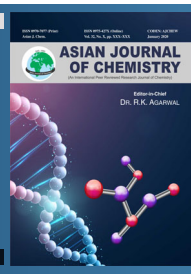
Asian Journal of Chemistry; Vol. 32, No. 3 (2020), 690-696

ASIAN JOURNAL OF CHEMISTRY

https://doi.org/10.14233/ajchem.2020.22491



Novel Fluorinated Imidazolium Ionic Liquids: Eco-friendly, Facile and Efficient Construction, Characterization, *in vitro* Anticancer Activity, Toxicity and *in silico* Analysis

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Received: 12 October 2019; *Accepted*: 8 December 2019; *Published online*: 31 January 2020; AJC-19779

An efficient and facile synthesis of novel fluorinated imidazolium-tagged ionic liquids under microwave irradiation is described. Novel prepared ionic liquids was identified and confirmed by spectroscopic and elemental analysis. Synthesized ionic liquids (**1-12**) was explored for their antiproliferative inhibition potency against three selected human cancer cell lines (MCF-7, HepG-2 and CACO2). Screening results have revealed that some tested ionic liquids exhibited promising activity compared with standard drugs, especially compounds **5** and **6** which consistently produced low IC_{50} values. Preliminary structure activity relationship (SAR) studies have been performed to identify the relation between molecular structure and activity. *in silico* Analysis of ionic liquids was carried out based on ADME, Lipinski rule, drug likeness, toxicity profiles and other physico-chemical properties. All compounds were safe in toxicity profile and computed LD_{50} values were in accepted range (2.55-2.89 mol/kg). *in silico* Results have shown that Lipinski rule of five was in accept range, except compound **1** and **2**.

Keywords: Microwave conditions, Ionic liquids, Environmental Benign method, Antitumor activity, *in silico* Prediction.

INTRODUCTION

At the moment, research on ionic liquids (ILs) have been attract more consideration owing to their outstanding characteristics which can be used as a strong alternative to volatile organic compounds (VOCs) [1]. Ionic liquids are generally defined as a large class of organic salts with a melting-point below 100 °C. They exhibit distinctive properties such as extremely zero vapour pressure, non-flammability, high thermal stability, high ionic conductivity, low volatility and excellent solubility with many compounds.

Therefore, a wide range of applications of ionic liquids have been reported in different fields *e.g.*, as solvents in organic synthesis [2], as corrosion inhibitors [3,4], in electrochemistry [5,6], as catalysts [7], in fuel cells [8], in polymer science [9], in separation science [10], in dye-sensitized solar cells [11] and in many other area of research.

The foregoing reasons and following on from our work on the synthesis and biological evaluation of ionic liquids have motivated us to continue the exploration of new category of fluorinated imidazolium-tagged ionic liquids [12-16]. Furthermore, the newly synthesized ionic liquids have been tested against breast, liver and colon cancer cell lines (CACO2, MCF-7 and HepG-2) in order to assess to their potential toxicities. To realization of biological results, *in silico* physico-chemical analysis was performed and used to predict their molecular properties.

EXPERIMENTAL

^{1}H, ^{13}C, ^{11}B, ^{19}F, ^{31}P NMR spectra have performed on Varian Unity-Plus (400 MHz) spectrometer and $CDCl_3$ was used as solvents. High resolution mass spectra has scanned on BrukerMaldi TOF MS. IR has performed on Shimadzu 8201 PC FT-IR spectrophotometer. The elemental analyses were

retrieved with the help of 2400 Series II CHNS/O elemental analyzer.

Preparation method: The synthesis of ionic liquid/salt (**1-4**) by conventional method and microwave irradiation is reported in published article [12].

Preparation of ionic liquids (5-12) by conventional method: Charged ionic liquids (**1-4**) (0.015 mol) in dichloromethane (20 mL). Then added appropriate metal salt (either $NaBF_4$ or KPF_6; 0.018 mol) and stir for 3 h at 70 °C. After completion, cooled the mass and filtered through Celite bed. Dichloromethane was evaporated to afford the desired ionic liquids (**5-12**) quantitatively.

Preparation by microwave-assisted metathesis reaction of (1-4) leading to ionic liquids (5-12): Prepared a solution of $NaBF_4$ or KPF_6 (0.015 mol) in a 10 mL of dichloromethane and charged into imidazolium halide ionic liquids (**1-4**). Resultant reaction mass was irradiated for 7 min at 70 °C. Then product was isolated by the conventional procedure outlined earlier.

