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SYNTHESIS, DOCKING AND BIOLOGICAL EVALUATION OF 3-(3-CHLOROBENZOYL)-N-PHENYLINDOLIZINE-1-CARBOXAMIDE DERIVATIVES AS ANTI-TUBERCULOSIS, ANTICANCER, ANTI-INFLAMMATORY AND ANTIBACTERIAL AGENTS

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ABSTRACT
A series of substituted 3-(3-chlorobenzoyl)-N-phenylindolizine-1-carboxamides have been synthesized from 3-chlorobenzoyl-indolizine-1-carboxylic acid with substituted aromatic amines in the presence of triethylamine and Pybop reagent. All the newly synthesized compounds were confirmed by Elemental, FTIR, ^{1}H NMR, ^{13}C NMR and Mass spectroscopic techniques. The obtained target compounds showed excellent *in vitro* anti-tuberculosis, anticancer, anti-inflammatory and antibacterial activity. Molecular docking studies have supported the *in vitro* anticancer activity of these molecules.
Keywords: Phenylindolizine-carboxamide, Anti-tuberculosis, Anticancer, Anti-inflammatory, Antibacterial, Molecular docking.
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INTRODUCTION

The design and synthesis of new nitrogen heterocycles with possible biological applications have been playing a crucial role in the early stages of drug discovery research.[1] Recently, much attention has been paid to fused heterocycles as they have been frequently employed as basic core skeletons in a number of bioorganic and medicinal chemistry applications.[2-4] Among them, nitrogen-fused bicyclic aromatic systems such as indolizine have been widely investigated to display various intriguing biological activities depending on the structure with different functional groups.[5] In addition, synthetic and natural indolizines[6,7] (Fig.-1) derivatives have also exhibited good results for anti-tubercular[8], anti-inflammatory[9], antiangiogenic[10], anticancer[11] and antibacterial[12] activities. In recent years, fused indolizines like indolizine–chalcones were reported as inhibitors of human farnesyltransferase[13] and spirooxindole-indolizine hybrids as TNF-α and nitrite inhibitors.[14] Fused indolizines are widespread in natural and pharmaceutically active compounds and are well known for their extensive range of biological activities.[15]

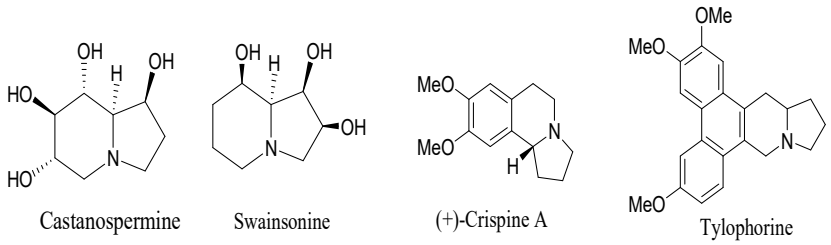

Fig.-1: Naturally Occurring Indolizidine Alkaloids

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As part of our research on the synthesis and biological activities of novel nitrogen heterocyclic molecules.[16] Herewith, we are reporting the synthesis and *in vitro* anti-tuberculosis, anticancer, anti-inflammatory and antibacterial applications of indolizine-carboxamide derivatives.

EXPERIMENTAL

Materials and Methods

All chemicals and solvents were obtained from Sigma Aldrich**.** Melting points have been determined by using Thomas Hoover, FTIR spectra were recorded in Shimadzu 8300 spectrophotometer, ^{1}H NMR(400 MHz, DMSO-d_6), and ^{13}C NMR (100 MHz, DMSO-d_6) spectra analyzed using Bruker 400 MHz, LCMS analysis done in Agilent LC1200, and elemental analyses were recorded in Perkin Elmer instrument.

