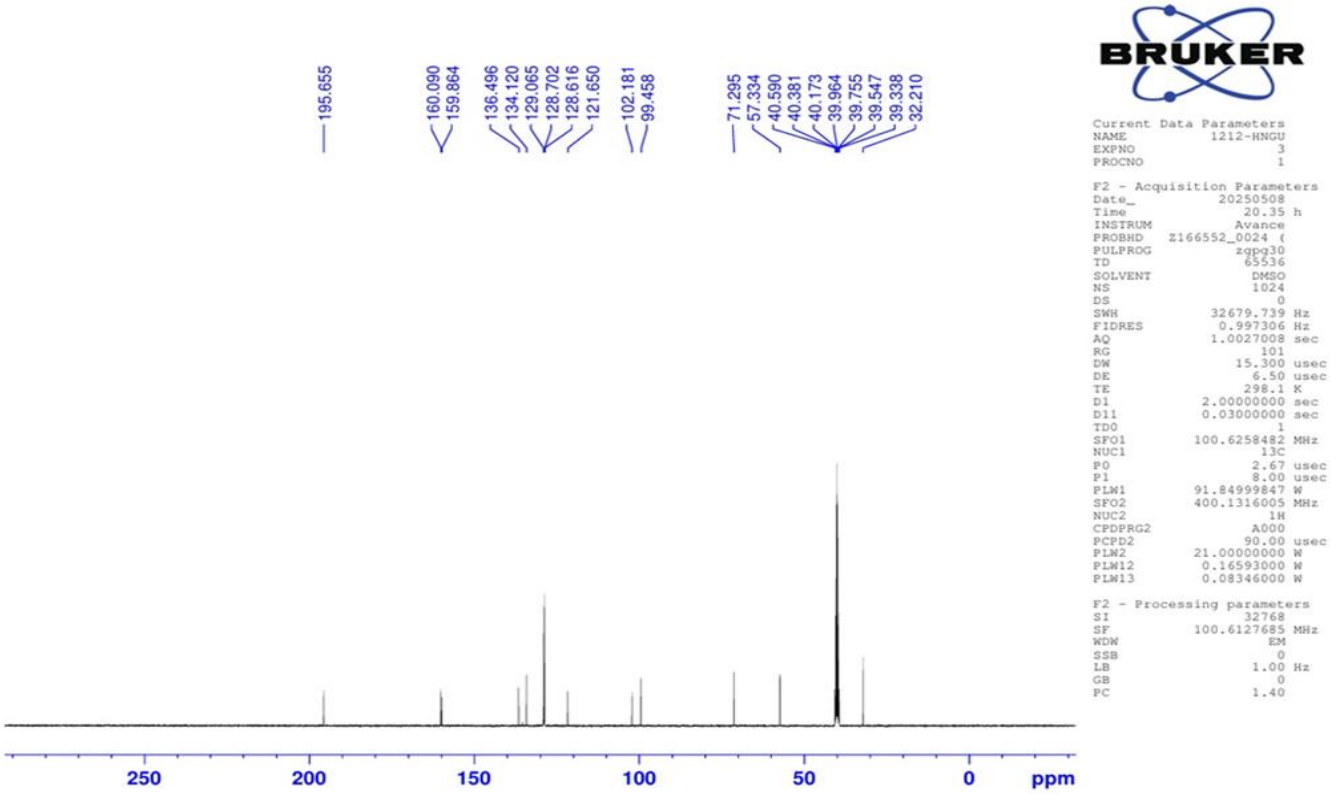

Fig. S7: ^{13}C NMR of S-1

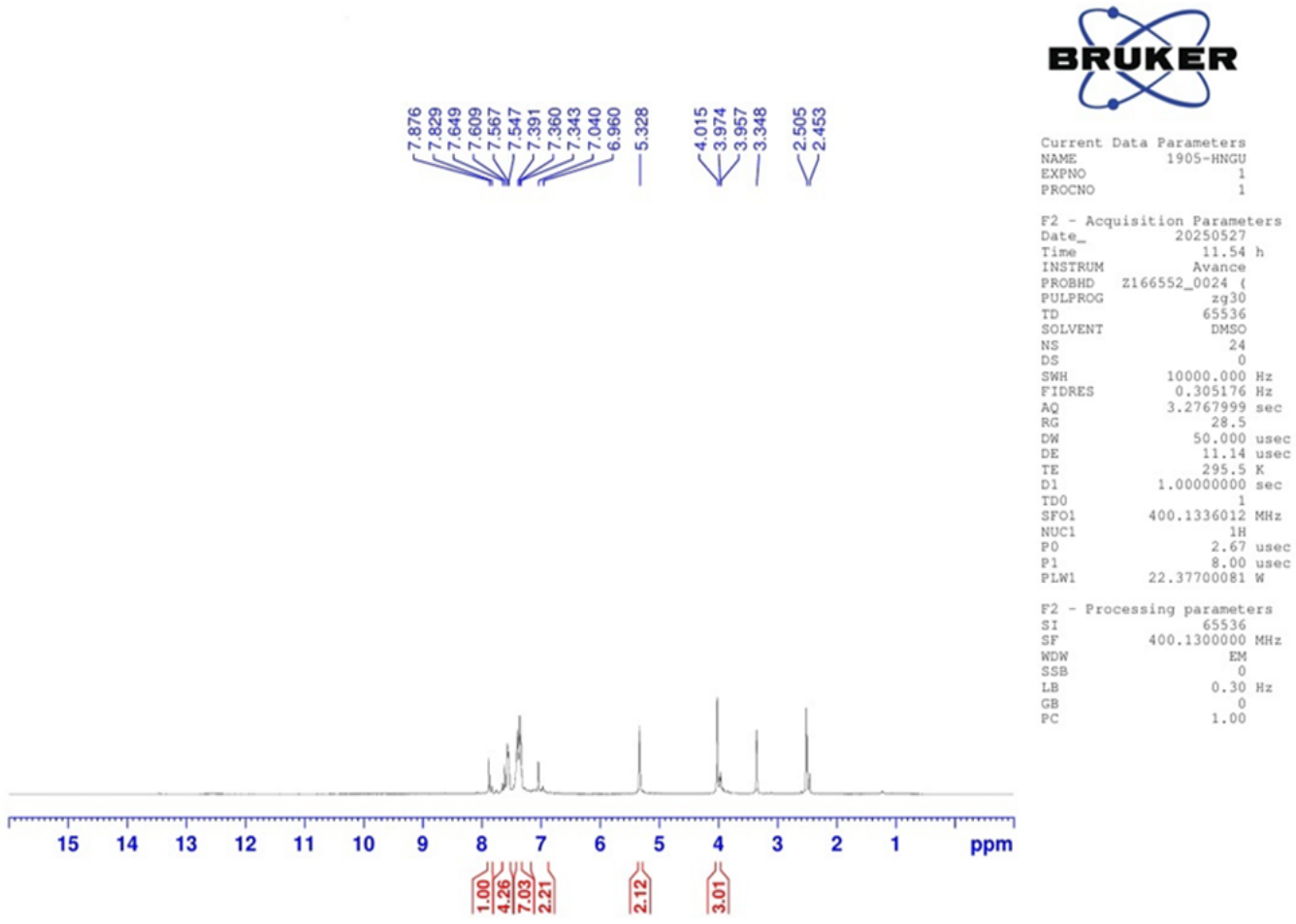

Fig. S8: ^{1}H NMR of SCH-1

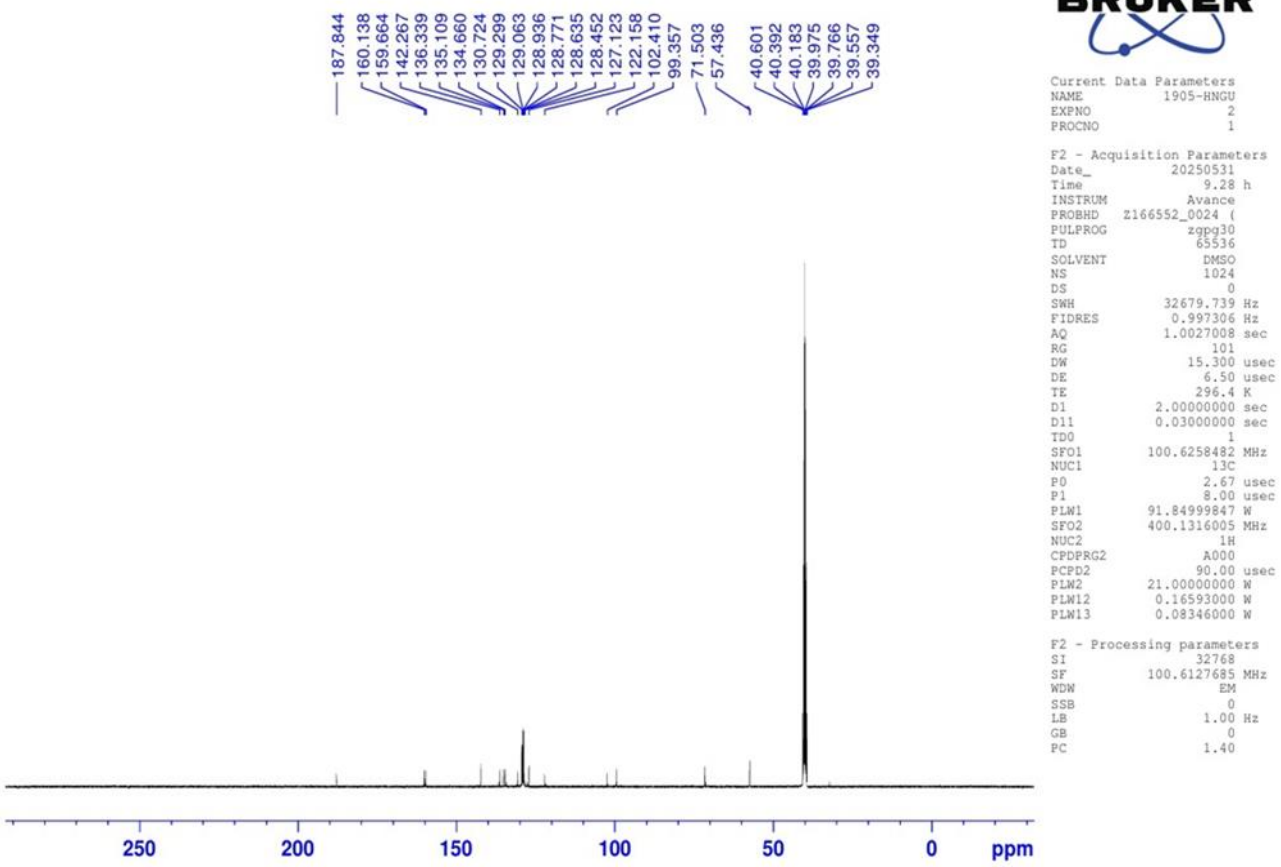

Fig. S9: ^{13}C NMR of SCH-1

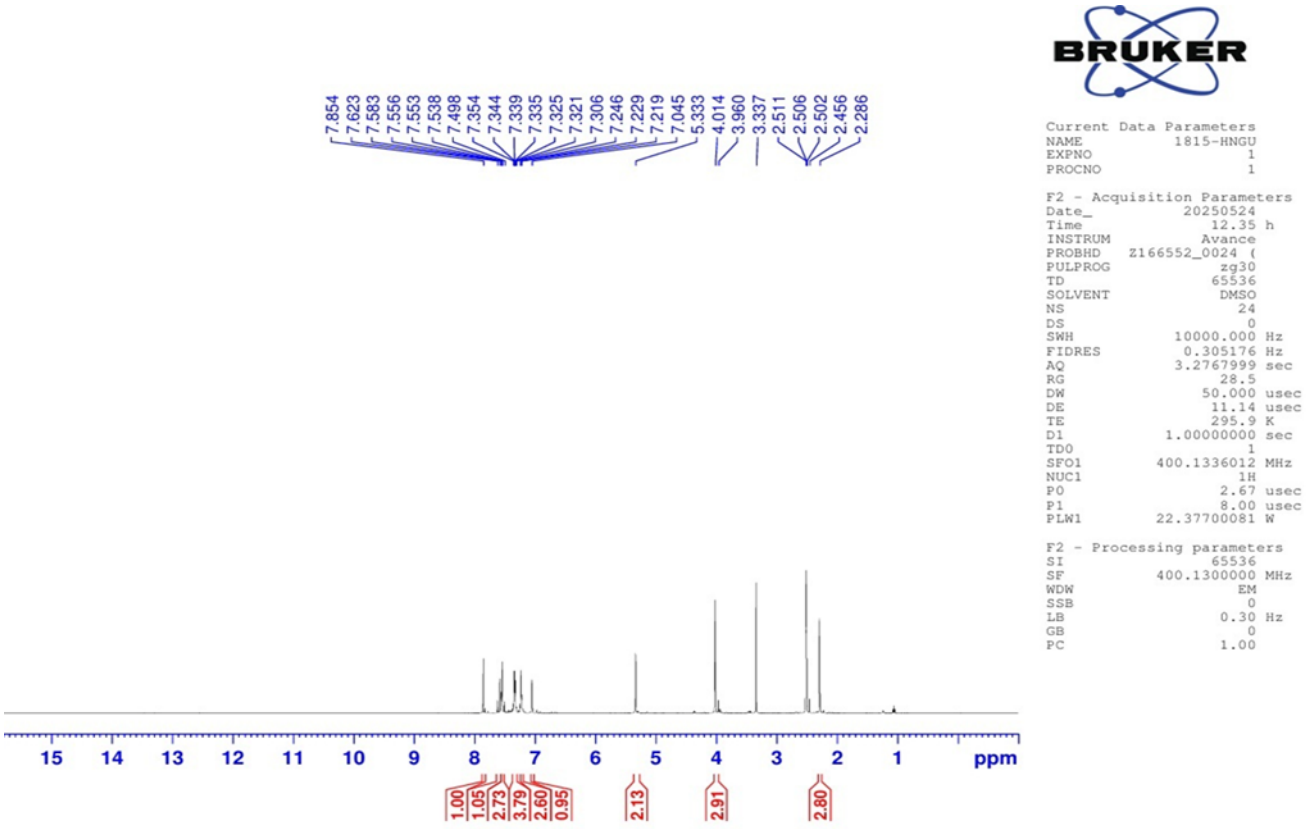

