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Structural, Spectroscopic, Molecular Docking and Biological Evaluation of some Novel Benzofuran Derivatives

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ABSTRACT

Benzofurans display a wide array of pharmaceutical activities. The present work incorporates the synthesis of some novel benzofuran derivatives. The compound **1** (z)-3-amino-7methoxy-N1-(2-oxoindolin-3-yliedene)benzofuran-2-carbohydrazide was synthesized by refluxing carbohydrazide and isatin. The compound **1** formed the key intermediate for the synthesis of compounds **2a-c**. The structures of prepared derivatives were established by physical and spectral methods such as elemental analysis, FTIR, ^{1}HNMR and Mass. The molecular docking studies was performed to detect the behavior of compounds towards target proteins. The derivatives were further screened for antibacterial and antifungal analysis.

Keywords: Benzofuran, Molecular docking, Antibacterial, Antifungal.

INTRODUCTION

Benzofuran moiety forms a basic structural fascinating unit responsible for the molecule's wide range of biological applications[1]. The inherent biological properties in benzofuran scaffold justifies the extensive interest in using benzofuran as building blocks of pharmacological agents[2,3]. The recently discovered novel macrocyclic benzofurans showed effective activity against hepatitis virus and cancer cells, hence they have been developed and utilized as therapeutic drugs[3]. The chemistry of Isatin (1H-indole-2, 3-dione) derivatives has been known from decades since it is largely used as precursors for drug synthesis[4,5]. Because of the omnipresent nature of oxygen-containing heterocycles, the isatin derivatives are considered as the key scaffolds of many biologically important molecules and pharmaceutical products. It has been studied that heterocyclic derivatives containing oxygen atoms make the world's largest-selling drugs[6-8].

In the view of above facts, the current work was focused to synthesize certain benzofuran derivatives and study their biological as well as docking properties.

MATERIALS AND METHODS

All the chemical used were obtained from sigma Aldrich (AR grade). The distillation of solvents mainly ethanol was carried out before usage. TLC (Thin layer chromatography) assisted to test the completion of the reaction. Melting point of each compound determined was uncorrected. The FTIR spectra were obtained by KBr pellet using Shimadzu model IR-435 spectrophotometer. The ^{1}HNMR spectra were predicted utilizing Bruker 400-MHz spectrometer. The mass spectra (m/z) has been recorded on micro mass Auto spec LCTKC455.

EXPERIMENTAL

Preparation of compound 1(z)-3-amino-7methoxy-N1-(2-oxoindolin-3-yliedene) benzofuran-2-carbohydrazide.

An equal amount of 3-amino-7-methoxy-1-benzofuran-2-carbohydrazide and indole-2, 3-dione (isatin) was refluxed for nearly 2 h in presence of glacial acetic acid and ethanol to yield (z)-3-amino-7methoxy-N1-(2-oxoindolin-3-yliedene)benzofuran-2-carbohydrazide. The obtained product was dried, well washed and recrystallized using ethanol.

Compound 1 (z)-3-amino-7methoxy-N1-(2-oxoindolin-3-yliedene)benzofuran-2-carbohydrazide

$C_{18}H_{14}N_4O_4$, pinkish brown color solid, yield: 75%, m.p.: 198^{0}C, IR(KBr, υ_{max}, cm^{-1}, KBr): 3262(NH stretching), 2912(OCH_3 stretching), 1743(C=O indolinone stretching), 1621(C=O carbohydrazide stretching); ^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 4.01(s, OCH_3, 3H), 1.32(s, NH, 1H amide), 1.20(s, NH,1H istain), 6.72-7.55(m, Ar-H,9H); LCMS m/z (observed, calculated): 350.32, 349.09.

General procedure for the preparation of compound 2(a-c)

The compound 1 (1M) was dissolved in DMF, to this solution slightly excess formaldehyde (1M) was added. The appropriate secondary amine (Morpholine, Piperidine, Diphenyl amine) (1M) was added and further the reaction mixture was subjected for heating in water bath for about 50 min. and kept overnight for precipitation to occur. The product formed was separated, washed, dried and recrystallized using the solvent ethanol.