General Procedure of Synthesis of Phenyl indolizine-carboxamide

3-(3-chlorobenzoyl)-N-phenylindolizine-1-carboxamide derivatives **3(a-f)** were synthesized from 3-(3-chlorobenzoyl) indolizine-1-carboxylic acid **1** was reported earlier.[16] The compound **1** (2 mmol) was dissolved in dichloromethane (20 mL) and added triethylamine (6 mmol) followed by Pybop (3 mmol) and stirred for 0.5 h at room temperature. Then substituted aromatic amines **2(a-f)** (3 mmol) were added to the reaction mixture and stirred for 10 h. The reaction mass was diluted with water and extracted with dichloromethane (2 x 100 mL). The combined organic layer was dried over sodium sulphate and concentrated to afford crude mass. It was purified by flash column chromatography using ethyl acetate-pet ether (7:3) to achieve the compounds phenyl indolizine-carboxamide derivatives **3(a-f)**.

3-(3-Chlorobenzoyl)-N-phenylindolizine-1-carboxamide (3a)

Yield: 85%, M.P. 90.3-91.1℃. IR (v, cm^{-1}): 3299 (N-H), 3110 (C-H, aromatic), 1595 (C=C, aromatic); ^{1}H NMR: 7.09-7.07 (m, 1H), 7.36-7.32 (m, 3H), 7.67-7.61 (m, 2H), 7.76-7.72 (m, 3H), 7.85-7.79 (m, 2H), 8.28 (s, 1H), 8.63-8.60 (m, 1H), 9.89-9.87 (m, 1H), 9.98 (s, 1H); ^{13}C NMR: 109.9, 116.5, 120.1, 120.8, 121.5, 123.7, 126.3, 128.0, 128.6, 128.8, 128.9, 129.0, 130.9, 131.6, 133.8(2C), 139.6, 140.2, 142.1, 162.3(2C), 183.1; LC-MS (*m/z,* EI): 375.1 [M+H] $^+$. Anal. Calcd. for $C_{22}H_{15}ClN_2O_2$: C, 70.50%; H, 4.03%; N, 7.47%. Found: C, 70.49%; H, 4.02%; N, 7.46%.

3-(3-Chlorobenzoyl)-N-(3, 4-difluorophenyl)indolizine-1-carboxamide (3b)

Yield 60%, M.P. 65.9-66.8℃. IR (v, cm^{-1}): 3663, 3431 (N-H), 3106, 2923 (C-H, aromatic), 1594 (C=C, aromatic); ^{1}H NMR: 7.46-7.33 (m, 3H), 7.67-7.63 (m, 2H), 7.84-7.74 (m, 3H), 7.96-7.90 (m, 1H), 8.24 (s, 1H), 8.62-8.59 (m, 1H), 9.89-9.87 (m, 1H); ^{13}C NMR: 109.3, 109.6, 116.7, 116.8, 117.5(2C), 120.0, 121.6, 126.3, 128.0, 128.8, 128.9, 131.7, 131.0, 131.7, 133.8, 136.6, 136.7, 140.2, 142.0, 162.4, 183.2; LC-MS (*m/z,* EI): 411.0 [M+H] $^+$. Anal. Calcd. for $C_{22}H_{13}ClF_2N_2O_2$: C, 64.32%; H, 3.19%; N, 6.82%; Found: C, 64.31%; H, 3.18%; N, 6.81%.

N-(4-Bromo-3-methylphenyl)-3-(3-chlorobenzoyl)indolizine-1-carboxamide (3c)

Yield 52%, M.P. 84.0-85.6℃. IR (v, cm^{-1}): 3293 (N-H), 2970, 2922 (C-H, aromatic), 1604 (C=C, aromatic); ^{1}H NMR: 2.34 (s, 3H), 7.35-7.34 (m, 1H), 7.56-7.51 (m, 2H), 7.67-7.62 (m, 2H), 7.76-7.73 (m, 2H), 7.84-7.79 (m, 2H), 8.27 (s, 1H), 8.62-8.60 (m, 1H), 9.89-9.87 (m, 1H), 10.01(s, 1H); ^{13}C NMR: 22.6, 107.7, 116.5, 119.8, 121.6, 126.2, 127.9, 128.6, 128.7, 128.9, 130.8, 131.5, 132.2, 133.1, 133.7(2C), 140.0, 141.9, 163.1(2C), 166.5, 173.1, 183.1; LC-MS (*m/z*, EI): 467.0 [M+H]$^+$. Anal. Calcd. for $C_{23}H_{16}BrClN_2O_2$: C, 59.06%; H, 3.45%; N, 5.99%. Found: C, 59.05%; H, 3.44%; N, 5.98%.

