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# A profile of the in vitro anti-tumor activity of imidazolium-based ionic liquids

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ABSTRACT

The anti-cancer activity and cytotoxicity of imidazolium-based ionic liquids has been determined for the first time via NCI's in vitro 60 human tumor cell lines. The preliminary SAR showed that the chain length of alkyl substitution at N-3 position of imidazole ring plays crucial role towards anti-tumor activity and cytotoxicity of these ionic liquids. The ionic liquids with alkyl substitution of C-12 chain length were found to be effective against all 60 tumor cell lines and show very low cytotoxicity in most of the cases. Further increase in chain length resulted in enhanced growth inhibition of tumor cell lines as well as high cytotoxicity. Interestingly, active compounds 1-dodecyl-3-methylimidazolium chloride (**8**), 1-dodecyl-3-methylimidazolium tetrafluoroborate (**9**), 1-hexadecyl-3-methylimidazoium chloride (**10**), 1-octadecyl-3-methylimidazolium chloride (**11**), 1-octadecyl-3-methylimidazolium hexafluorophosphate (**12**), 1-octadecyl-3-methylimidazolium bis(triflic)imide (**13**) and 1-octadecyl-3-methylimidazolium tris(pentafluoroethyl)trifluorophosphate (**14**) were highly active against leukemia cell lines, especially compounds **13** and **14** where the cytotoxicity was also very low as given by $LC_{50}$ >100 μM in all six leukemia cell lines.



The development of new anti-cancer agents that reduce the toxicity associated with existing chemotherapies and those targeted at circumventing tumor resistance mechanism is a major focus of drug discovery efforts.[1] However, 'toxicity' could be a desirable property as has been seen with many toxins which were originally used as poisons but found to be medically important. Centuries ago Paracelsus famously quoted 'The poison is in the dose'.[2] This is because, toxins by their very nature are biodynamic substances, as they affect the functioning of the bio-species (victim's body), which also suggests that they could potentially become important source of medicines.[3] Of course, understanding and managing the toxicity of small molecule toxins is a major challenge in the discovery and development of new drugs.[1] Once the mechanism of compound toxicities is understood, it can be used to advantage as has been seen in case of Thalidomide a drug originally introduced in the late 1950s but withdrawn in 1961 due to its teratogenic effects.[4] It was found that only (*R*) enantiomer of thalidomide is effective against morning sickness but the (*S*) enantiomer is teratogenic and causes birth defects. It is now known that the 'safe' isomer (*R*) can also be converted to the teratogenic one in human body. Lately, it is attracting growing interests for therapeutic uses for cancer and other diseases.[4,5]

Ionic liquids/salts have emerged as a new class of compounds with unique properties and therefore, finding applications in a wide range of fields. One of the attractive features of ILs is the potential to tailor their physiochemical properties, not seen previously in the molecular compounds. This feature has been exploited skillfully in finding their applications that is, synthesis, materials, specialty chemicals, etc.[6] There are only limited studies on the toxicity of ionic liquids, reporting mixed results for their safety.[7] This has caused skeptics for their use for biomedical applications, specifically as therapeutic agents. Salt formation of Active Pharmaceutical Ingredients (APIs) is an attractive and commonly used approach to overcome the problems of solubility and stability of APIs. Numerous acids and bases with varying physico-chemical properties are utilized for this purpose with an estimated half of all APIs administered as salts.[8] There are many well known examples where biological active cations and anions combine together and the resulted salt exhibits the therapeutic effects of both of its components.[9] Many of these ionic salts exhibit similar characteristics as seen now in the ionic liquids.[10] Therefore, it is quite reasonable to think that ionic liquids/salts with their tunable properties and toxicities could potentially be designed as anti-cancer, anti-viral and other therapeutic agents/drugs. These 'Therapeutic Ionic Liquids' expectantly offer distinctly different properties. If there is a therapeutic response then the major advantage of ionic liquids would be in managing/tuning their toxicity while tailoring the physio-chemical and pharmacological properties necessary for desired therapeutic application. This possibility motivated us to explore the anti-cancer activity of ionic liquids belonging to different classes.[11] In the present study, we wish to report the anti-cancer activity evaluation of a series of imidazolium-based ionic liquids shown in Table 1 using the National Cancer Institute's