Compound 2a

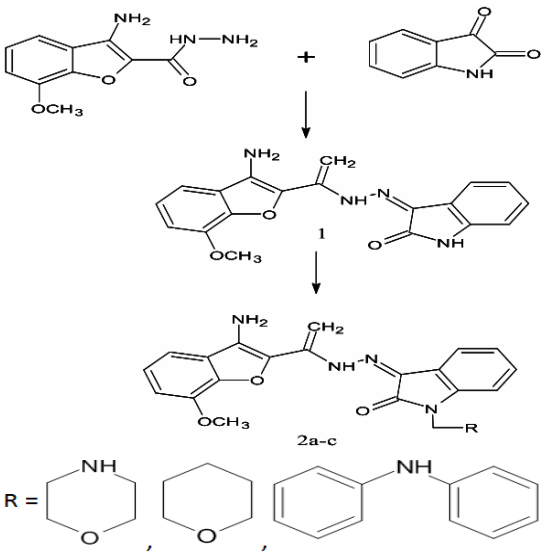
$C_{23}H_{23}N_5O_5$, Brown color solid, yield: 85%, m.p.: 222^{0}C, IR(KBr, υ_{max}, cm^{-1}, KBr): 3410(NH stretching), 2930(OCH_3 stretching), 1603(C=O indolinone stretching), 1446(C=O carbohydrazide stretching), 2852 (CH_2 stretching); ^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 3.94(s, OCH_3, 3H), 2.49 (s, NH, 1H, istain), 2.97 (s, NH, 1H amide), 6.41-8.30 (m, Ar-H,18H) LCMS m/z (observed, calculated): 449.17, 450.08.

Compound 2b

$C_{24}H_{25}N_5O_4$, Brown color solid,yield: 80%, m.p.: 257^{0}C, IR(KBr, υ_{max}, cm^{-1}, KBr): 3419(NH stretching), 2922(OCH_3 stretching), 2869 (CH_2 stretching), 1708 (C=O indolinone stretching), 1621 (C=O carbohydrazide stretching); ^{1}H-NMR (400 MHz, $CDCl_3$, δppm): 3.81(s, OCH_3, 3H), 2.16 (s, NH,1H, amide), 1.25(s, NH,1H, istain), 6.41-8.30 (m, Ar-H,20H); LCMS m/z (observed, calculated): 447.19, 448.19.

Compound 2c

$C_{31}H_{25}N_5O_4$, Brown color solid, yield: 72%, m.p.: 288^{0}C, IR(KBr, υ_{max}, cm^{-1}, KBr): 3340 (NH stretching), 2912 (OCH_3 stretching), 2860 (CH_2 stretching), 1734 (C=O indolinone stretching), 1595 (C=O carbohydrazide stretching); ^{1}H-NMR (400 MHz, $CDCl_3$, δppm): 3.73(s, OCH_3, 3H), 2.17 (s, NH,1H, amide), 1.11(s, NH,1H, istain), 7.09-10.23 (m, Ar-H, 20H); LCMS m/z (observed, calculated): 531.19, 532.57.



Scheme

RESULTS AND DISCUSSION

The stepwise reaction of the synthesis of benzofuran derivatives has been represented in the Scheme. The compound 1 (z)-3-amino-7methoxy-N1-(2-oxoindolin-3-yliedene) benzofuran-2-carbohydrazide was synthesized by reaction of carbohydrazide and indole-2, 3-dione. The compound 1 formed the key intermediate for the synthesis of compound 2(a-c). The compound 2(a-c) were prepared by condensation of compound 1 with respective secondary amine (Morpholine, Piperidine, Diphenyl amine). All the newly synthesized compounds were confirmed using physical and spectral techniques like elemental analysis, FTIR, ^{1}HNMR, and Mass.

The analytical data of FTIR, 1HNMR and Mass is represented in table 1,2 (Fig. 1-10). In the IR spectra, the absorption band found between 3262 to 3419 cm^{-1} has been attributed to -NH group, the region from 1603 to 1743 cm^{-1} is due to -C=O group attached to indolinone and carbohydrazide ring in 2(a-c) series. The ^{1}HNMR spectra were detected in δvalues (ppm) considering tetramethylsilane (TMS) as standard reference. The peaks at δ 8.30, 9.5, and 10.23ppm have been assigned to $–NH_2$ group attached to the furan ring in compounds 2a, 2b, and 2c. The presence of peaks in compounds 2a, 2b, and 2c at δ3.8,3.7and 3.9 98ppm is assignable to $–CH_3$ group. The new peaks at 1.26,1.11 and 1.25ppm is assigned to -NH isatin ring and peaks at 2.16, 2.17 and 2.55ppm is assigned to the -NH amide group in the carbohydrazide ring in compounds 2(a-c). Further, the mass spectra of the synthesized compounds coincide with the calculated mass, therefore further confirming the formation of compounds.