3-(3-Chlorobenzoyl)-N-(3-methoxyphenyl)indolizine-1-carboxamide (3d)

Yield 73%, M.P. 80.6-81.8℃. IR (v, cm^{-1}): 3302 (N-H), 3061, 2925 (C-H, aromatic), 1599 (C=C, aromatic); ^{1}H NMR: 3.75 (s, 3H), 6.67-6.66 (m, 1H), 7.24 (t, J = 8.00 Hz, 1H), 7.34-7.31 (m, 2H), 7.44 (t, J = 2.00 Hz, 1H), 7.67-7.62 (m, 2H), 7.76-7.74 (m, 1H), 7.85-7.80 (m, 2H), 8.27 (s, 1H), 8.63-8.61 (m, 1H), 9.89-9.87 (m, 1H), 9.95 (s, 1H); ^{13}C NMR: 55.4, 106.3, 109.2, 109.8, 112.9, 116.6, 120.1, 121.4, 126.3, 128.0, 128.6, 128.8, 128.9, 129.7, 130.9, 131.7, 133.8, 140.2, 140.8, 142.1, 159.8, 162.4, 183.1;

MS (*m/z*, EI): 405.0 $[M+H]^+$. Anal. Calcd. for $C_{23}H_{17}ClN_2O_3$: C, 68.23%; H, 4.23%; N, 6.92%. Found: C, 68.22%; H, 4.22%; N, 6.91%.

3-(3-Chlorobenzoyl)-N-(4-methoxyphenyl)indolizine-1-carboxamide (3e)
Yield 84%, M.P. 69.1-70.3℃. IR (ν, cm^{-1}): 3289 (N-H), 2926 (C-H, aromatic), 1599 (C=C, aromatic); ^{1}H NMR: 3.75 (s, 3H), 6.93-6.91 (m, 2H), 7.35-7.31 (m, 1H), 7.66-7.59 (m, 4H), 7.84-7.73 (m, 3H), 8.24(s, 1H), 8.63-8.60 (m, 1H), 9.87-9.86 (m, 1H), 9.89 (s, 1H); ^{13}C NMR: 55.6, 110.1, 114.1, 116.4, 120.1, 121.4, 122.4, 126.2, 128.0, 128.4, 128.8, 128.9, 130.9, 131.6, 132.6, 133.8(2C), 140.1, 142.1, 155.7, 162.0(2C), 183.1; LC-MS (*m/z*, EI): 405.1 $[M+H]^+$. Anal. Calcd. for $C_{23}H_{17}ClN_2O_3$: C, 68.23%; H, 4.23%; N, 6.92%. Found: C, 68.22%; H, 4.22%; N, 6.91%.