Fig. S10: ^{1}H of NMR SCH-2

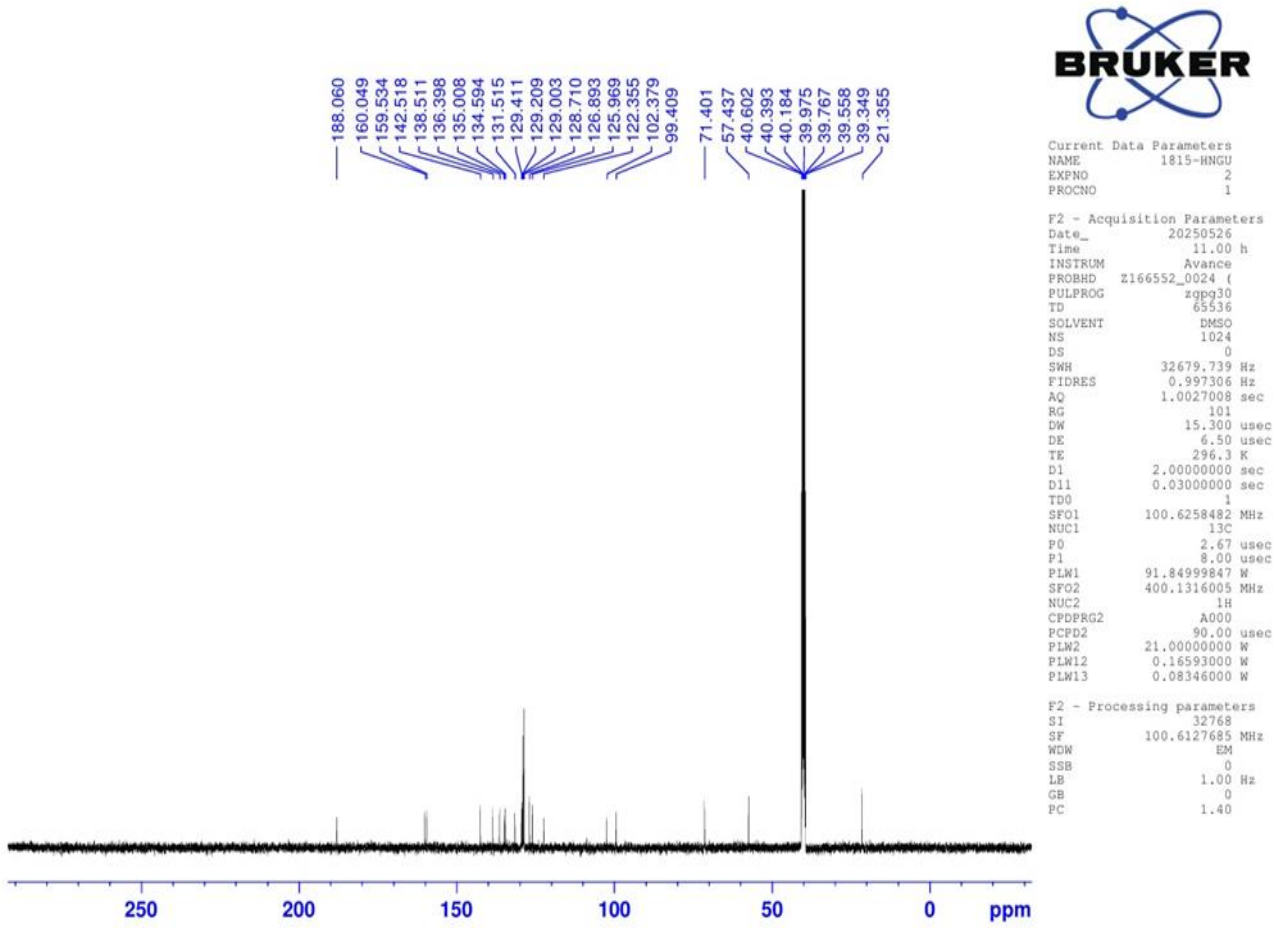

Fig. S11: ^{13}C NMR of SCH-2

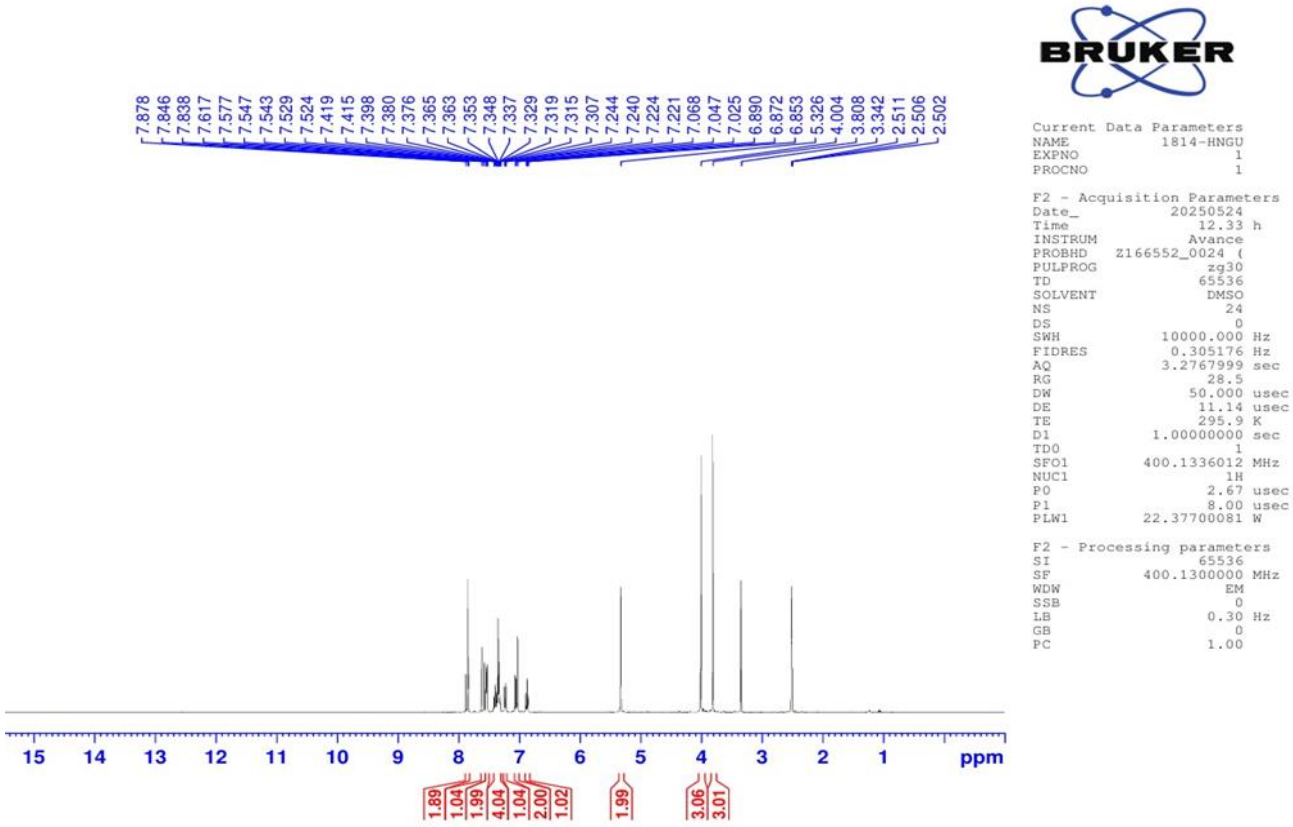

Fig. S12: ^{1}H NMR of SCH-3

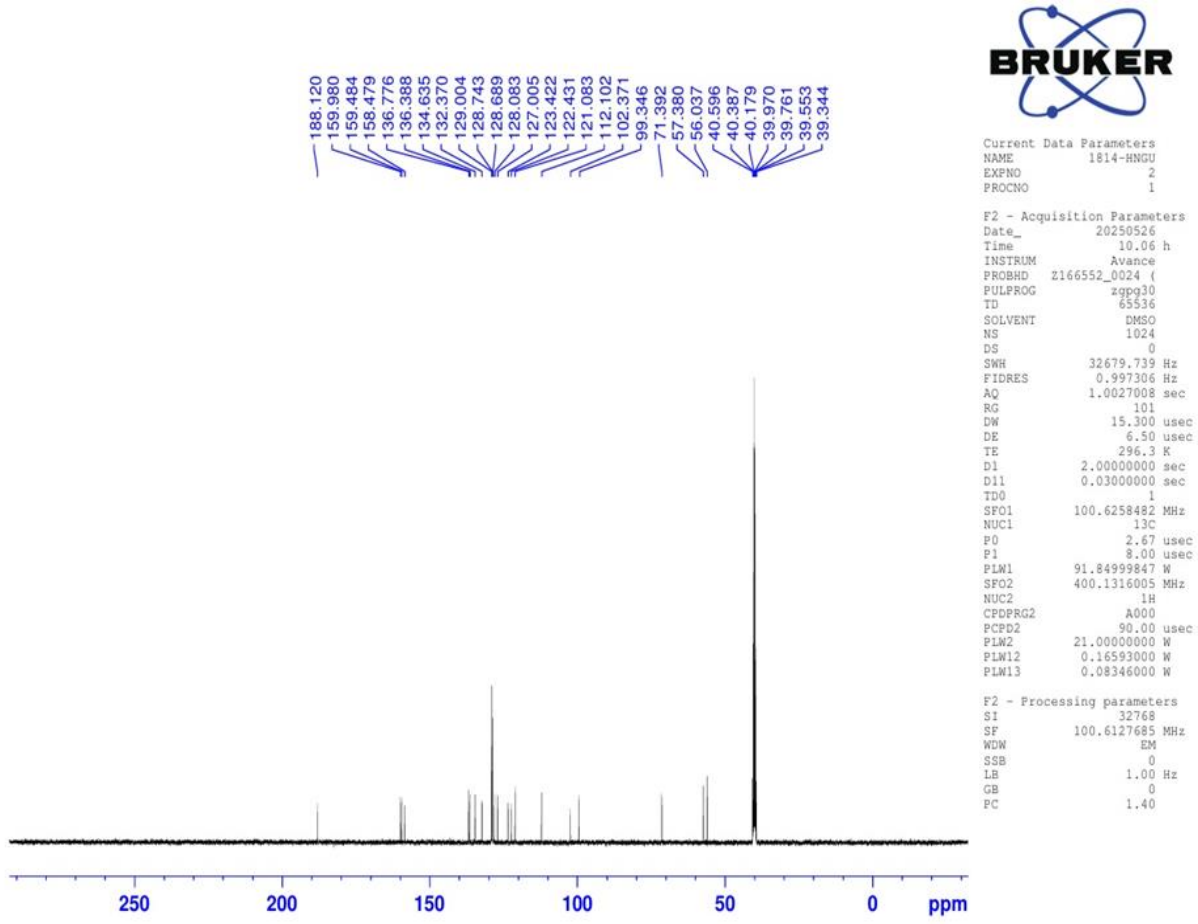