Characterization

(1-Hexyl-3-(3-phenylpropyl)-1*H*-imidazol-3-ium tetrafluoroborate (5): Yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 0.81 (t, 3H, CH_3), 1.24 (m, 6H, CH_2), 1.80 (quin, 2H, CH_2), 2.17 (quin, 2H, CH_2), 2.63 (t, 2H, CH_2), 4.13 (t, 2H, CH_2), 4.22 (t, 2H, CH_2), 7.11-7.19 (m, 5H, Ar-H), 7.34 (d, 1H, Ar-H), 7.39 (d, 1H, Ar-H), 9.18 (s, 1H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 13.9 (CH_3), 22.3 (CH_2), 25.7 (CH_2), 30.0 (CH_2), 31.0 (CH_2), 31.4 (CH_2), 32.3 (CH_2), 49.5 (CH_2), 50 (CH_2), 122.3 (CH), 122.5 (CH), 126.3 (CH), 128.3 (CH), 128.7 (CH), 135.8 (CH), 139.8 (C); ^{19}F NMR ($CDCl_3$, 376.5 MHz): δ = -150.78; ^{11}B NMR ($CDCl_3$, 162 MHz): δ = -0.93, MS $[M–BF_4]^+$ 271.33 found for $C_{18}H_{27}N_2^+$, (Found: C, 60.46; H, 7.55; N, 7.89 %. Calcd. for $C_{18}H_{27}N_2BF_4$: C, 60.35; H, 7.60; N, 7.82 %).

1-Hexyl-3-(3-phenylpropyl)-1*H*-imidazol-3-ium hexafluorophosphate (6): Yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 0.86 (t, 3H, CH_3), 1.28 (m, 6H, CH_2), 1.81 (quin, 2H, CH_2), 2.18 (quin, 2H, CH_2), 2.65 (t, 2H, CH_2), 4.08 (t, 2H, CH_2), 4.17 (t, 2H, CH_2), 7.15-718 (m, 3H, Ar-H), 7.23-7.27 (m, 4H, Ar-H), 8.49 (s, 1H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 13.9 (CH_3), 22.3 (CH_2), 25.7 (CH_2), 29.8 (CH_2), 31 (CH_2), 31.3 (CH_2), 32.3 (CH_2), 49.6 (CH_2), 50.1 (CH_2), 122.4 (CH), 122.4 (CH), 126.4 (CH), 128.4 (CH), 128.6 (CH), 134.9 (CH), 139.9 (C); ^{19}F NMR (DMSO-d_6, 376.5 MHz): δ = -70.79 to -72.68 (septt); ^{31}P NMR ($CDCl_3$, 162 MHz): δ = -144.21, MS $[M–PF_6]^+$ 271.31 found for $C_{18}H_{27}N_2^+$, (Found: C, 51.83; H, 6.60; N, 6.80 %. Calcd. for $C_{18}H_{27}N_2PF_6$, C, 51.92; H, 6.54; N, 6.73 %).

1-Hexyl-3-phenethyl-1*H*-imidazol-3-ium tetrafluoroborate (7): Yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 0.81 (t, 3H, CH_3), 1.20 (m, 6H, CH_2), 1.72 (quin, 2H, CH_2), 3.14 (t, 2H, CH_2), 4, 08 (t, 2H, CH_2), 4.47 (t, 2H, CH_2), 7.14- 7.18 (m, 5H, Ar-H), 7.29 (d, 1H, Ar-H), 7.34 (d, 1H, Ar-H), 9.04 (s, 1H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 13.9 (CH_3), 22.3 (CH_2), 25.6 (CH_2), 30.0 (CH_2), 30.9 (CH_2), 36.3 (CH_2), 49.9 (CH_2), 50.9 (CH_2), 122.0 (CH), 122.6 (CH), 127.3 (CH), 128.8 (CH), 128.9 (CH), 135.8 (CH), 135.9 (C); ^{19}F NMR ($CDCl_3$, 376.5 MHz): δ = -150.68; ^{11}B NMR ($CDCl_3$, 400 MHz): δ = -0.94, MS $[M–BF_4]^+$ 257.22 found for $C_{17}H_{25}N_2^+$, (Found: C, 59.37; H, 7.36; N, 8.10 %. Calcd. for $C_{17}H_{25}N_2BF_4$: C, 59.32; H, 7.32; N, 8.14 %).

1-Hexyl-3-phenethyl-1*H*-imidazol-3-ium hexafluorophosphate (8): Yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 0.85 (t, 3H, CH_3), 1.19 (m, 6H, CH_2), 1.72 (quin, 2H, CH_2), 3.12 (t, 2H, CH_2), 4, 03 (t, 2H, CH_2), 4.38 (t, 2H, CH_2), 7.13 (d, 2H, Ar-H), 7.21-7.24 (m, 5H, Ar-H), 8.29 (s, 1H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 13.9 (CH_3), 22.3 (CH_2), 25.6 (CH_2), 29.8 (CH_2), 30.9 (CH_2), 36.1 (CH_2), 50.0 (CH_2), 51.0 (CH_2), 122.1 (CH), 122.4 (CH), 127.4 (CH), 128.7 (CH), 129 (CH), 135.0 (CH), 135.9 (C); ^{19}FNMR (DMSO-d_6, 376.5 MHz): δ = -70.69-72.59 (sept); ^{31}P NMR ($CDCl_3$, 162 MHz): δ = -144.22, MS $[M–PF_6]^+$ 257.23 found for $C_{17}H_{25}N_2^+$, (Found: C, 50.81; H, 6.30; N, 7.01 %. Calcd. for $C_{17}H_{25}N_2PF_6$: C, 50.75; H, 6.26; N, 6.96 %).