3-(3-Chlorobenzoyl)-N-(3, 5-dimethoxyphenyl)indolizine-1-carboxamide (3f)
Yield 78%, M.P. 75.6-76.5℃. IR (ν, cm^{-1}): 3314 (N-H), 2955, 2924, (C-H, aromatic), 1602 (C=C, aromatic); ^{1}H NMR: 3.74 (s, 6H), 6.24 (t, J = 2.40 Hz, 1H), 7.04 (d, J = 2.40 Hz, 2H), 7.36-7.32 (m, 1H), 7.67-7.62 (m, 2H), 7.73-7.76(m, 1H), 7.84-7.79 (m, 2H, Ar-H), 8.26 (s, 1H), 8.64-8.61 (m, 1H), 9.89-9.87 (m, 1H), 9.90 (s, 1H); ^{13}C NMR: 55.5(2C), 95.8, 98.8, 109.8, 116.6, 120.1, 121.5, 126.2(2C), 128.0, 128.6, 128.8, 128.9, 131.0, 131.7(2C), 133.8, 140.2, 141.3, 142.1, 160.8, 162.4, 183.2; LC-MS (*m/z*, EI): 435.0 $[M+H]^+$. Anal. Calcd. for $C_{24}H_{19}ClN_2O_4$: C, 66.29%; H, 4.40%; N, 6.44%. Found: C, 66.28%; H, 4.39%; N, 6.43%.

Biological Evaluation
***In vitro* Anti-tuberculosis Activity**
The compounds **3(a-f)** were subjected for anti-tuberculosis activity against *mycobacterium tuberculosis* (H37 *RV strain*, *Vaccine strain* (ATCC No. 27294) via Microplate Alamar Blue assay (MABA) & BACTEC radiometric method with different concentrations.[17]

***In-vitro* Anticancer Activity**
The compounds 3(a-f) were further tested for anticancer activity by MTT assay.[18]

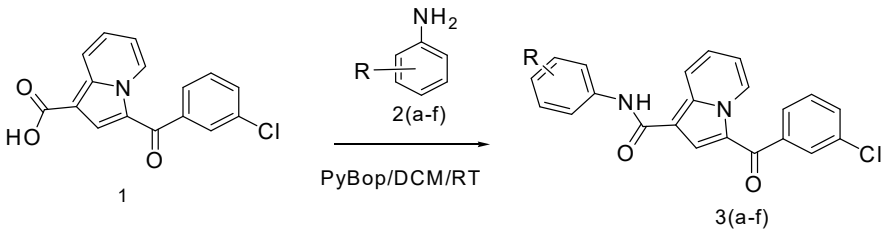
***In-vitro* Anti-inflammatory Activity**
The anti-inflammatory activity was performed by the Gelatin Zymography method.[19]

***In-vitro* Antibacterial Activity**
The antibacterial activity was carried out by the disk diffusion method with different concentrations.[20]

RESULTS AND DISCUSSION

Chemistry
The research focused on the efficient synthesis of novel 3-(3-chlorobenzoyl)-N-phenylindolizine-1-carboxamide derivatives **3(a-f)**. The compound **1** reacts with amine derivatives **2(a-f)** in the presence of triethylamine, Benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (PyBop) to afford 3-(3-chlorobenzoyl)-N-phenylindolizine-1-carboxamide derivatives 3(a-f) and confirmed by Elemental, FTIR, ^{1}H NMR, ^{13}C NMR and Mass. The complete synthetic route is depicted in Scheme-1.

Biological Activity
***In vitro* Anti-tuberculosis Activity**
The novel compound **3(a-f)** analogs were tested against *Mycobacterium tuberculosis* and the results are incorporated in Table-1. The compound **3c** sensitive at concentration 3.2 µg/ml and was found to be a potent activity compared with the Pyrazinamide (3.2 µg/ml), Isoniazid (1.6 µg/ml), Ethambutol (1.6 µg/ml), Rifampicin (0.8 µg/ml) and Streptomycin (0.8 µg/ml). Compound **3a** & **3b** sensitive at 12.5 µg/ml and 6.25 µg/ml showed moderate potent activity [Fig.-2(a) and 2(b)]. Among the series, compound **3c** would be a lead compound to develop a new library of compounds.



