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AN EFFICIENT IONIC LIQUID MEDIUM FOR THE SYNTHESIS OF NEW NAPHTHOL-INDOLE HYBRIDS AND THEIR ANTI CANCER EVALUATION

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ABSTRACT:
A one-pot three-component condensation of 2-naphthol **1** with indol aldehydes **2** and amides **3** in the presence of ionic liquid medium [BMIM] BF4 has been described as an environmentally friendly and efficient process for the synthesis of N-((2-hydroxynaphthalen-1-yl)(1-methyl-1H-indol-3-yl)methyl)acetamide derivatives **4**. This innovative process has various advantages, including high yields, quick reaction times, operational simplicity, and no time-consuming set-up. Further, the synthesized compounds were examined for their anticancer potential towards PC-3 and SKOV-3 cells. Among the screened, compound 4b and 4f are found to be the promising compounds with IC50 values ranges from 7.9 to 9.1µM against PC-3 and SKOV-3 cells. In additional, the docking studies revealed that compound 4b and 4f showed good binding affinities in relation to human RET protein tyrosine kinase.

KEYWORDS: [BMIM]BF_4, naphthol-Indol hybrids , eco-friendly & one-pot component reaction.

INTRODUCTION:

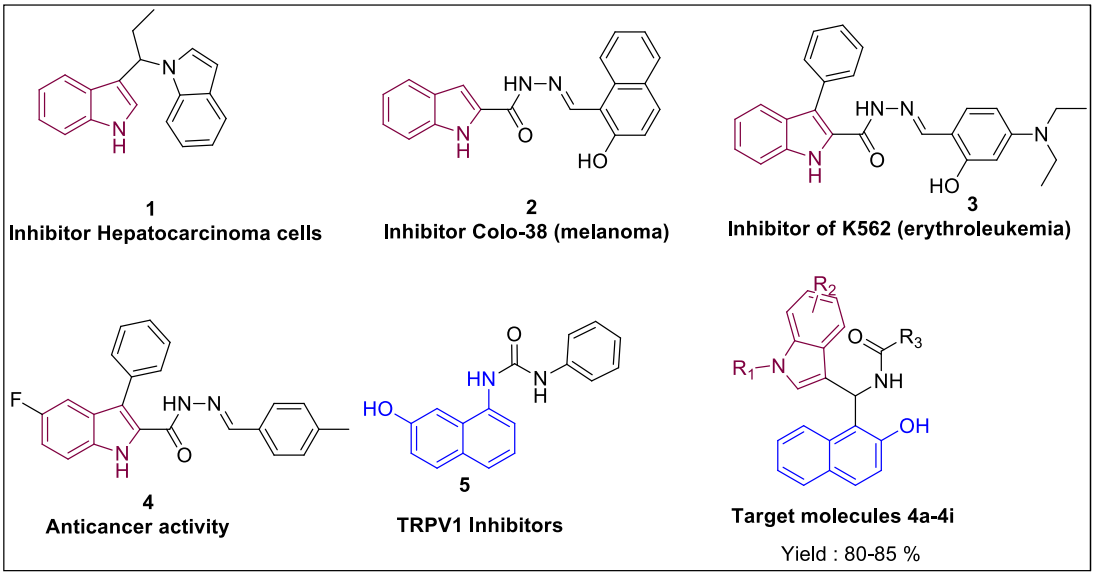
The most significant challenge in the chemical industry and modern chemistry is the creation and enhancement of efficient and environmentally friendly technologies. MCRs (multi component reactions) have been an effective and strong tool in contemporary heterocyclic synthetic chemistry [i-ii] due to their high efficiency and atom economy, as well as procedural simplicity in the building of complicated structures from three or more reactants. Furthermore, the advancement of existing multi component reactions as well as the discovery of new multi component reactions are very consistent with the goals of green and sustainable chemistry[iii].

Ionic liquids (ILs) are made up of organic cations and anions, and they've gotten a lot of attention as a chemistry solvent because of their superior properties like high thermal stability, high electrical conductivity, low nucleophilicity, a large electrochemical window, and the ability to provide a weekly coordinating or non-coordinating environment, as well as excellent solvent properties for a wide range of inorganic, organic, polymeric, and organ

metallic compounds. However, the high cost of ionic liquid and concerns about toxicity have led chemists to investigate the utility of more benign salts in molten salts as useful alternatives to investigate the utility of more benign salts in molten salts to investigate the utility f more benign salts in molten salts to investigate the utility of more benign salts in molten salts to investigate the utility of more benign salts in the molten salts as useful alternatives [iv-vi].