3-(4-Acetoxybutyl)-1-hexyl-1*H*-imidazol-3-ium tetrafluoroborate (9): Dark brown oil, ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 0.84 (t, 3H, CH_3), 1.28 (m, 6H, CH_2), 1.66 (quin, 2H, CH_2), 1.86 (quin, 2H, CH_2), 1.96 (quin, 2H, CH_2), 2.01 (s, 3H, CH_3), 4.06 (t, 2H, CH_2), 4.18 (t, 2H, CH_2), 4.25 (t, 2H, CH_2), 7.39 (d, 1H, Ar-H), 7.47 (d, 1H, Ar-H), 8.87 (s, 1H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 13.9 (CH_3), 20.9 (CH_3), 22.3 (CH_2), 25.2 (CH_2), 25.8 (CH_2), 26.9 (CH_2), 30.0 (CH_2), 31.0 (CH_2), 49.5 (CH_2), 50.1 (CH_2), 63.3 (CH_2), 122.4 (CH), 122.6 (CH), 136.6 (CH), 171.2 (C=O); ^{19}F NMR ($CDCl_3$, 376.5 MHz): δ = -150.97; ^{11}B NMR ($CDCl_3$, 128 MHz): δ = -1.0, MS $[M–BF_4]^+$ 267.19 found for $C_{15}H_{27}N_2O_2^+$, (Found: C, 50.82; H, 7.74; N, 7.88 %. Calcd. for $C_{15}H_{27}N_2O_2BF_4$: C, 50.87; H, 7.68; N, 7.91 %).

3-(4-Acetoxybutyl)-1-hexyl-1*H*-imidazol-3-ium hexafluorophosphate (10): Dark brown oil, ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 0.81 (t, 3H, CH_3), 1.25 (m, 6H, CH_2), 1.64 (quin, 2H, CH_2), 1.82 (quin, 2H, CH_2), 1.92 (quin, 2H, CH_2), 1.98 (s, 3H, CH_3), 4.02 (t, 2H, CH_2), 4.12 (t, 2H, CH_2), 4.18 (t, 2H, CH_2), 7.33 (d, 1H, Ar-H), 7.38 (d, 1H, Ar-H), 8.55 (s, 1H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 13.8 (CH_3), 20.6 (CH_3), 22.2 (CH_2), 25.1 (CH_2), 25.7 (CH_2), 26.7 (CH_2), 29.8 (CH_2), 30.9 (CH_2), 49.5 (CH_2), 50.1 (CH_2), 63.2 (CH_2), 122.4 (CH), 122.5 (CH), 135.0 (CH), 171.2 (C=O); ^{19}F NMR ($CDCl_3$, 376.5 MHz): δ = -71.02 to -72.91 (septt); ^{31}P NMR ($CDCl_3$, 162 MHz): δ = -144.38, MS $[M–PF_6]^+$ 267.18 found for $C_{15}H_{27}N_2O_2^+$, (Found: C, 43.65; H, 6.57; N, 6.84 %. Calcd. for $C_{15}H_{27}N_2O_2PF_6$: C, 43.69; H, 6.60; N, 6.79 %).

1-Hexyl-3-(2-methoxyethyl)-1*H*-imidazol-3-ium tetrafluoroborate (11): Dark brown oil, ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 0.70 (t, 3H, CH_3), 1.15 (m, 6H, CH_2), 1.75 (quin, 2H, CH_2), 3.20 (s, 3H, CH_3), 3.60 (t, 2H, CH_2), 4.13 (t, 2H, CH_2), 4.33 (t, 2H, CH_2), 7.36 (d, 1H, Ar-H), 7.44 (d, 1H, Ar-H), 9.14 (s, 1H, Ar-H); ^{13}C NMR (400 MHz, $CDCl_3$): δ_C = 13.8 (CH_3), 22.2 (CH_2), 25.6 (CH_2), 29.9 (CH_2), 30.9 (CH_2), 49.5 (CH_2), 49.9 (CH_2), 58.7 (CH_3), 69.9 (CH_2), 121.9 (CH), 123.2 (CH), 136.0 (CH); ^{19}F NMR ($CDCl_3$, 376.5 MHz): δ = -151.10; ^{11}B NMR ($CDCl_3$, 128 MHz): δ = -1.15, MS $[M–BF_4]^+$ 211.1 found for $C_{12}H_{23}N_2O^+$, (Found: C, 48.41; H, 7.84; N, 9.36 %. Calcd. for $C_{12}H_{23}N_2OBF_4$: C, 48.34; H, 7.78; N, 9.40 %).

1-Hexyl-3-(2-methoxyethyl)-1*H*-imidazol-3-ium hexafluorophosphate (12): Dark brown oil, ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 0.82 (t, 3H, , CH_3), 1.25 (m, 6H, CH_2), 1.82 (quin, 2H, CH_2), 3.30 (s, 3H, CH_3), 3.66 (t, 2H, CH_2), 4.12 (t, 2H, CH_2), 4.29 (t, 2H, CH_2), 7.31 (d, 1H, Ar-H), 7.37 (d, 1H, Ar-H), 8.48 (s, 1H, Ar-H); ^{13}C NMR (400 MHz, $CDCl_3$): δ_C =13.8 (CH_3), 22.2 (CH_2), 25.6 (CH_2), 29.8 (CH_2), 30.9 (CH_2), 49.7 (CH_2), 50.0 (CH_2) 58.7 (CH_3), 69.7 (CH_2), 122 (CH), 123.1 (CH), 135.4 (CH); ^{19}F NMR ($CDCl_3$, 376.5 MHz): δ = -71.06 to -72.95 (septt); ^{31}P NMR ($CDCl_3$, 162 MHz): δ = -144.39, MS $[M–PF_6]^+$ 211.08 found for $C_{12}H_{23}N_2O^+$, (Found: C, 40.42; H, 6.46; N, 7.90 %. Calcd. for $C_{12}H_{23}N_2OPF_6$: C, 40.45; H, 6.51; N, 7.86 %).