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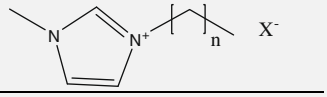
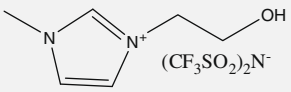
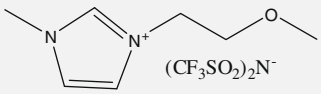
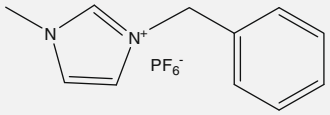
**Table 1**
List of compounds screened for NCI 60 cell lines

| Compound# | NSC# |  | | Activity[a] |
|---|---|---|---|---|
| | | *n* | X | |
| **1** | 747124 | 3 | $(CF_3SO_2)_2N$ | Not active |
| **2** | 747261 | 5 | $(CF_3SO_2)_2N$ | Not active |
| **3** | 747262 | 5 | $(C_2F_5)_3F_3P$ | Not active |
| **4** | 747266 | 7 | $BF_4$ | Not active |
| **5** | 747263 | 7 | $C_8H_{17}SO_4$ | Not active |
| **6** | 747264 | 7 | Cl | Not active |
| **7** | 747265 | 7 | $PF_6$ | Not active |
| **8** | 747267 | 11 | Cl | Active |
| **9** | 747268 | 11 | $BF_4$ | Active |
| **10** | 747260 | 15 | Cl | Active |
| **11** | 747269 | 17 | Cl | Active |
| **12** | 747270 | 17 | $PF_6$ | Active |
| **13** | 747271 | 17 | $(CF_3SO_2)_2N$ | Active |
| **14** | 747272 | 17 | $(C_2F_5)_3F_3P$ | Active |
| **15** | 747122 |  | | Not active |
| **16** | 747123 |  | | Not active |
| **17** | 747125 |  | | Not active |

60 tumor cell line panel. This is indeed the first report where the anti-tumor activity of imidazolium-based ionic liquids has been explored.

All the ionic liquids were purchased from Merck KgaA (EMD Chemicals), Darmstadt, Germany with purity >95% and were used without any further purification except 1-methyl-3-methoxyethylimdazolium bistriflicimide ([MoemIm][Tf2N], Table 1, entry 16), which was synthesized and characterized as reported previously.[12] Details of the NCI-60 human tumor cell line screening methodology are described at http://dtp.nci.nih.gov/branches/btb/ivclsp.html.[13] Briefly, the panel is organized into nine subpanels representing diverse histologies: leukemia, melanoma, and cancers of lung, colon, kidney, ovary, breast, prostate, and central nervous system. The cells are grown in supplemented RPM1 1640 medium for 24 h. The test compounds **1**–**17** were dissolved in DMSO and incubated with cells at five concentrations with 10-fold dilutions, the highest being $10^{-4}$ M and the others being $10^{-5}$, $10^{-6}$, $10^{-7}$, and $10^{-8}$ M. The assay is terminated by addition of cold trichloroacetic acid, and the cells are fixed and stained with sulforhodamine B. Bound stain is solubilized, and the absorbance is read on an automated plate reader. The cytostatic parameter which determines 50% growth inhibition ($GI_{50}$) of the tumor cells is calculated from time zero, control growth, and the five concentration level absorbance. The cytotoxic parameter that is, $LC_{50}$ (concentration of drug resulting in a 50% reduction in the measured protein at the end of the drug treatment as compared to that at the beginning) indicating a net loss of cells following treatment represent the average of two independent experiments.[13]

Screening a compound in the NCI 60 cell line panel at the National Cancer Institute can potentially produce several results. The two-stage screening process started with the evaluation of all the ionic liquids against the 60 human tumor cell lines at a single dose of 10.0 μM. The output from the single dose screen was reported as a mean graph (given in the Supplementary data with general interpretation). Only the compounds which showed more then 60% of growth inhibition in at least 8 tumor cell lines were selected for further testing and the others were assumed as inactive. This primary one dose screening showed that compounds (ILs) **1**–**7** and **15**–**17** were essentially inactive, while compounds **8**–**14** were declared active (Table 1). Therefore, a secondary screening was performed on active compounds **8**–**14**, in order to determine their cytostatic activity, against the 60 cell panel. The compounds were evaluated at five concentration levels (100, 10, 1.0, 0.1 and 0.01 μM). On the bases of growth inhibition parameters, a structure–activity relationship was obtained.