Among other ionic liquids,1-butyl-3-methyl inidazolium salts have recently received a lot of attention as an environmentally friendly and efficient medium with a lot of applications in various heterocyclic transformations like hydrogenations[vii], Heck reactions[viii], Friedel-craft reactions[ix], and Bishler-napieral reactions[x]. Among them, the ionic liquid 1-butyl-3-methyl imidazolium tetra fluoroborate ([BMIM]BF4) has shown great promise in numerous chemical conversions during the last decade[xi]. The {BMIM]BF_4's electrochemical stability is poor. Other advantageous physical and chemical qualities include mildness and lack of flammability, neutrality, commercial availability, and volatility, environmentally sustainable and admirable solubility with many organic products make this ionic liquid greater than others[xii].

Tocco et al produced bis indoles and tested them against hepatocarcinima cells; compound **1** 3-(1H-indol-1-yl)propyl)-1 H-indole (IC50=20-100 M) was shown to be more potent than the usual medication indole -3-carbinol[xiii]. Romagnoli and colleagues synthesised and screened a variety of 3-substituted-2-oxindole hybrid compounds the same year. Demurtas et al. studied indole hydrazone derivatives in K562 (erythroleukemia) and colo-38 (melanoma) cell lines. The relevance of phenol and naphthol substitution was validated by SAR investigations.compound **2** (E)-N'-((2-hydroxynaphthalen-1-yl)methylene)-1H-indole-2-carbohydrazide (IC50 < 0.83± 0.09 µM) and Compounds **3** (E)-N'-(4-(diethylamino)-2-hydroxybenzylidene)-3-phenyl-1H-indole-2-carbohydrazide (IC50 < 0.63± 0.05 µM) were found to be highly potent[xiv]. Ustundag et al disclosed that synthesis and evaluation of hydrazide-hydrazone, thiazolidinones derivatives of indole and performed SAR study highlighted the role of methyl substitution compound **4** (E)-5-fluro-N'-(4-methylbenzylidene)-3-phenyl-1 H-indole-2-carbohydrazide (G150=0.13-24 µM) has notable anticancer activity as compared with standard drug 5-fluorouracil (G150=0.01-79.4 µM)[x]. Klaus et reported the naphthol derivative **5** which showed the TRPV1 inhibitors for the treatment of urinary incontinence[xiv].



Based on the above results in our mind, here we now wish to report a new series of N-((2-hydroxynaphthalen-1-yl)(1-methyl-1H-indol-3-yl)methyl)acetamide derivatives have been developed by one-pot three component synthesis using 2-naphthol **1** with indol aldehydes **2** and amides **3** in the presence of ionic liquid medium [BMIM] BF_4 at 80-85^o C temperature for 60-120 min in [BMIM]BF_4 as medium.

EXPERIMENTAL SECTION:

Melting points are measured in a sulphuric acid bath using open capillary tubes. On a VERTEX 70 Brucker, FT-IR spectra are captured using KBr. For recording 1H and 13C NMR spectra, a Bruker DRX-400 spectrometer with 400 and 100 MHz was utilised, using DMSO-d6 as the solvent and TMS as the internal standard. On an Agilent-LCMS equipment, mass spectra were recorded.

GENERAL PROCEDURE:

2-Naphthol **1** (1mmol), 1-H-indole-3-carbaldehydes **2a-2d** (1mmol) and acetmide/ benzamide **3a-3b** (1mmol) were added into [BMIM]BF_4 (5 mmol) and heated at 80-85 ^{o}C for 60-120 min. The progress of reaction was monitored by TLC. After completion of the reaction, cooled the reaction mass to RT and added cold water to the reaction mass and stirred the mass for 30-40 min. Solid part was separated which was undergo filtration to get crude product. Finally, the crude product was recrystallised from ethanol solvent , dried wet solid at 60-65 ^{o}C for 8-10 hr to obtain **4**.