RESULTS AND DISCUSSION

On the basis of recent research [12-14], our team has resolved to advance the preparation of novel biologically active ionic liquids. Herein, the metathesis reactions of already reported ionic liquids (**1-4**) [12], were carried out leading to new series of fluorinated ionic liquids **5-12**.

Tetrafluoroborate and hexafluorophosphate anions were subsequently ushered in by a metathesis-induced reaction (CP: dichloromethane, 70 °C, 3 h) (**Scheme-I**) [11]. The pure metathesis products were acquired upon thorough filtration followed by filtrate evaporation and resultant residue cleansing with DCM, in addition to a comprehensive filtration process deployed to remove the excess of anion salts ($NaBF_4$, KPF_6). Finally, an evaporation of the filtrate resulted in considerably high yields of the desired ionic liquids (93-95 %).

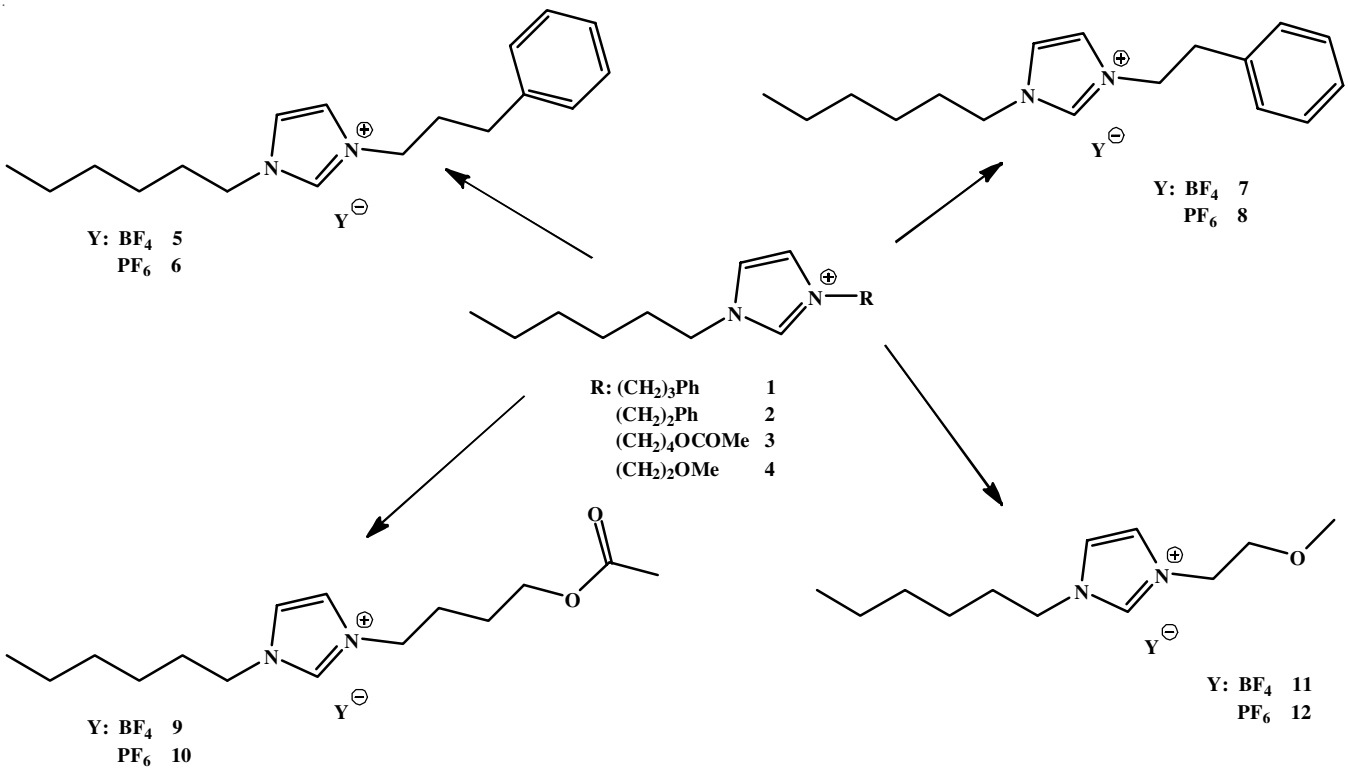
In this way, we had managed to execute the preparation of imidazoliumtetrafluoroborate or hexafluorophosphate based-ionic liquids. The results are displayed in Table-1 showing that excellent yields (97-99 %) were acquired within the span of a mere 10 min. Thus, it is safe to conclude that the use of microwave irradiation as a capable and environmental benign process for preparation of this new class of ionic liquids provided many advantages, namely, the long reduction time of reaction [12-15]. As observed, regardless of the procedure, the reaction yield is not affected.