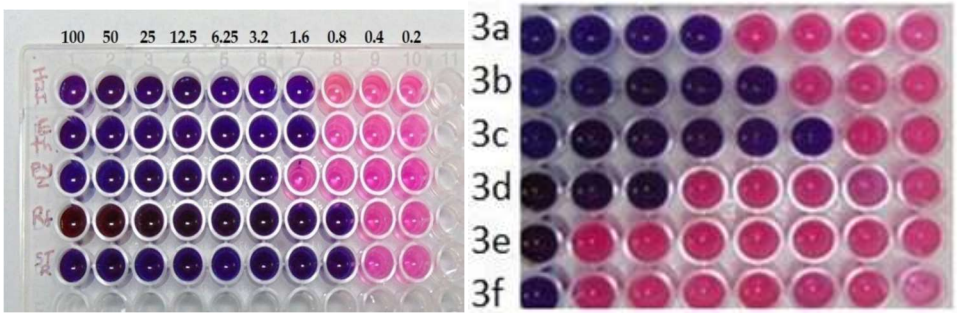
3a: R = H
3b: R = 3, 4-F
3c: R = 4 Br, 3 CH3
3d: R = 3 OCH3
3e: R = 4 OCH3
3f: R = 3,5 OCH3

Scheme-1: Synthesis of 3-(3-chlorobenzoyl)-*N*-phenylindolizine-1-carboxamide Analogs

Table-1: *In vitro* Anti-tuberculosis Activity of 3(a-f) Derivatives

Compounds	100 µg/ml	50 µg/ml	25 µg/ml	12.5 µg/ml	6.25 µg/ml	3.12 µg/ml	1.6 µg/ml	0.8 µg/ml
3a	S	S	S	S	R	R	R	R
3b	S	S	S	S	S	R	R	R
3c	S	S	S	S	S	S	R	R
3d	S	S	S	R	R	R	R	R
3e	S	R	R	R	R	R	R	R
3f	S	R	R	R	R	R	R	R
Isoniazid	-	-	-	-	-	-	S	R
Ethambutol	-	-	-	-	-	-	S	R
Pyrazinamide	-	-	-	-	-	S	R	R
Rifampicin	-	-	-	-	-	-	-	S
Streptomycin	-	-	-	-	-	-	-	S

S: Sensitive, R: Resistant.



(a) (b)

Fig.-2: (a) *In vitro* Anti-tuberculosis Activity Images of Standard Drugs and (b) Synthesized Compounds **3(a-f)**

In-vitro Anticancer Activity

The molecules **3(a-f)** were assessed against PA-1 (*Ovarian cancer cell line*) by MTT assay. In this experiment the compound **3a** (IC_{50} = 8.20 µg/ml) and compound **3f** (IC_{50} = 8.27 µg/ml) displayed potent activity compared with standard drug Cisplatin (IC_{50} = 1.12 µg/ml) (Table-2, Fig.-3).

Table-2: *In vitro* Anticancer Activity of 3(a-f) Derivatives

Compounds	200 µg/ml		100 µg/ml		50 µg/ml		25 µg/ml		12.5 µg/ml		6.25 µg/ml		IC_{50} (µg/ml)
3a	26.32	25.56	26.69	28.57	29.70	31.20	34.21	36.09	42.11	44.36	48.50	49.22	8.20
3b	33.46	38.72	36.84	38.72	48.12	43.98	49.25	47.74	52.26	55.26	68.05	64.29	27.03
3c	33.83	29.70	37.22	32.71	67.29	68.80	75.94	78.20	88.35	89.85	93.23	94.74	79.56
3d	51.13	44.36	55.26	54.14	60.53	59.02	77.07	81.20	85.34	87.59	96.24	96.99	137.1
3e	33.83	31.20	34.21	35.34	46.99	45.86	53.38	50.38	62.41	57.89	63.16	67.29	30.38
3f	33.46	34.59	34.96	36.84	36.84	38.35	38.72	40.23	44.36	48.12	52.26	58.65	8.27
Cisplatin													1.12