N-((2-hydroxynaphthalen-1-yl)(1-methyl-1H-indol-3-yl)methyl)acetamide 4a: Yield: 85 %, Melting Range: >220 ^{o}C; ^{1}H-NMR (DMSO-d6, 400 MHz): δ 1.8 (s, 3H, -CH_3), δ 3.8 (s, 3H, -CH_3), δ 7.0-8.0 (m, 13H, Ar-H, -OH and CH), δ 10.1 (s, 1H, -NH); ^{13}C NMR (DMSO-d6, 100 MHz): δ 21.6, 32.9, 49.1, 113.0, 115.5, 116.8, 118.7, 121.0, 126.5, 128.3, 132.9, 137.0, 137.6, 143.7, 143.9, 161.0, 163.1, 165.1 ; [M+H$^+$]: 345.

N-((1-ethyl-1H-indol-3-yl)(2-hydroxynaphthalen-1-yl)methyl)acetamide 4b: Yield: 83 %, Melting Range: >220 ^{o}C; ^{1}H-NMR (DMSO-d6, 400 MHz): δ 1.3 (t, 3H, -CH_3), δ 1.8 (s, 3H, -CH_3), δ 4.2 (q, 2H, -CH_2), δ 7.0-8.0 (m, 13H, Ar-H, -OH and CH), δ 10.1 (s, 1H, -NH) ^{13}C NMR; (DMSO-d6, 100 MHz): δ 15.8, 22.3, 42.8, 49.5, 111.2, 114.3, 115.6, 118.6, 120.2, 125.6, 127.4, 131.8, 137.1, 137.8, 143.6, 143.9, 161.1, 163.2, 165.2 ; [M+H$^+$]: 359.

N-((1-benzyl-5-nitro-1H-indol-3-yl)(2-hydroxynaphthalen-1-yl)methyl)acetamide 4c: Yield: 84 %, Melting Range: >220 ^{o}C; ^{1}H-NMR (DMSO-d6, 400 MHz): δ 1.8 (s, 3H, -CH_3), δ 4.2 (s, 2H, -CH_2), δ 7.0-8.0 (m, 17H, Ar-H, -OH and CH), δ 10.2 (s, 1H, -NH); ^{13}C NMR (DMSO-d6, 100 MHz): δ 21.4, 45.9, 52.6, 109.9, 110.3, 111.3, 115.1, 116.2, 118.5, 121.3, 122.3, 123.5, 125.7, 126.4, 127.5, 130.9, 137.3, 137.6, 143.3, 143.8, 160.2, 162.3, 164.3 ; [M+H$^+$]: 466.

N-((2-hydroxynaphthalen-1-yl)(5-nitro-1-(phenylsulfonyl)-1H-indol-3-yl)methyl)acetamide 4d: Yield: 82 %, Melting Range: >220 ^{o}C; ^{1}H-NMR (DMSO-d6, 400 MHz): δ 1.8 (s, 3H, -CH_3), δ 7.0-8.0 (m, 17H, Ar-H, -OH and CH), δ 10.1 (s, 1H, -NH); ^{13}C NMR (DMSO-d6, 100 MHz): δ 21.5, 46.8, 110.5, 112.4, 116.2, 116.7, 118.6, 120.4, 122.5, 123.6, 125.8, 126.5, 128.4, 130.3, 137.4, 137.8, 142.3, 143.9, 160.3, 162.4, 164.5 ; [M+H$^+$]: 516.

N-((2-hydroxynaphthalen-1-yl)(1-methyl-1H-indol-3-yl)methyl)benzamide 4e: Yield: 84 %, Melting Range: >220 ^{o}C; ^{1}H-NMR (DMSO-d6, 400 MHz): δ 3.9 (s, 3H, -CH_3), δ 7.0-8.0 (m, 18H, Ar-H, -OH and CH), δ 10.2 (s, 1H, -NH); ^{13}C NMR (DMSO-d6, 100 MHz): δ 34.0, 49.0, 117.8, 118.8, 121.6, 124.6, 126.0, 129.2, 133.0, 134.6, 137.2, 140.8, 143.5, 144.8, 161.0, 165.0 ; [M+H$^+$]: 407.

N-((1-ethyl-1H-indol-3-yl)(2-hydroxynaphthalen-1-yl)methyl)benzamide 4f: Yield: 82 %, Melting Range: >220 ^{o}C; ^{1}H-NMR (DMSO-d6, 400 MHz): δ 1.4 (t, 3H, -CH_3), δ 4.4 (q, 2H, -CH_2), δ 7.0-8.0 (m, 18H, Ar-H, -OH and CH), δ 10.2 (s, 1H, -NH); ^{13}C NMR (DMSO-d6, 100 MHz): δ 15.9, 43.9, 49.6, 111.3, 114.4, 116.7, 118.5, 121.2, 124.7, 126.5, 130.9, 136.2, 137.9, 142.7, 143.9, 160.1, 163.3, 165.3 ; [M+H^+]: 421.