TABLE-1
PREPARATION OF IONIC LIQUIDS USING CONVENTIONAL PREPARATION (CP) AND UNDER MICROWAVE IRRADIATION (MW)

Ionic liquid	R	MY	Yield (%) anion metathesis	
			CP[a]	MW[b]
5	$(CH_2)_3Ph$	$NaBF_4$	94	98
6		KPF_6	95	99
7	$(CH_2)Ph$	$NaBF_4$	93	98
8		KPF_6	94	97
9	$(CH_2)_4OCOCH_3$	$NaBF_4$	93	98
11		KPF_6	93	97
12	$(CH_2)_2OCH_3$	$NaBF_4$	95	99
15		KPF_6	94	98

[a]3 h, 70 °C in DCM; [b]10 min, 70 °C, Power (300 W).

Identification and confirmation of structure of ionic liquids and/or salts **5-12** was established by ^{1}H NMR, ^{13}C NMR, FT-IR, MS and elemental analysis. One special note of observation is that the ^{1}H and ^{13}C spectra of **5-12** indicated practically what's having been recorded in those of ionic liquids **1-4** [8]. In this case, apart from ^{1}H and ^{13}C NMR spectra, other specific NMR such as ^{11}B, ^{19}F and ^{31}P NMR were essential to verify the efficiency of metathesis reactions.



Scheme-I: Anion metathesis using conventional preparation (CP): MY, dichloromethane (DCM), 70 °C, 3 h; and microwave irradiation conditions (MW): DCM, 70 °C, 10 min. M = Na, K

Firstly, NMR interpretation has started with ionic liquids (**5**) to establishment of structure contains an alkyl chain **5-8**. PMR spectra of ionic liquid **5** displayed the triplet estimated at 0.81 ppm which assigned hexyl group containing aliphatic methyl protons. Peaks at 1.24 ppm arise due to eight methylene groups, signal appeared at 1.24 ppm which confirmed three methylene protons and another two signal as quintet form at slightly downfield *i.e.* 1.80 and 2.17 ppm appeared owing to two methylene protons. Proton signal at 2.63 ppm as triplet has arisen due to CH_2CH_2Ph and signal appeared at 4.13 and 4.22 ppm for NCH_2CH_2. However ionic liquid **5** contain imidazolium moiety which has shown signals itself as doublet at 7.34 and 7.39 ppm and as singlet at 9.18 ppm. Remaining aromatic proton promptly recorded at 7.11 to 7.19 ppm.

^{13}C NMR of compound **5** contained a signal at 13.9 ppm which is obviously owing to CH_3 group. ^{13}C NMR of ionic liquid **5** also displayed signals at 49.5 ppm which assigned for CH_2 and another signal at 50 ppm which has arisen due to -NCH_2 moiety and remaining six aliphatic –CH_2 groups were recorded as usual as appeared in carbon NMR which included 32.3, 31.4, 31.0, 30.0, 25.7 and 22.3 ppm. Moreover, corresponding signal between 122.3 to 139.8 ppm has came out for characteristic imidazolium ring. Further, ^{13}C-DEPT NMR has proven above supporting results without ambiguity.

Anion exchange approach is proved without ambiguity by ^{11}B NMR and ^{19}F NMR since their spectra contained peaks just about δ_B -1 and δ_F -148 ppm for distinctive B or F in BF_4.

Furthermore, probable structure has also been justify by FT-IR which has shown bands at 2982 and 2912 cm^{-1} corresponding to C=CH stretching and maintained a considerably high level of consistency with CH_2 and CH_3 moiety. In addition of above characterization, our proposed structure elucidated by mass spectra of ionic liquid **2** with obtained known mass as 271.330 *m/z*, were established in uniformity.

Novel synthesized ionic liquids **9-10** containing imidazolium moiety with ester group was fully characterized. The ionic liquid **10** became established to prove the metathesis reaction of the ionic liquid **3**. Given the fact that particular portion of ionic liquid **10** was present in ionic liquid **5**. Three proton units chosen to the CH_3CO in ^1H NMR spectra of ionic liquid **10** has demonstrated singlet at δ_H 1.98 m and characteristic signal of one of the methylene group of the ester functionality (CH_2CH_2O) appeared at δ_H 4.02 ppm.

Furthermore, the ^{13}C NMR spectrum of ionic liquid **10** contained a congruous signal with the presence of a carbonyl group (CO) at δ_C 171.2 ppm. The spectrum showed also two peaks related the methyl group, respectively, at δ_C 13.8 ppm for (CH_3CH_2 CH_2) and at δ_C 20.6 ppm for CH_3CO. All these peaks were confirmed clearly by DEPT-C NMR. The ^{31}P NMR and ^{19}F NMR spectra were necessary to confirm the success of the anion exchange. The spectra contained a septuplet at δ_P -144 related to PF_6. In FT-IR, ionic liquids 10 has demonstrated characteristic carbonyl band attached to ester at 1742 cm^{-1}. Finally, the mass spectra of ionic liquids **10** generated a diagram zenith consistent as 267.18 *m/z*. Finally, Structures of the desired ionic liquids **11**-**12** were confirmed by all spectroscopic analyses. Characterization data has discussed by taking ionic liquid **11** to verify their structures.