The results show that the chain length of alkyl substitution at N-3 position of the imidazolium cation is very crucial for the anti-cancer activity of these compounds. It is evident from the one dose screening data that compounds **1**–**7** with alkyl chain length up to C-8 were inactive, irrespective of the anions (Table 1). Also, it is worth to mention that the aryl substitution or functionalization with methoxyether or hydroxyl group on the short alkyl side chain of imidazolium cation does not show any improvement in the anti-cancer activity (e.g., for compounds **15**–**17**) (Table 1). When the chain length of alkyl substituents of imidazolium cation was increased to 12 or more, significant enhancement in the growth inhibition of tumor was observed in multiple cell lines. Compounds **8** (with $Cl^-$ anion) and **9** (with $BF_4^-$ anion), both having 1-methy-3-undecylimidazolium cation showed remarkable activity against 60 human tumor cell lines with overall potency in terms of $GI_{50}$ values ranging from 0.109 to 22.60 μM for **8** and 0.312 to 24.60 μM for **9**. Also, the $LC_{50}$ values are >100 μM in most of the cases, which gives a very high therapeutic window for both of these compounds (Table 2). In general, Compound **8** and **9** were found to be most sensitive to growth inhibition of leukemia cell lines as indicated by $GI_{50}$ <1 μM in most of the cases with relatively

**Table 2**
Anti-tumor activity ($GI_{50}/\mu M$)[a] and toxicity ($LC_{50}/\mu M$)[b] data of compounds selected for 5 dose studies for the NCI60-cell lines screen