N-((1-benzyl-5-nitro-1H-indol-3-yl)(2-hydroxynaphthalen-1-yl)methyl)benzamide 4g: Yield: 80 %, Melting Range: >220 ^{o}C; ^{1}H-NMR (DMSO-d6, 400 MHz): δ 4.3 (s, 2H, -CH_2), δ 7.0-8.2 (m, 22H, Ar-H, -OH and CH), δ 10.2 (s, 1H, -NH); ^{13}C NMR (DMSO-d6, 100 MHz): δ 45.5, 52.9, 109.8, 111.2, 111.5, 116.2, 116.8, 118.6, 121.4, 122.4, 123.4, 124.2, 124.7, 125.5, 125.7, 126.0, 126.5, 127.4, 130.8, 135.4, 137.3, 142.3, 143.9, 160.1, 162.2, 164.2 ; [M+H^+]: 528.

N-((2-hydroxynaphthalen-1-yl)(5-nitro-1-(phenylsulfonyl)-1H-indol-3-yl)methyl)benzamide 4d: Yield: 82 %, Melting Range: >220 ^{o}C; ^{1}H-NMR (DMSO-d6, 400 MHz): δ 7.0-8.0 (m, 22H, Ar-H, -OH and CH), δ 10.2 (s, 1H, -NH); ^{13}C NMR (DMSO-d6, 100 MHz): δ 46.9, 110.4, 111.3, 111.5, 116.5, 116.9, 118.7, 121.5, 122.5, 122.9, 124.3, 124.9, 125.6, 125.8, 126.1, 126.4, 127.8, 130.7, 134.3, 136.4, 142.0, 143.8, 160.2, 162.2, 164.3 ; [M+H^+]: 578.

CYTOTOXICITY ASSAY:

Cell viability of PC-3 (Human prostate carcinoma) and SKOV-3 (Human ovarian carcinoma) cells were measured by using colorimetric method such as MTT assay (Sigma USA) [xv-xvi]. Cells were seeded at a density of 1×10 6 cells in 100 µL of DMEM cell culture medium and grown for a time of 24 h in 96 well sterilized plate prior to addition of the test compounds. Test compounds with different concentrations were added to the cells. After 48 hr incubation, each well was washed with PBS (200 µl) and then incubated with 10 % MTT solution for 2 hr at 37 °C. The optical density of the solubilized formazan crystals was recorded at 570 nm using multimode reader (Tecan Infinite 200 PRO, Switzerland).

MOLECULAR DOCKING:

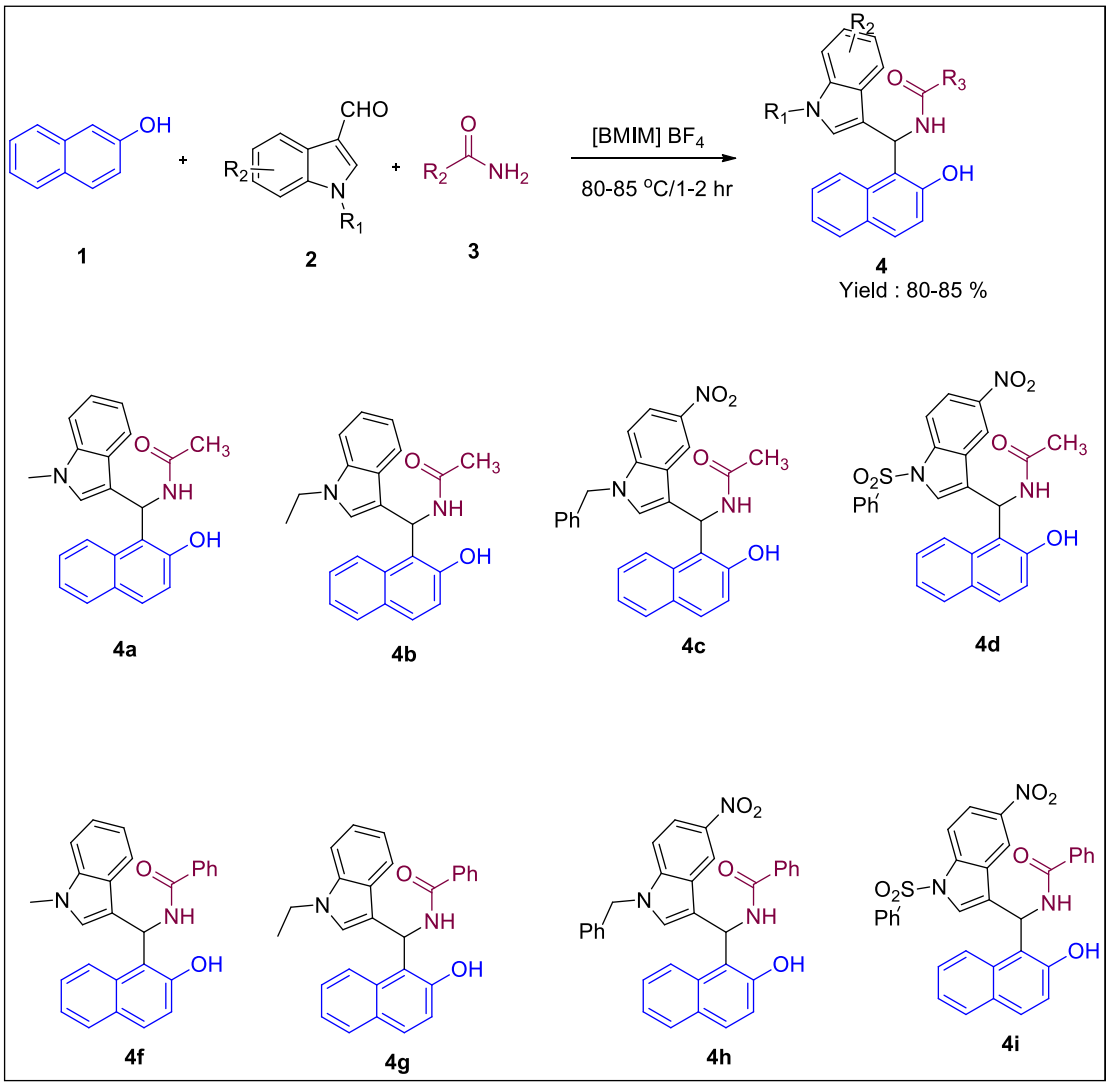
The molecular binding of synthesized compounds with respect to inhibit the activity of human RET protein tyrosine kinase, we implemented docking studies using AutoDockTools 4.2[xvii]. The crystal structure (3D) of human RET protein tyrosine kinase (PDB ID: 6NEC) was downloaded from RCSB Protein Data Bank and used as the protein model for docking. The protein structure was processed by the removal of water molecules and co-crystalized hetero compounds. Further, the 3D structures of active ligands such as 4b and 4f were constructed using ChemDraw ultra 19.0 software and saved in .pdb format. Further, MOPAC (semiempirical quantum mechanics) with AM1 MOZYME geometry acceleration with 100 iterations with RMS gradient of 0.10 was used for energy minimization. A total of ten different conformations were generated for each docked ligand and the best pose was selected with respect to the relative lower binding free energy (Kcal/mol). The co-crystal ligand XIN (methyl (3Z)-3-{[(4-{methyl[(4-methylpiperazin-1-yl)acetyl]amino}phenyl)amino](phenyl)methylidene}-2-oxo-2,3-dihydro-1H-indole-6-carboxylate) was redocked with the target protein to confirm the docking results. The 3D and 2D visualizations of the docked complexes were analysed using PyMol and LIGPLOT, respectively [xviii].

RESULTS AND DISCUSSION:

CHEMISTRY

As described in **Scheme-1**, the one-pot three component reaction of 2-naphthol **1** (1 mmol), 1-methyl-1H-indole-3-carbaldehyde **2a** (1mmol), and acetamide **3** (1mmol) in [BMIM]BF_4 (5 mmol) as ionic liquid medium at 80-85 ^oC gave desired compound N-((2-hydroxynaphthalen-1-yl)(1-methyl-1H-indol-3-yl)methyl)acetamide **4a** with 85% yield for 60 min **(Table-1 entry-1)**. The chemical structure of the compound **4a** was fully characterized and confirmed by ^{1}H-NMR, and mass spectroscopy. This multi-component reaction has been done in various ionic liquids mediums like [BMIM]BF_4, [BMIM]Cl, [BMIM]Br, and [BMIM]OH at various temperatures for optimization to get product formation **(Table-1)**. Nevertheless, it has been identified that the one-pot reaction of **1** with **2a,** and **3** in the presence of [BMIM]BF_4 as medium at 80-85^{o}C for 60 min gave excellent yield 85% product **4a (Table-1 entry-1).**

With the continue intention of to find out the particular affect of temperature on the product formation, the model one-pot three component reaction has been conducted at 70-75 ^{o}C and 90-95 ^{o}C. It was observed that the reaction has been completed at 90-95 ^{o}C for 45 min with 75% yield only and at 70-75 ^{o}C temperature the reaction has been completed after prolonged time for 7 hr with 80% yield.