In the ^1H NMR spectrum, the methyl group-based proton (OCH_3)-based activity of ionic liquid **11** has been at 3.20 ppm. In contrast, the varying methylene groups (NCH_2CH_2O) protons have been exhibited at their characteristic chemical shifts at 3.60 and 4.33 ppm. On the other hand, the ^{13}C NMR spectrum of ionic liquid **11** showed two peaks at δ_C 13.8 and 58.7 attributed $\boldsymbol{C}H_3$ groups. In addition, remaining aliphatic methylene groups were observed at 22.2, 25.6, 29.9, 30.9, 49.5, 49.9, 69.9 ppm. Furthermore, ^{11}B NMR and ^{19}F NMR were used to verify the success of the metathesis reaction, since their spectra contained peaks at δ_B -1.1 and δ_F -151.1 ppm. The IR spectra of ionic liquid **11** exhibited band at around 1162 cm^{-1} assigned to an ether group. In conclusion, confirmed structure has been further verify by the LCMS spectra with a high point consistent desired mass ions $[M\text{-}BF_4]^+$. Further, purity of all novel synthesized ionic liquids **5-12** expressed through the presence of elemental analysis.

***in vitro* Cytotoxic activity of ionic liquids (1-12):** Ionic liquids **1-12** were screened *in vitro* cytotoxicity against MCF-7 (human breast adenocarcinoma), HepG-2 (human hepatocellular carcinoma) and $CACO_2$ (colon carcinoma). The measurement of cell growth and viability was confirmed throughout the research study [17]. All results were tabulated in Table-2. Experimental study has found reduction in survival as dose was increased.

in vitro Results have found interesting and positive IC_{50} data (6.19 to 970 µg/mL) which has been tabulated in Table-3. Table-3 clearly demonstrated that the ionic liquid **9** showed higher value. Remarkably, ionic liquids **6** and **7** were obviously active with consistently produced low IC_{50} values for HEPG-2, MCF7 and $CACO_2$ (6.19 to 14.8 µg/mL) compared with the tested standard drug 5-FU which (12.1 to 27.8 µg/mL).

***in silico* Analysis:** To qualify the drug candidate, some preliminary requirement such as pharmacokinetic parameters should be fulfill by any chemical entity. But most of the synthetic drugs are manifested by their side effects. POM is well established *in silico* tools to qualify the drug candidate [13,18-21]. The advantages of *in silico* analysis is screening of molecules either qualify the pharmacokinetic profile or not to save the time and to avoid the failure in clinical trial stage. Hence to observed the impact of moiety in molecule for cytotoxicity activity, performed the *in silico* analyses for series of ionic liquids (**1-12**).

***in silico* Physico-chemical calculation of ionic liquids and/or salts 1-12:** To evaluate physico-chemical profile were calculated using molinspiration calculation. The ionic liquids were evaluated to *in silico* ADME/T screening. Physico-chemical properties such as lipophilicity (clog P), topological polar surface area (TPSA), volume (VOL), number of O-NH interactions, number of violation and molecular weight (MW). These parameters affect the absorption and bioavailability of drug. Physicochemical was evaluated according to Lipinski's rule which states molecular weight < 500 Da, NH or OH > 5 and TPSA value between 3.24-29.54, which is in good agreement and responsible for drug distribution and rotatable bond indicate good bioavailability [22]. Druglikeness value has been calculated attributed available moiety of the ionic liquids synthesized and all parameters were found in acceptable range (Table-4).