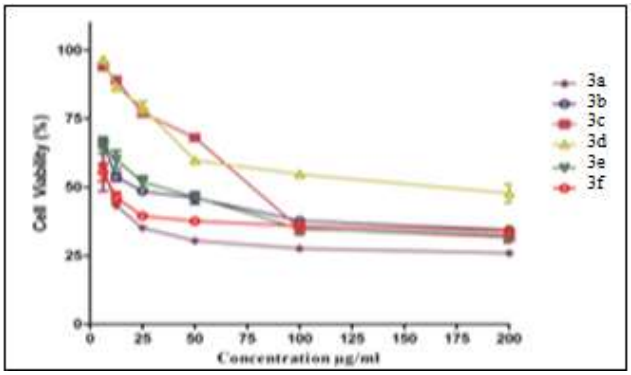


Fig.-3: Dose-response Curve

***In vitro* Anti-inflammatory Activity**

The compounds **3(a-f)** were tested against *MMP-2* and *MMP-9* with the standard drug Tetracycline hydrochloride carried out by the Gelatin Zymography method. Among the compounds **3(a-f)**, compound **3f** has very good anti-inflammatory activity against *matrix metalloproteinase-2* with 90% inhibition and moderate activity against *matrix metalloproteinase*-9 with 50% inhibition compared with standard drug (Table-3). At this juncture, we can pose compound **3f** will be good stuff for the further development of potent anti-inflammatory compounds.

Table-3: *In vitro* Anti-inflammatory Activity of Compounds 3(a-f)

Compound	*MMP-2* (% Inhibition)	*MMP-9* (% Inhibition)
3a	70	55
3b	65	20
3c	65	25
3d	60	5
3e	78	5
3f	90	50
Tetracycline Hydrochloride	100	98

***In-vitro* Antibacterial Activity**

Further, compounds **3(a-f)** were tested for antibacterial activity against different pathogenic strains and the results were tabulated in Table-4. In series **3(a-f),** compound **3f** showed good inhibition towards tested microbial strains, while remaining compounds in the same series reported moderate inhibition compared with standard Ciprofloxacin.

Table-4: *In vitro* Antibacterial Activity of 3(a-f) Derivatives

Compounds	Concentration mg/mL	Zone of Inhibition Gram Positive		Zone of Inhibition Gram Negative	
		Enterococcus faecalis	*Staphylococcus aureus*	*Klebsiellapne umoniae*	*Escherichia coli*
3a	100%	18.66±1.52	12.66±1.15	10.66±1.15	11.66±1.15
	50%	15.66±0.57	10.33±0.57	5.66±1.15	7.66±1.15
	25%	10.33±0.57	05±11	00	08±0.65
3b	100%	17±0.65	15.45±1.15	05.56±1.15	13.66±1.15
	50%	13.56±1.52	12.23±0.57	03±1.15	10.66±1.15
	25%	10.56±1.15	10±11	00	08±0.65
3c	100%	16.66±5.56	14.56±1.57	-	-
	50%	12.66±0.52	11.46±0.42	-	-
	25%	08.33±0.57	07.33±0.67	-	-
3d	100%	17.46±1.52	13.66±1.16	11.66±1.45	14.66±1.57
	50%	14.66±0.57	9.33±0.52	8.61±1.35	9.67±1.16
	25%	11.32±0.54	8±1.12	5±1.16	10±0.65
	100%	18±0.67	16.43±1.25	15.56±1.65	13.66±1.25

3e	50%	14.36±1.57	13.23±0.57	11±1.14	9.46±1.16
	25%	9.56±1.25	10±1.16	8±1.12	7±0.46
3f	100%	19.67±1.57	17.76±1.26	16.65±1.67	18.34±1.75
	50%	15.34±0.57	13.35±0.56	11.35±1.15	12.66±1.55
	25%	11.35±0.54	08±1.17	09±1.15	09±0.16
Ciprofloxacin		24.33±1.15	26.66±1.52	25.33±0.57	24.66±1.52

Molecular Docking Studies

The docking study was performed using the Autodock 4.2 program.[21] This program was designed to predict how small molecules were bound to a receptor of a known 3D structure. To determine the possible binding modes of the 3-(3-Chlorobenzoyl)-N-phenylindolizine-1-carboxamide, docking was carried out using the high-resolution crystal structure of the Peripheral Benzodiazepine receptor (PBR) cancer protein (PDBID: 1EQ1).