| Panel/cell line | 8 | | 9 | | 10 | | 11 | | 12 | | 13 | | 14 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | $GI_{50}$ | $LC_{50}$ | $GI_{50}$ | $LC_{50}$ | $GI_{50}$ | $LC_{50}$ | $GI_{50}$ | $LC_{50}$ | $GI_{50}$ | $LC_{50}$ | $GI_{50}$ | $LC_{50}$ | $GI_{50}$ | $LC_{50}$ |
| *Leukemia* | | | | | | | | | | | | | | |
| CCRF-CEM | 0.540 | 30.61 | 1.620 | 56.50 | 0.164 | 2.450 | 0.127 | 0.720 | 0.129 | 0.980 | 0.458 | >100 | 0.324 | >100 |
| HL-60(TB) | 0.331 | 7.780 | 0.324 | 9.930 | 0.131 | 0.816 | 0.143 | 0.791 | 0.185 | >100 | 0.293 | >100 | 0.238 | >100 |
| K-562 | 0.498 | >100 | 0.363 | >100 | 0.190 | 3.490 | 0.385 | >100 | 0.935 | >100 | 0.312 | >100 | 0.238 | >100 |
| MOLT-4 | 2.900 | >100 | 2.580 | 77.50 | 0.306 | 3.860 | 0.189 | 2.160 | 0.589 | >100 | 0.650 | >100 | 0.336 | >100 |
| RPMI-8226 | 0.109 | 6.130 | 0.312 | 9.48 | 0.240 | 0.764 | 0.027 | 1.210 | 0.017 | 0.811 | 0.062 | >100 | 0.086 | >100 |
| SR | 0.597 | 97.60 | 1.060 | >100 | 0.100 | 4.380 | 0.154 | 3.792 | 1.850 | >100 | 1.240 | >100 | 3.370 | >100 |
| *Non-small cell lung cancer* | | | | | | | | | | | | | | |
| A549/ATCC | 5.920 | >100 | 7.140 | >100 | 1.070 | 8.310 | 0.639 | 10 | 1.090 | 9.374 | 1.180 | >100 | 0.458 | >100 |
| EKVX | 0.873 | >100 | 0.792 | >100 | 0.358 | 6.770 | 0.649 | 7.781 | 1.120 | 7.644 | 0.673 | 5.758 | 0.346 | 8.910 |
| HOP-62 | 4.860 | >100 | 9.480 | >100 | 1.170 | 6.893 | 0.967 | 7.796 | 1.450 | 7.771 | 1.110 | 9.785 | 0.390 | 6.090 |
| HOP-92 | 5.300 | >100 | 7.840 | >100 | 1.020 | 7.298 | 1.140 | 6.853 | 0.927 | 6.683 | 0.350 | >100 | 0.211 | 22.00 |
| NCI-H226 | 3.550 | >100 | 4.620 | >100 | 0.861 | 5.045 | 0.869 | 5.994 | 1.170 | 5.736 | 1.260 | 8.002 | 0.435 | 8.230 |
| NCI-H23 | 0.885 | >100 | 2.440 | >100 | 0.504 | >100 | 0.392 | 7.720 | 0.424 | 7.983 | 0.407 | 7.697 | 0.224 | 12.70 |
| NCI-H322M | 22.60 | >100 | 24.60 | >100 | 1.740 | 7.054 | 1.300 | 5.954 | 1.610 | >100 | 1.520 | 6.401 | 0.406 | 5.540 |
| NCI-H460 | 3.390 | >100 | 4.290 | >100 | 0.498 | 5.380 | 0.405 | 3.920 | 0.636 | 4.38 | 0.663 | 5.240 | 0.323 | 4.850 |
| NCI-H522 | 2.370 | >100 | 2.960 | >100 | 1.010 | 6.834 | 0.364 | 6.449 | 1.160 | 6.773 | 1.020 | >100 | 0.285 | 4.316 |
| *Colon cancer* | | | | | | | | | | | | | | |
| COLO 205 | 2.620 | >100 | 3.410 | >100 | 0.343 | >100 | 0.285 | >100 | 0.389 | >100 | 0.350 | 4.020 | 0.196 | 0.778 |
| HCC-2998 | 1.890 | >100 | 4.180 | >100 | 0.192 | 7.294 | 0.296 | 7.773 | 0.293 | 5.865 | 0.494 | 9.066 | 0.271 | 25.50 |
| HCT-116 | 3.590 | >100 | 2.360 | >100 | 0.349 | 6.215 | 0.343 | >100 | 0.411 | >100 | 0.651 | >100 | 0.294 | >100 |
| HCT-15 | 20.80 | >100 | 18.10 | >100 | 1.000 | 4.650 | 0.461 | 4.110 | 1.010 | 4.660 | 1.070 | 5.940 | 0.309 | 4.410 |
| HT29 | 2.600 | >100 | 2.190 | >100 | 0.311 | 5.059 | 0.315 | 5.515 | 0.408 | >100 | 0.378 | 9.131 | 0.315 | >100 |
| KM12 | 2.090 | 85.80 | 1.850 | 23.00 | 0.357 | 3.570 | 0.275 | 2.960 | 0.471 | 3.996 | 0.454 | 5.455 | 0.214 | 0.929 |
| SW-620 | 2.970 | >100 | 7.250 | >100 | 0.461 | 4.230 | 0.446 | 4.720 | 0.519 | 4.315 | 0.520 | 6.484 | 0.328 | 3.740 |
| *CNS cancer* | | | | | | | | | | | | | | |
| SF-268 | 4.680 | >100 | 5.980 | >100 | 1.020 | 4.930 | 0.978 | 5.878 | 1.260 | 6.058 | 1.140 | 6.287 | 0.481 | 5.792 |
| SF-295 | 2.360 | >100 | 2.930 | >100 | 0.383 | 5.020 | 0.332 | 5.590 | 0.503 | 6.023 | 0.484 | 6.606 | 0.275 | 5.770 |