TABLE-2
in vitro SCREENING OF SYNTHESIZED COMPOUNDS **1-12**

Cell line	Conc. (mg/mL)	Viability (%)											
		1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
HEPG2	1000	2.57	2.95	4.37	12.59	28.71	2.16	2.78	10.36	45.83	6.83	11.56	23.89
	500	4.38	5.86	9.72	24.61	41.36	3.97	4.63	24.52	72.36	15.29	26.78	35.67
	250	7.96	11.49	14.89	38.76	54.08	7.23	9.79	35.91	91.40	28.94	35.24	46.53
	125	15.23	20.37	25.69	49.53	79.56	13.49	16.41	43.84	98.78	42.35	47.15	59.47
	62.5	23.45	32.55	39.56	68.76	92.47	21.78	22.68	60.79	100	58.96	65.23	76.20
	31.25	35.20	40.93	63.84	85.02	98.65	30.82	35.09	78.27	100	79.41	80.97	88.16
	15.6	46.82	54.28	79.60	94.58	100	41.39	43.81	91.32	100	91.78	91.76	94.28
	7.8	60.67	68.19	88.74	98.79	100	48.15	50.92	99.75	100	97.66	98.24	99.63
	3.9	76.12	81.42	93.21	100	100	56.92	67.48	100	100	100	100	100
	2	83.64	90.68	99.76	100	100	78.26	82.76	100	100	100	100	100
	0	100	100	100	100	100	100	100	100	100	100	100	100
MCF7	1000	4.87	4.92	8.75	14.31	27.86	2.59	3.42	8.64	48.14	17.24	19.58	29.43
	500	8.56	9.81	19.54	25.89	41.25	4.98	5.97	19.78	79.25	30.83	32.75	45.20
	250	17.23	21.46	30.47	40.62	58.72	10.73	11.48	31.49	94.06	44.72	45.64	69.61
	125	26.74	31.79	38.36	57.28	76.39	18.64	20.75	45.37	99.23	62.35	71.28	87.69
	62.5	38.65	42.60	49.54	73.19	90.73	27.51	30.68	68.12	100	79.04	89.41	95.27
	31.25	51.43	53.94	72.31	88.06	98.04	36.92	38.96	90.64	100	91.38	97.28	99.13
	15.6	64.08	70.25	86.24	97.63	100	45.27	47.54	98.51	100	99.21	100	100
	7.8	79.56	84.37	96.38	100	100	53.18	72.39	100	100	100	100	100
	3.9	90.42	94.29	99.17	100	100	60.95	84.61	100	100	100	100	100
	2	98.17	99.63	100	100	100	78.23	90.58	100	100	100	100	100
	0	100	100	100	100	100	100	100	100	100	100	100	100
$CACO_2$	1000	2.38	3.16	5.92	9.04	20.95	1.98	2.17	8.64	36.21	9.85	15.74	18.26
	500	4.92	6.73	10.85	18.75	36.41	3.64	3.89	19.78	68.94	20.99	24.83	27.19
	250	10.65	14.98	18.74	31.92	49.27	6.13	6.74	31.49	89.56	35.17	37.60	48.86
	125	19.48	23.04	29.43	44.17	72.38	11.96	13.58	45.37	97.13	46.29	49.82	67.24
	62.5	30.81	34.92	37.68	62.39	88.60	19.88	18.72	68.12	100	70.12	74.95	89.73
	31.25	41.29	46.87	70.91	80.95	95.21	28.75	26.53	90.64	100	85.93	92.41	97.04
	15.6	54.38	69.46	86.23	91.43	99.74	36.94	39.16	98.51	100	94.67	99.73	100
	7.8	68.73	85.98	95.14	97.68	100	43.87	48.24	100	100	98.56	100	100
	3.9	83.04	92.45	98.72	100	100	58.69	70.31	100	100	100	100	100
	2	89.67	97.31	100	100	100	72.34	85.62	100	100	100	100	100
	0	100	100	100	100	100	100	100	100	100	100	100	100

TABLE-3
IC_{50} (mg/mL) VALUES OF IONIC LIQUIDS **1-12**

Cell line	5-FU	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
HepG-2	12.1	13.8	20.6	49.1	123	330	6.98	8.81	102	921	96.2	115	216
MCF7	27.8	34.7	42.1	61.9	180	375	10.9	14.8	225	970	213	229	325
$CACO_2$	13.3	20.8	29	50.9	105	246	6.19	7.49	112	789	115	125	242

TABLE-4
in silico PREDICTION OF PHYSICO-CHEMICAL CALCULATIONS OF IONIC LIQUIDS **1-12**

Compd.	MW (g/mol)	Physico-chemical properties				Drug likeness					
		TPSA	O/NH	VIOL	VOL	GPC	ICM	KI	NRL	PI	EN
1	351	3.24	0	1	312	0.19	0.06	-0.08	0.08	0.07	0.12
2	337	3.24	0	1	295	0.13	0.04	-0.13	0.00	0.00	0.10
3	302	29.54	0	0	298	0.06	0.02	-0.23	0.02	0.02	0.14
4	291	12.47	0	0	250	-0.26	-0.16	-0.42	-0.42	-0.38	-0.10
5	339	3.24	0	0	350	0.23	0.20	-0.02	0.15	0.16	0.11
6	397	3.24	0	0	349	0.21	0.06	-0.02	0.14	0.16	0.10
7	325	12.36	0	0	333	0.20	0.19	-0.03	0.11	0.13	0.10
8	383	3.24	0	0	332	0.19	0.04	-0.03	0.11	0.15	0.09
9	335	29.54	0	0	340	0.12	0.16	-0.12	0.12	0.13	0.14
10	393	29.54	0	0	339	0.12	0.02	-0.11	0.12	0.15	0.12
11	279	12.47	0	0	287	-0.04	0.09	-0.17	-0.14	-0.12	0.01
12	337	12.47	0	0	287	0.04	-0.07	-0.08	-0.04	-0.01	0.03

***in silico* Toxicity and log P:** Calculated log P value has given in Table-5 which has suggested that all ionic liquids have showed log P value in the range and assumed to be good lipophilic properties. Table-5 also represents toxicity screening

for synthesized ionic liquids. In discovery of new drug, toxicity analysis is require for qualifying of any drug, it mean that toxicity study is important for new drug before going in clinical trial. *in silico* Results exhibited that all ionic liquids are non-mutagenic, non-carcinogenic and safe.