Table-5: Molecular Docking of Compounds 3(a-f)

Compounds	H-Bonds	H-Bond length (Å)	Binding Affinity (Kcal/mol)	RMSD
3a	1	2.755	-8.6	2.1
3b	1	2.683	-7.6	2.0
3c	2	2.547	-6.8	1.6
3d	2	2.559	-6.1	1.6
3e	2	2.481	-5.8	1.6
3f	3	2.237	-5.3	0.9
Peripheral benzodiazepine protein receptor			-23.15 kcal/mol	

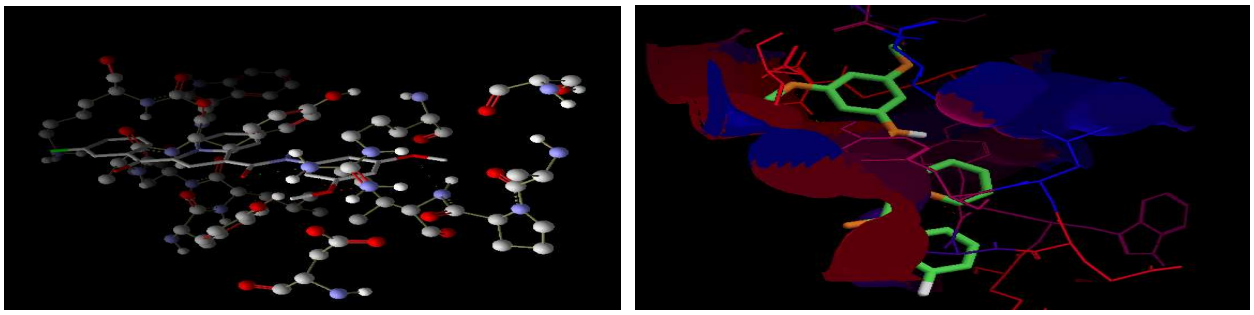


Fig.-4: 2D and 3D Representation Images of Compounds **3f**

The binding energy of the ligand **3f** with Peripheral benzodiazepine protein receptor is -23.15 kJ/mol. The 3f is found to be three hydrogen bonding with the protein molecule. The docking results were calculated and compared with respect to binding energy and RMSD values. The docking of PBR receptor (1EQ1) protein with newly synthesized compounds **3(a-f)** observed well-established bonds with one or more amino acids in the receptor active pocket. The methoxy group of the amino acid ring in TYR 415 forms a hydrogen bond with an amino group of **3f** with a hydrogen bond distance of 2.237Å (Table-5). Similarly, halogen derivatives show two hydrogen bonds with the protein molecules, as shown in Fig.-4 respectively. However, in this research, molecular docking analysis suggested that synthesized compound **3f** has more specificity towards the peripheral benzodiazepine receptor than the rest of the molecules.

CONCLUSION

In this research, all the reactions were performed keeping green-chemistry principles in mind and were carried out at ambient temperature. Further, all the synthesized compounds **3(a-f)** have been subjected to *in vitro* assays like anti-tuberculosis, anticancer, anti-inflammatory and antimicrobial applications. Among the series of compounds, compound **3c** (3.2 µg/ml) exhibited potent anti-tuberculosis activity compared with standard drug Pyrazinamide (3.2 µg/ml) and it is considered a good candidate in the series. Compound **3f** (90% inhibition) exhibited potent anti-inflammatory with *MMP-2* compared with standard drug Tetracycline hydrochloride (100% inhibition). The compound **3a** (IC_{50} = 8.20 µg/ml) and **3f** (IC_{50} = 8.27 µg/ml) displayed better anticancer activity with standard drug Cisplatin (IC_{50} = 1.12 µg/ml).

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