Scheme 1. Synthesis of **4a-4i** by one-pot three component reaction.

Table 1. Optimization of Ionic liquids & Temperature to form **4a**.

Entry	**Ionic liquid (8 mmol)**	**Temp./º C**	**Time (min)**	**Yield (5a%)**
1	**[BMIM]BF_4**	**80-85**	**60**	**85**
2	[BMIM]Cl	80-85	240	72
3	[BMIM]Br	80-85	240	70
4	[BMIM]OH	80-85	90	65
5	[BMIM]BF_4	70-75	420	80
6	[BMIM]BF_4	90-95	45	75

In order to optimize the one-pot three component reaction, amount of ionic liquid equivalence study has been also conducted with various amount of [BMIM]BF_4 at 80-85 ^oC using naphthol **1** (1mmol), 1H-indole-3-carbaldehydes **2a** (1mmol) and acetmide 3**a** (1mmol) to from desired **4a (Table-2).** However, the one pot three component reaction for the preparation of 4**a** gave good yield 85% in a relatively shorter time 60 min with 5 mmol of [BMIM]BF_4 as medium at 75-80 ^oC.

Table 2. Optimization of amount of [BMIM]BF_4 at 80-85 ^oC to form **4a**.

Entry	**[BMIM]BF_4 (mmol)**	**Temp./º C**	**Time (min)**	**Yield (5a%)**
1	**3**	80-85	240	76
2	**5**	**80-85**	**60**	**85**
3	**8**	80-85	50	80

Based on the above excellent optimized one-pot reaction condition, the desired N-((2-hydroxynaphthalen-1-yl)(1-methyl-1H-indol-3-yl)methyl)acetamide derivatives **4a-4i** were synthesized in [BMIM]BF_4 as medium at 80-85 ^oC using naphthol **1** (1mmol), 1H-indole-3-carbaldehydes **2a-2d** (1mmol) and acetmide/ benzamide **3a-3b** (1mmol) at 80-85 ^oC temperature for 60-120 min in [BMIM]BF_4 (5 mmol) as medium with 80-85% yield by investigating the scope of 1H-indole-3-carbadehydes substrates **2(a-d)** and acetmide/ benzamide **3a-3b** which listed in **Table-3.** It was found that various substrates were converted into the corresponding compounds with excellent yields. Their structures have been confirmed on the basis of spectral properties such as IR, NMR & Mass spectra.

ANTICANCER ACTIVITY:

A sum of 8 different analogues of naphthol-Indole hybrids were synthesized and examined for their cytotoxic potential towards two different human cancerous cell lines such as PC-3 and SKOV-3. The compounds are active and exhibited good to moderate activity against the tested cell lines (Table 3). Among the synthesized, compound 4f is the most active compound against PC-3 and SKOV-3 cells with an IC_{50} values of 8.2 to 7.9 µM, respectively. Further, the compound 4b is also showed good activity against PC-3 and SKOV-3 cells with IC_{50} values of 9.1 and 8.4 µM, respectively. Compound 4a and 4e exhibited moderate activity against the tested cell lines with IC_{50} values ranges from 13.2 to 16.6 µM. While the other compounds (4c, 4d, 4g, 4h) in the series displayed poor inhibition activity.

Test compound	**IC_{50} value in µM (Mean ± S.D)**	
	PC-3	**SKOV-3**
4a	14.4 ± 0.22	13.2 ± 0.14
4b	9.1 ± 0.26	8.4 ± 0.27
4c	43.5 ± 0.18	52.3 ± 0.39
4d	54.7 ± 0.27	66.8 ± 0.25
4e	15.9 ± 0.36	16.6 ± 0.31
4f	8.2 ± 0.32	7.9 ± 0.17
4g	53.8 ± 0.14	42.2 ± 0.19
4h	46.6 ± 0.12	59.3 ± 0.44
Doxorubicin	0.9 ± 0.06	0.7 ± 0.08

Table 3: Anticancer results of the synthesized compounds against human prostate cancer cells (PC-3) and human ovarian cancer cells (SKOV-3). Doxorubicin was used as a positive control. Each experiment was performed in triplicates and the results are expressed as Mean ± S.D, (n=3).