Fig. S13: ^{13}C NMR of SCH-3

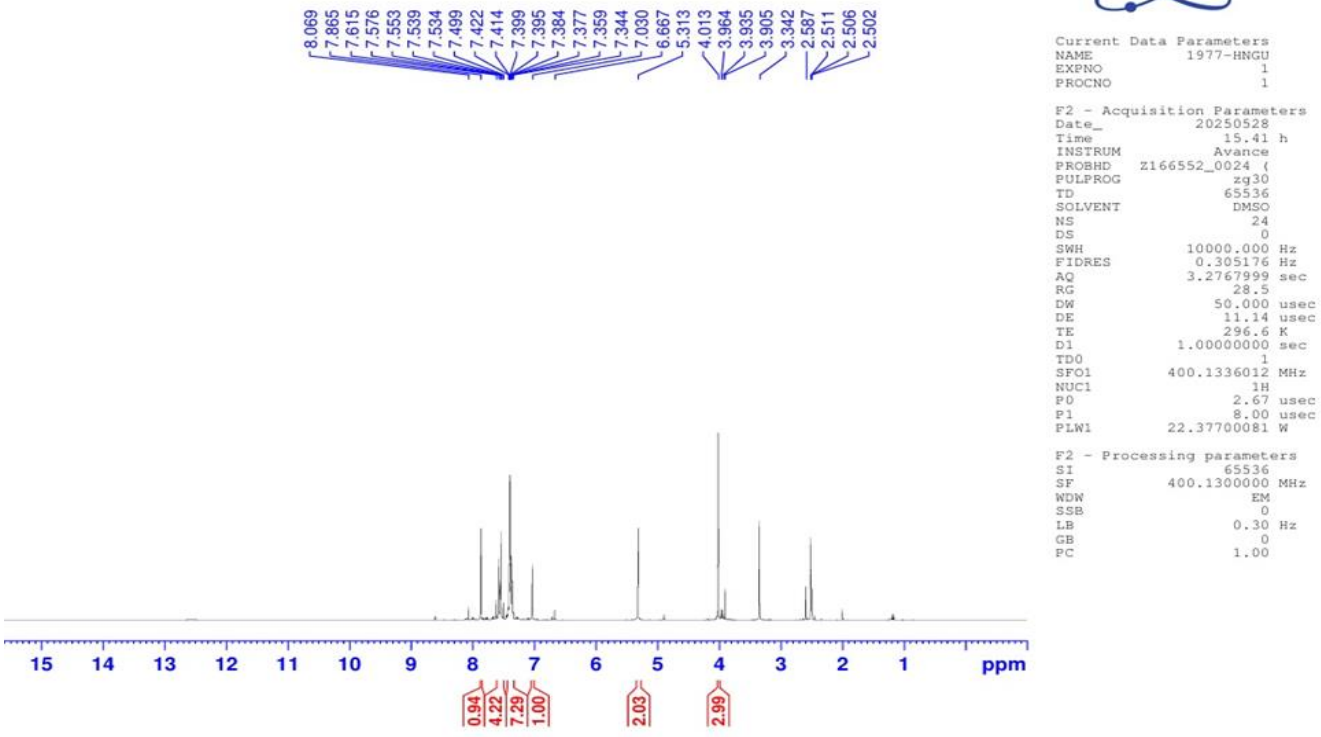

Fig. S14: ^{1}H NMR of SCH-4

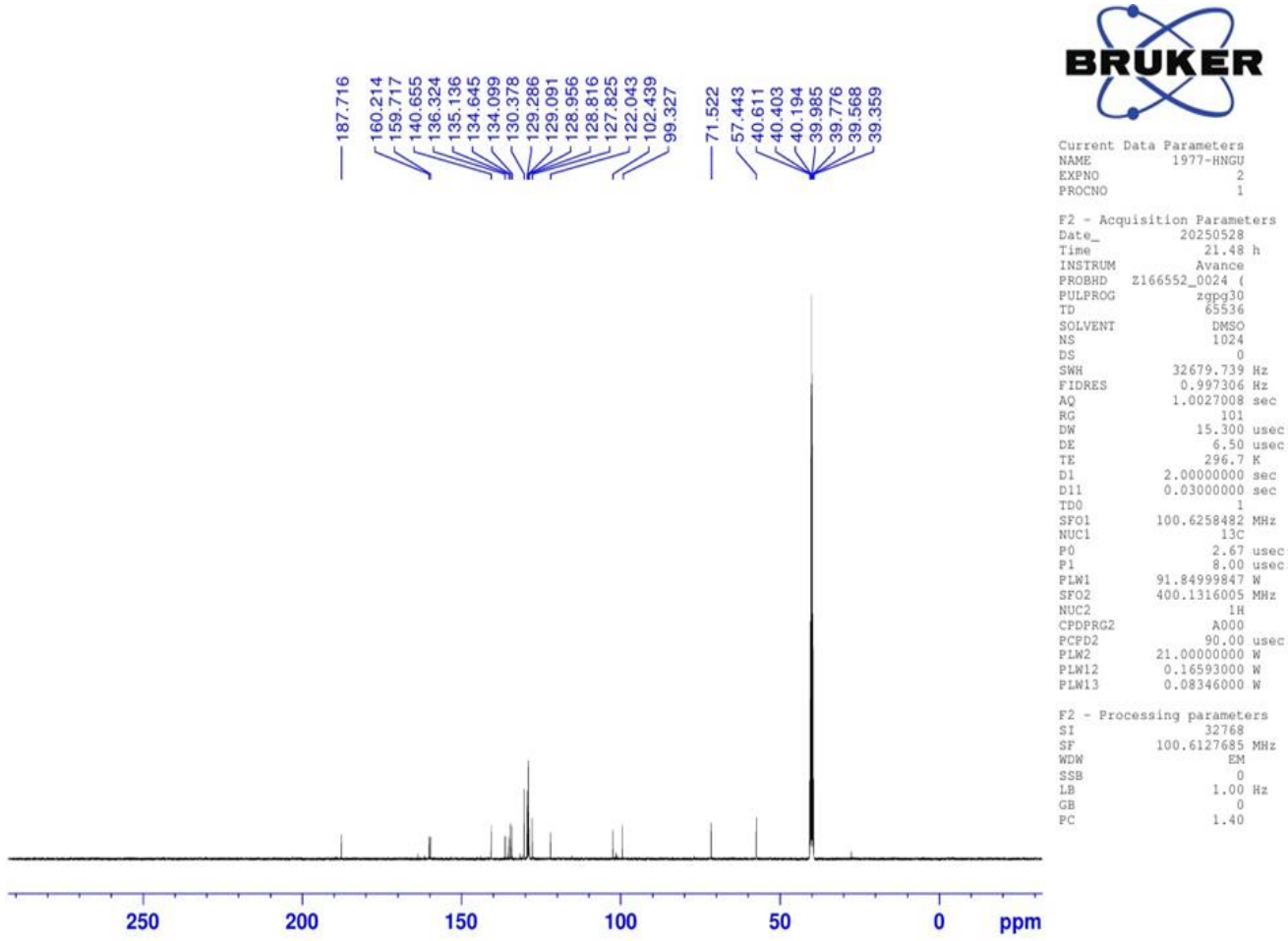

Fig. S15: ^{13}C NMR of SCH-4

Antifungal Activity: Among all synthesized compounds, S-1, SCH-1, and SCH-4 show notable antifungal activity against *Candida albicans*. They were found to be equipotent to those of the standard drug griseofulvin with MIC 500 µg/ml, while SCH-2 and SCH-3 have poor activity. The results of antibacterial and antifungal activities are presented in table 1, and their graphical representation is presented in fig. 1.

Conclusion

In conclusion, the purpose of the present study was to synthesize some new chalcone derivatives with the optimism of discovering novel structures and examining the antibacterial, antifungal activities. A series of chalcones (SCH-1 to SCH-4) were efficaciously synthesized. All the newly synthesized compounds were characterized spectroscopically, such as FT-IR, ^{1}H NMR, ^{13}C NMR, and mass spectrometry. All these synthesized compounds revealed that SCH-1 and SCH-2 show moderate activity against Gram-positive and Gram-negative bacteria respectively while others show poor activity as compared with standard drugs.

Furthermore, compounds S-1, SCH-1, and SCH-4 showed equipotent antifungal activity while SCH-2, SCH-3 have poor activity as compared to the standard drug.

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