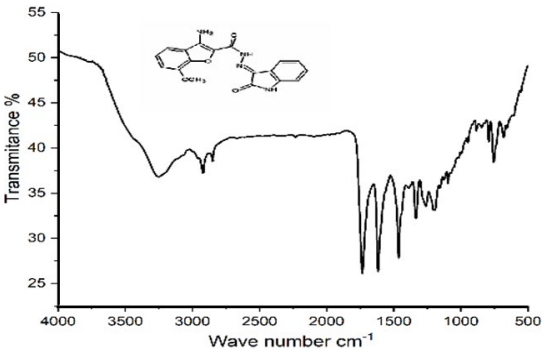


Fig. 1. FTIR spectrum of compound 1

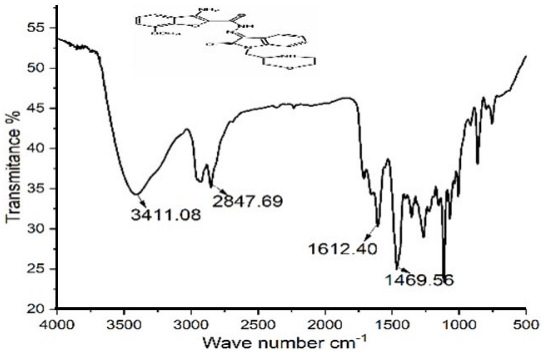


Fig. 2. FTIR spectrum of compound 2a

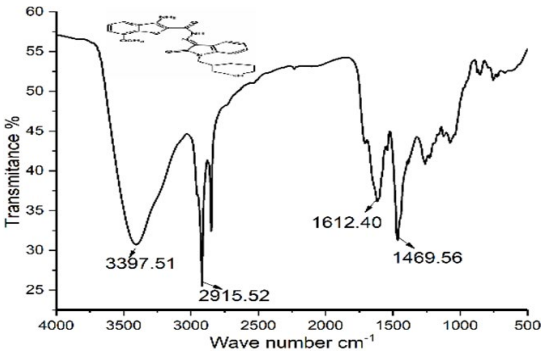


Fig. 3. FTIR spectrum of compound 2b

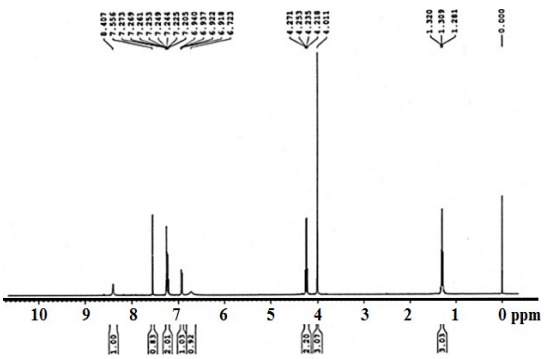


Fig. 4. ^{1}HNMR of compound 1

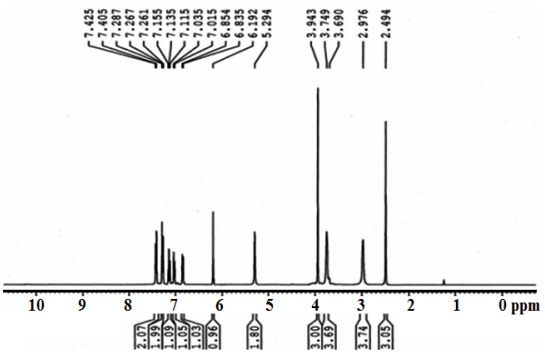


Fig. 5. ^{1}HNMR of compound 2a

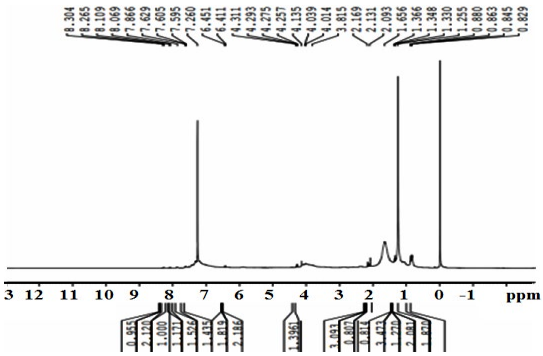


Fig. 6. ^{1}HNMR of compound 2b

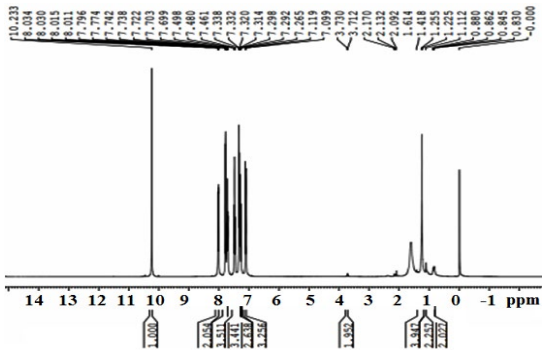


Fig. 7. ^{1}HNMR of compound 2c

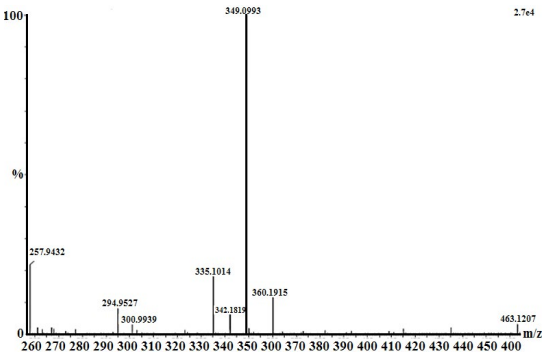


Fig. 8. Mass spectrum of compound 1

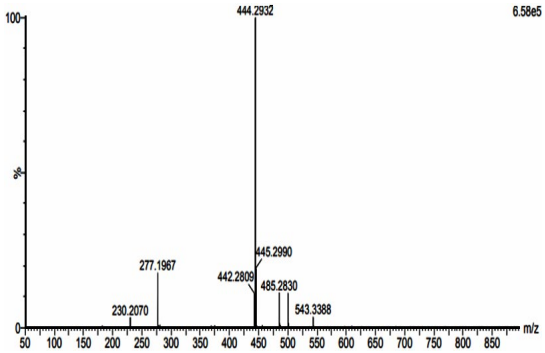


Fig. 9. Mass spectrum of compound 2b

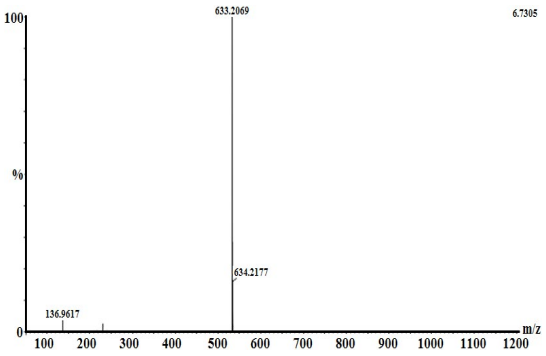


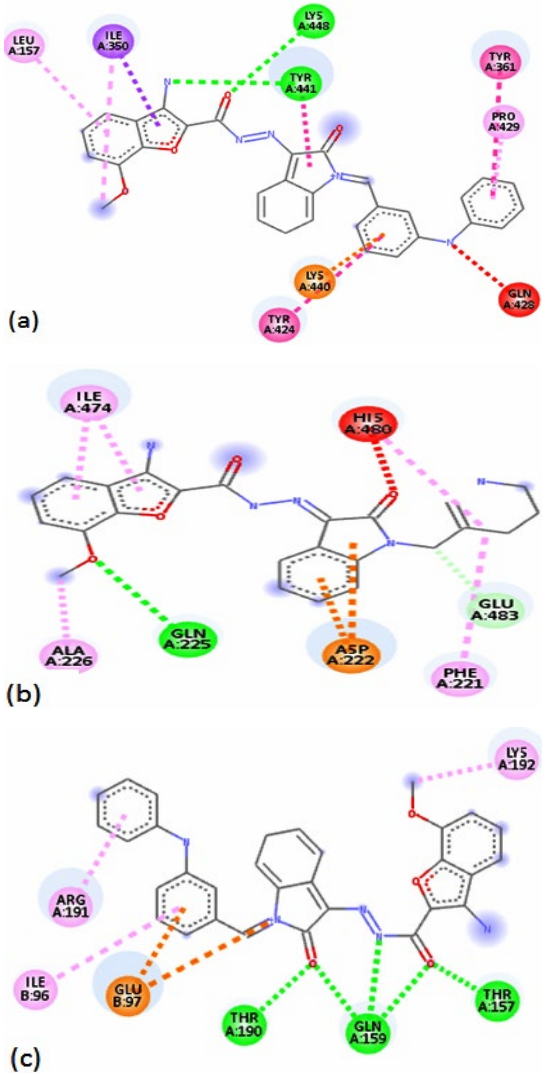
Fig. 10. Mass spectrum of compound 2c

Molecular docking