***In silico* binding studies:**

To understand the structural relation of synthesized naphthol-Indole hybrids with the binding of human RET protein tyrosine kinase, Insilico binding studies were implemented. Based on initial results of cytotoxicity, the active compounds 4b and 4f were selected and examined for binding with RET protein tyrosine kinase co-crystalized with XIN. Both docked ligands (4b and 4f) displayed good binding interactions and affinities towards target protein. Hydrogen and hydrophobic interactions are involved and played the major role in the binding of ligands with the target protein and affected the docking results. Almost ten different conformations per each ligand was generated and the best pose was depicted in the Figure 2. The findings of docking analysis demonstrated that compounds 4b and 4f were dwelled the same binding pocket of the co-crystalized ligand (XIN) binding site (Fig 3A). Docked ligands exhibited the binding energies of -7.6, and -7.4 Kcal/mol for compounds 4f and 4b, respectively (Fig 3B). The results disclosed that compound 4f was the best docked ligand as compared to compound 4b. Further, the co-crystal ligand XIN exhibited -11.1 Kcal/mol binding energy. Further, the amino acid residues of protein involved in the interacted with docked ligands were tabulated in Table 4.

Ligand	**Protein–Ligand interactions**	
	H-bond/s	**Hydrophobic bonds**
4b	Trp942, Glu971	Pro953, Met970, Thr946, Asp974, Pro973, Arg972
4f	Arg770, Ser774, Asn777	Arg897, Val778, Gln781, Asp898
XIN (Co-crystal ligand)	Lys758, Glu805, Ala807, Asp 892	Ser891, Ile788, Val804, Glu775, Val738, Ala756, gly810, Ser811, Glu818, Gly731, Glu732, Leu730, Tyr806, Leu881, leu772

Table 4: Amino acid residues of the target protein involved in the interactions with ligands.