TABLE-5
in silico SCREENING OF TOXICITY AND log P OF IONIC LIQUIDS **1-12**

Compd.	AMES toxicity	Carcinogenecity	Rat acute toxicity LD_{50} (mol/kg)	log P
1	Non-toxic	Non-toxic	2.55	5.54
2	Non-toxic	Non-toxic	2.55	5.04
3	Non-toxic	Non-toxic	2.68	3.70
4	Non-toxic	Non-toxic	2.76	3.20
5	Non-toxic	Non-toxic	2.63	1.82
6	Non-toxic	Non-toxic	2.68	3.30
7	Non-toxic	Non-toxic	2.63	1.30
8	Non-toxic	Non-toxic	2.68	2.79
9	Non-toxic	Non-toxic	2.76	0.12
10	Non-toxic	Non-toxic	2.81	1.59
11	Non-toxic	Non-toxic	2.82	-0.51
12	Non-toxic	Non-toxic	2.89	0.96

***in silico* Pharmacokinetic evaluation:** Oral bioavailability and pharmacokinetic profile is related each other and necessary to qualify for good oral bioavailability of ionic liquids. *in silico* Pharmacokinetic evaluation of synthesized ionic liquids was presented in Table-6. The skin permeability (P_{Skin}) of pharmaceuticals is a key feature [23] and the calculated P_{Skin} (-3.56 to -5.86) indicating least permeability through the skin. The distribution properties were evaluated in terms of blood brain barrier (BBB) permeability proposing that moderate amount of ionic liquids will pass the BBB. The computed metabolism of ionic liquids (Table-6) revealed no inhibitor of CYP1A2 and CYP2D6.

***in silico* Bioavailability screening:** *in silico* Bioavailability screening has summarized in Table-7. All ionic liquids follow Lipinski's rule and Veber rule, except compound **10** in respect of Veber rule. In case of Ghose rule, only 6 ionic liquids (compounds **1-4**, **7** and **11**) have follow with good bioavailability score (0.55). *in silico* data has revealed that all ionic liquids were in good agreement in term of bioavailability.

TABLE-7
in silico BIOAVAILABILITY PREDICTION

Comp.	*in silico* Bioavailability			
	Lipinski	Ghose	Veber	Bioavailability score
1	Yes	Yes	Yes	0.55
2	Yes	Yes	Yes	0.55
3	Yes	Yes	Yes	0.55
4	Yes	Yes	Yes	0.55
5	Yes	No; 1 violation	Yes	0.56
6	Yes	No; 1 violation	Yes	0.56
7	Yes	Yes	Yes	0.56
8	Yes	No; 1 violation	Yes	0.56
9	Yes	No; 1 violation	Yes	0.56
10	Yes	No; 1 violation	No; 1 violation	0.56
11	Yes	Yes	Yes	0.56
12	Yes	No;1 violation	Yes	0.56

Conclusion

Present study reports the design and synthesis of novel ionic liquids **5-12** having imidazolium moiety containing fluorinated anions under microwave irradiation and conventional conditions. Ionic liquids **1-12** were evaluated for their anticancer activity and compared with the used standard drug, two of them, namely, ionic liquids **6** and **7** displayed cytotoxicity potency against all examined cancer cell lines. After excellent *in vitro* cyctotoxicity screening results, further confirmed the realization of biological data by *in silico* screening. *in silico* screening provide the support to antiproliferative activity. Physico-chemical evaluation showed good druglikeness and interacted with various enzymatic targets. In addition, toxicity analysis has revealed that all compounds were safe for mutagenecity and carcinogenicity and computed LD_{50} values were in accepted range (2.55-2.89 mol/kg). In addition, all ionic liquids has pursue Lipinski and violation rule. *in silico* Bioavailability analysis has demonstrated that synthesized ionic liquids follow Lipinski's rule and Veber rule, apart from compound **10** with good bioavailability score.

TABLE-6
in silico PHARMACOKINETICS PREDICTION OF SYNTHESIZED IONIC LIQUIDS **1-12**

Compound	*in silico* Pharmacokinetics					
	GI absorption	BBB permeant	P-gp	CYP1A2 inhibitor	CYP2D6 inhibitor	log K_p(skin permeation), cm/s
1	High	Yes	No	No	No	-4.48
2	High	Yes	No	No	No	-4.65
3	High	Yes	No	No	No	-5.52
4	High	Yes	No	No	No	-5.86
5	High	No	No	No	No	-3.91
6	Low	No	Yes	No	No	-3.56
7	High	Yes	No	No	No	-4.08
8	Low	No	No	No	No	-3.76
9	High	Yes	No	No	No	-5.10
10	Low	No	No	No	No	-4.75
11	High	Yes	No	No	No	-5.30
12	Low	No	No	No	No	-4.94

GI: Gastro Intestinal; P-gp: P-glycoprotein; BBB: Blood Brain Barrier; CYP1A2: Cytochrome P450 family 1 subfamily A member 2 (PDB: 2HI4); CYP2D6: Cytochrome P450 family 2 subfamily D member 6 (PDB: 5TFT)

ACKNOWLEDGEMENTS

The authors are indebted to King Abdulaziz City for Science and technology for financial support of this work through the funded project No. 1-17-01-006-0027.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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