Molecular docking plays a vital role in structure based drug design and discovery. The docking aids to predominantly explore the behaviour of ligand with the target protein. The compound 1 and 2(a-c) were docked with protein molecules 3EQM, 4HOE and 1XFF (PDB ID'S) respectively[9]. The 3D structure of protein aromatase cytochrome P450 [3EQM (PDB ID)], candida albicans dihydrofolate reductase [4HOE (PDB ID)] and glucosamine 6-phosphate synthase [1XFF (PDB ID)] were retrieved from RCSB protein data bank. The docking was carried out using AutoDock vina software. The AutoDock vina evaluates the binding affinity of ligand -protein interaction in terms of sum of binding constant (Kd) and the Gibbs free energy (δGL)[10].

Initially the target protein and ligand were prepared using AutoDock MGL tools. The water molecules and unwanted ligands were discarded. The protein structure was protonated and Kollman charges were also added. The protein was saved as pdbqt. The ligand structure drawn in chemdraw was converted to PDB format and saved as pdbqt. A grid box was created with X, Y, Z centres and a grid spacing in A^0 was adjusted to be sufficiently large enough to cover the entire protein as blind mode of docking was performed[11-14]. AutoDock vina ranks the docked ligand on the basis of interaction with the target protein. Lowest 2the binding affinity value, highest is the interaction of the ligand with that protein. The best docking score was further analyzed to study the type of interactions using BIOVIA discovery studio and pyMol visualize tools.

Among the subjected ligands, the compound 2c exhibits highest binding interaction showing a binding affinity value of -10.2, -9.3 and -9.1 for 3EQM, 4HOE and 1XFF target proteins. The type of interactions involve H-bonding, hydrophobic, vander waals and electrostatic. The results are interpreted in Table 3 (Figures 11, 12).