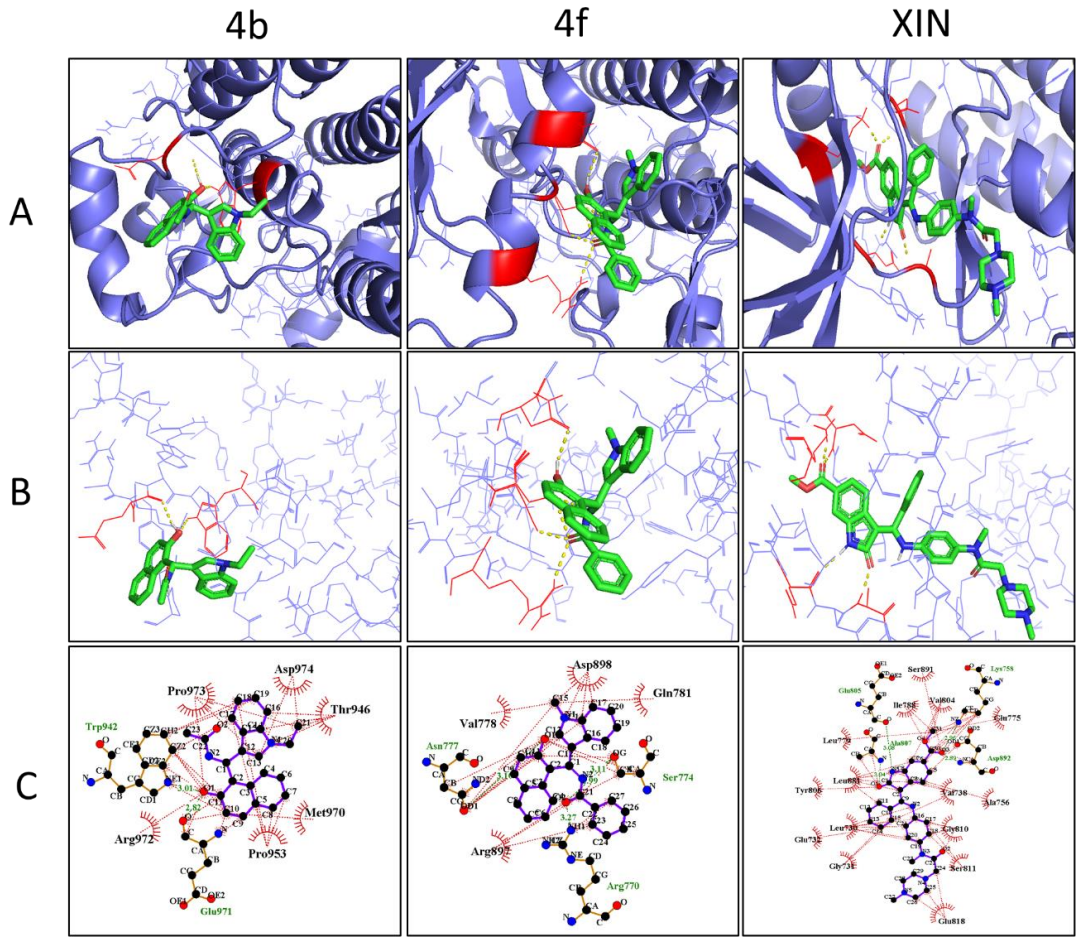


Figure 2: (A) Three-dimensional binding conformations of the synthesized derivatives such as 4b and 4f towards human RET protein tyrosine kinase (PDB ID: 6NEC) along with co-crystalized ligand (XIN). (B) Line representation of target protein with docked molecules. (C) 2D binding interactions of the 4b, 4f and XIN with the target protein.

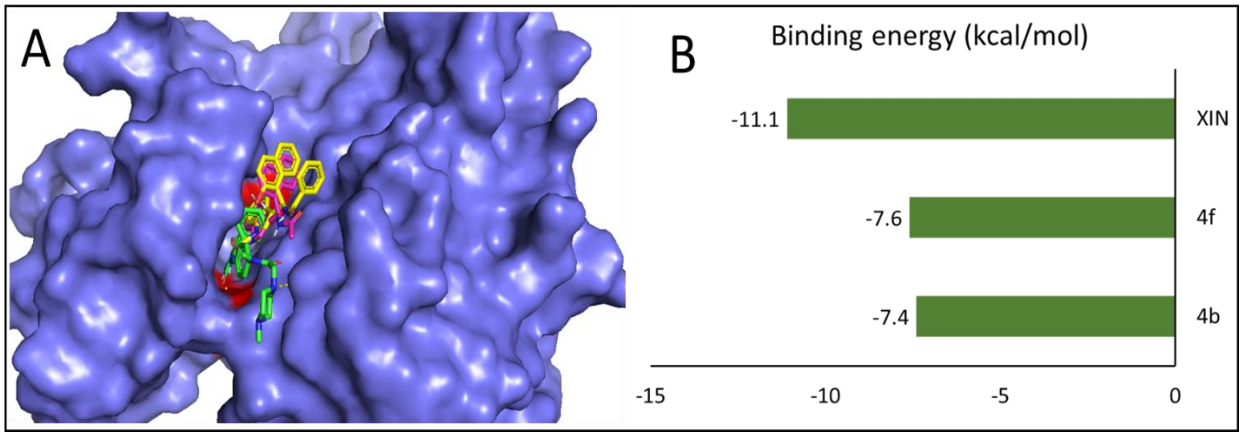


Figure 3: (A) The overlayed 3D structures of compound 4b and 4f along with XIN (co-crystalized ligand) in the binding site of target protein. (B) The predicted binding energies (Kcal/moL) of the docked ligands with human RET protein tyrosine kinase.

CONCLUSION

Here, we developed an efficient and green synthesis protocol for the preparation of desired N-((2-hydroxynaphthalen-1-yl)(1-methyl-1H-indol-3-yl)methyl)acetamide derivatives in $[BMIM]BF_4$ as ionic liquid medium. A total of eight derivatives were synthesized and examined for their cytotoxic potential towards PC-3 and SKOV-3 cells. The compounds showed good to moderate activity and few compounds (4c, 4d, 4g, 4h) exhibited poor inhibitory activity. The compound 4b and 4f are the potential compounds in the synthesized derivatives and exhibited good IC50 values ranges from 7.9 to 9.1µM towards PC-3 and SKOV-3 cells. Further, the molecular binding studies disclosed that compound 4b and 4f showed good binding affinities such as -7.4 and -7.6 Kcal/mol towards human RET protein tyrosine kinase.

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