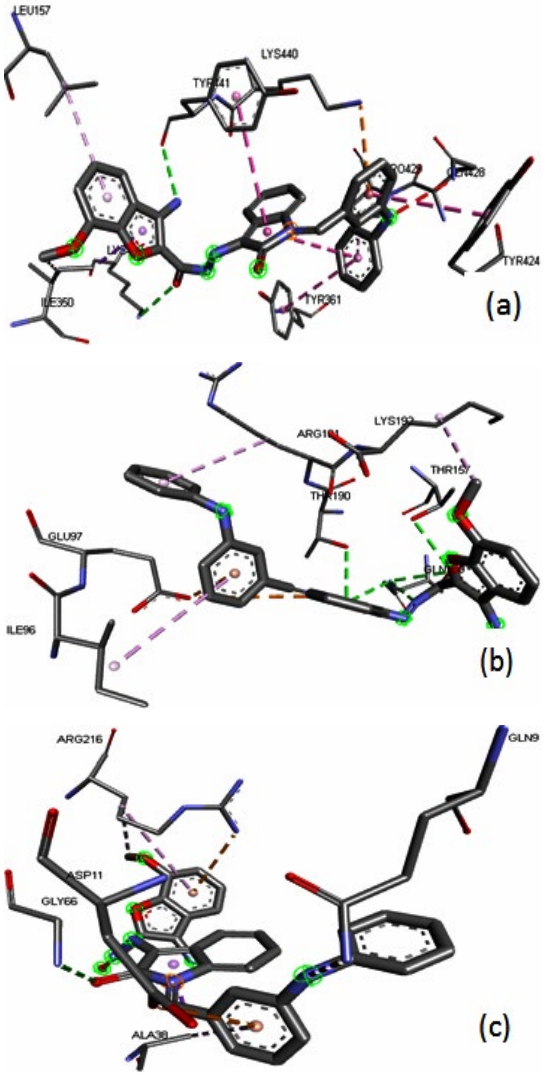


Fig. 11. Represents 2D interactions of compound 2c with (a) 3EQM, (b) 4HOE and (c) 1XFF protein molecules

Fig. 12. Represents 3D interactions of compound 2c with (a) 3EQM, (b) 4HOE and (c) 1XFF protein molecules

Table 1: Showing Molecular formula, MP, Yield and Elemental analysis data of synthesized compounds

Compounds	Molecular formula	m.p.^{0}C	Yield%	Elemental analysis Observed/calculated		
				C %	H%	N%
1	$C_{18}H_{14}N_4O_4$	198	75	61.71(61.69)	4.03(3.99)	15.99(15.99)
2a	$C_{23}H_{23}N_5O_5$	222	85	61.46(61.44)	5.16(5.12)	15.58(15.58)
2b	$C_{24}H_{25}N_5O_4$	257	80	64.42(64.40)	5.63(5.59)	15.65(15.65)
2c	$C_{31}H_{25}N_5O_4$	288	72	70.04(70.03)	4.74(4.70)	13.18(13.17)

Table 2: Representation of analytical data (FTIR, 1HNMR and Mass) of the synthesized compounds

Compound	FTIR (KBr) (cm^{-1})	^{1}HNMR δ(ppm)	MASS m/z (Observed, calculated)
1	3262 (NH stretching), 2912(OCH_3 stretching), 1621(C=O indolinone stretching)	δppm-4.01 (s, OCH_3, 3H), 1.32(s, NH, 1H amide), 1.20(s,NH, 1H istain), 6.72-7.55 (m, Ar-H, 9H)	350.32349.09
2a	3410 (NH stretching), 2930(OCH_3 stretching), 1603(C=O indolinone stretching), 2852(CH_2 stretching)	δppm-3.94 (s, OCH_3, 3H), 2. 49 (s,NH,1H, istain), 2.97 (s,NH, 1H amide), 6.41-8.30 (m, Ar-H, 18H)	449.17450.08
2b	3419 (NH stretching), 2922(OCH_3 stretching), 2869 (CH_2 stretching), 1708 (C=O indolinone stretching)	δppm-3.81 (s, OCH_3, 3H), 2.16 (s, NH,1H, amide), 1.25 (s, NH,1H, istain), 6.41-8.30 (m,Ar-H, 20H)	447.19448.19
2c	3340 (NH stretching), 2912(OCH_3 stretching), 2860 (CH_2 stretching), 1603 (C=O indolinone stretching)	δppm-3.73 (s,OCH_3, 3H), 2.17(s, NH,1H, amide), 1.11 (s, NH,1H, istain), 7.09-10.23 (m, Ar-H, 20H)	531.19532.57

Table 3: Results of docking studies of synthesized compounds with different proteins

Protein (PDB ID)	Ligand	Binding affinity (kcal/mol)	Bonded Amino acids	Distance (A^o)
1XFF	Compound 1	-8.4	ARG22, ARG22, ARG201, THR200, ARG201, ARG202, GLU235, GLU235, PRO198, MET184, ARG202, PRO198, ARG202	2.98, 3.02, 3.20, 3.20, 2.86, 3.90, 3.50, 3.95, 5.05, 5.18, 4.78, 5.36, 4.09
3EQM	Compound 1	-8.1	GLN367, ARG403, GLN367, ARG403, LYS473, LEU479, LYS473, PRO368, PRO368	3.17, 2.96, 3.08, 3.83, 3.82, 4.35, 4.66, 4.81, 5.05, 5.44, 5.22
4HOE	Compound 1	-8.1	ASN124, ASN124, LYS192, ARG191, ILE96, ARG191, LEU126, ILE96, ARG191	3.25, 3.00, 4.51, 4.51, 3.68, 4.24, 4.19, 5.01, 5.23
1XFF	Compound 2a	-8.4	THR67, ALA8, THR67, ALA38, ASP11, ALA38, ALA38, ALA38.	2.98,2.91,3.36,3.66,4.94,4.46, 4.16,4.76
3EQM	Compound 2a	-8.4	LYS354, TYR361, VAL422, VAL422,PHE418, LYS440, GLU357, TYR424, TYR441, PRO429	3.04,2.81,3.02,3.76,3.05,3.80, 4.92,3.77,5.90,5.24
4HOE	Compound 2a	-8.1	THR157, GLN159, ASN124, GLN159,LYS192, ASN124, GLU97, GLU97, ASN123, ARG191,	3.15,3.01,2.91,3.52,3.57,3.68, 4.20,3.86,4.02,4.13,4.80
1XFF	Compound 2b	-8.4	THR67, ALA8, ASP11, ASP11, ALA38, ALA38, ALA38, ALA38	2.95,3.04,3.64, 4.91, 3.97, 4.45, 4.18, 4.63
3EQM	Compound 2b	-8.5	GLN225, GLU483, ASP222, ASP222, ALA226, PHE221, HIS480, ILE474,ILE474	3.04,3.42,4.65,3.88, 4.32, 5.31, 4.18, 4.81, 4.31
4HOE	Compound 2b	-8.2	THR157, GLN159, ASN124, GLN159, GLU97, GLU97, ASN123, ARG191, ARG191	3.22, 3.02, 3.02, 3.44, 4.11, 3.78, 4.02, 4.28, 4.81
3EQM	Compound 2c	-10.2	LYS448, TYR441, LYS440, ILE350, TYR424, TYR361, TRY441, ILE350, LEU157, PRO429	3.22, 3.33, 4.17, 3.17, 4.45, 4.98, 5.26, 4.88, 5.30, 4.78
4HOE	Compound 2c	-9.3	GLU97, THR157, GLN159, GLN159, GLN159, THR190, GLU97, LYS192, ILE96, ARG191	5.51, 3.11, 2.92, 2.89, 3.10, 3.18, 3.66, 4.22, 5.41, 4.97
1XFF	Compound 2c	-9.1	GLY66, ARG216, ASP11, ALA38, ARG216, ARG216, ALA38	2.99, 4.04, 4.68, 3.60, 4.16, 5.25, 5.31

Biological applications

Antimicrobial activity

The newly synthesized compounds 1, 2a, 2b and 2c were subjected to antibacterial activity against bacteria *E. coli, K. pneumonia, S. aureus* and *S. epidermidis*. The analysis was done by agar diffusion method and the media used was Muller Hinton Agar. The fungi used for analysis were *C. albicans* and *A. niger*. The media used was Sabouraud's Dextrose Agar media (Table 4, 5).

Table 4: Results of antibacterial analysis

Compounds	Diameter of Zone of inhibition (mm)							
	Gram-positive				*Gram-negative*			
	S.aureus		*S. epidermidis*		*K. pneumonia*		*E. coli*	
	20μg/mL	50μg/mL	20μg/mL	50μg/mL	20μg/mL	50μg/mL	20μg/mL	50μg/mL
1	10	13	11	14	12	15	16	17
2a	10	12	12	15	14	16	15	16
2b	11	14	11	13	12	16	16	18
2c	12	15	12	14	13	16	14	15

Table 5: Results of antifungal analysis

Compounds	Diameter of Zone of inhibition (mm)			
	C. albicans		*A. niger*	
	20μg/mL	50μg/mL	20μg/mL	50μg/mL
1	18	20	14	16
2a	20	22	18	20
2b	18	19	10	15
2c	16	18	15	17

CONCLUSION

The structures assigned to the synthesized compounds were concurrent with the spectral data analyzed. The results of molecular docking provides a positive path on the usage of these derivatives as potent drugs. Further the antimicrobial studies reveal that derivatives possess moderate activity.

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Conflicts of Interest

The main author and also co-authors declare that there is no conflict of interest pertaining to this work.

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