| SF-539 | 2.720 | >100 | 2.880 | >100 | 1.340 | 5.467 | nd | nd | nd | nd | 0.937 | 5.280 | 0.288 | 4.190 |
| SNB-19 | 6.760 | >100 | 10.90 | >100 | 1.220 | 9.593 | 1.220 | >100 | 1.450 | 7.889 | 1.180 | 4.950 | 0.422 | 3.950 |
| SNB-75 | 2.740 | 56.80 | 3.710 | 90.30 | 0.555 | 5.651 | 0.473 | 7.405 | 0.991 | 6.501 | 0.530 | 5.711 | 0.419 | >100 |
| U251 | 2.150 | >100 | 2.810 | >100 | 0.334 | 3.870 | 0.372 | 3.880 | 0.482 | 4.200 | 0.397 | 3.970 | 0.322 | 3.70 |
| *Melanoma* | | | | | | | | | | | | | | |
| LOX IMVI | 1.720 | 45.30 | 1.360 | 34.90 | 0.334 | 3.780 | 0.189 | 1.48 | 0.385 | 3.840 | 0.406 | 5.240 | 0.164 | 0.678 |
| MALME-3M | 4.960 | >100 | 5.060 | 99.70 | 0.549 | 5.682 | 0.368 | 5.825 | 1.020 | 7.690 | 0.454 | 5.080 | 0.271 | 4.251 |
| M14 | 1.920 | >100 | 4.150 | >100 | 0.343 | 5.519 | 0.330 | 6.628 | 0.424 | 6.250 | 0.537 | 6.839 | 0.402 | >100 |
| SK-MEL-2 | nd | nd | nd | nd | nd | nd | nd | nd | nd | nd | 2.090 | >100 | 0.372 | >100 |
| SK-MEL-28 | 4.570 | 71.60 | 10.10 | 21.00 | 0.948 | 5.400 | 0.879 | 5.750 | 1.090 | 5.160 | 1.140 | 6.510 | 0.374 | 3.980 |
| SK-MEL-5 | 1.220 | 7.800 | 1.660 | 54.50 | 0.461 | 4.188 | 0.414 | 3.966 | 0.617 | 4.368 | 0.532 | 4.207 | 0.313 | 3.310 |
| UACC-257 | 1.680 | 92.10 | 3.060 | 42.30 | 1.120 | 8.337 | 0.125 | 6.774 | 1.690 | 9.657 | 1.530 | >100 | 0.523 | 9.709 |
| UACC-62 | 3.120 | 37.50 | 4.250 | | 1.040 | 4.941 | 0.848 | 5.070 | 1.180 | 5.201 | 1.040 | 5.100 | 0.500 | 4.660 |
| *Ovarian cancer* | | | | | | | | | | | | | | |
| IGROV1 | nd | nd | 0.533 | >100 | 0.048 | >100 | 0.175 | >100 | nd | nd | 0.516 | >100 | 0.219 | 1.445 |
| OVCAR-3 | 2.840 | 59.80 | 3.330 | 56.20 | 0.414 | 4.290 | 0.375 | 4.010 | 0.453 | 4.393 | 0.442 | 4.712 | 0.316 | 3.790 |
| OVCAR-4 | 3.170 | >100 | 2.590 | >100 | 0.594 | 7.196 | 0.778 | >100 | 1.030 | 6.332 | 0.351 | >100 | 0.320 | >100 |
| OVCAR-5 | 3.750 | >100 | 7.490 | >100 | 0.912 | 7.238 | 0.819 | 7.892 | 1.080 | 7.236 | 0.909 | 9.136 | 0.489 | 32.70 |
| OVCAR-8 | 2.180 | >100 | 3.250 | >100 | 0.865 | 9.128 | 0.998 | 7.405 | 1.300 | 9.800 | 0.913 | >100 | 0.491 | >100 |
| SK-OV-3 | 4.760 | >100 | 5.970 | >100 | 1.270 | >100 | 1.240 | >100 | 1.810 | 4.200 | 1.160 | 5.820 | 0.355 | 3.830 |
| *Renal cancer* | | | | | | | | | | | | | | |
| 786-0 | 3.360 | >100 | 5.770 | >100 | 1.180 | 7.215 | 0.669 | 6.020 | 1.250 | 8.576 | 0.952 | >100 | 0.425 | 5.360 |
| A498 | 4.280 | >100 | 7.530 | >100 | 1.110 | 7.390 | 1.070 | 8.940 | 1.150 | 7.551 | 1.070 | 6.221 | 0.371 | 3.390 |
| ACHN | 7.240 | >100 | 10.00 | >100 | 0.832 | 4.570 | 0.446 | 4.230 | 0.934 | 4.620 | 0.920 | 4.780 | 0.281 | 3.550 |
| CAK-1 | 1.790 | >100 | 2.990 | >100 | 0.385 | >100 | 0.429 | 7.448 | 0.791 | 8.902 | 0.263 | 6.716 | 0.293 | 7.459 |
| RXF 393 | 5.900 | >100 | 6.520 | >100 | 0.379 | 5.925 | 0.265 | 4.899 | 0.467 | 5.978 | 1.030 | 6.546 | 0.930 | 8.310 |
| SN12C | 2.760 | 34.90 | 3.350 | 42.80 | 1.000 | 4.640 | 0.679 | 4.773 | 1.200 | 5.280 | 1.250 | 5.720 | 0.353 | 4.180 |
| TK-10 | 1.920 | 61.60 | 2.040 | 58.10 | 0.295 | 3.730 | 0.244 | 2.773 | 0.463 | 4.760 | 0.407 | 4.426 | 0.310 | 4.120 |
| UO-31 | 10.20 | >100 | 15.90 | >100 | 1.100 | 6.515 | 0.608 | 5.941 | 0.657 | 5.354 | 1.480 | >100 | 0.365 | 5.310 |
| *Prostate cancer* | | | | | | | | | | | | | | |
| PC-3 | 1.820 | >100 | 2.080 | >100 | 0.268 | 3.856 | 0.212 | 2.854 | 0.286 | 3.544 | 0.311 | 5.259 | 0.276 | 8.030 |
| DU-145 | 0.688 | >100 | 10.90 | >100 | 0.719 | 4.480 | 0.635 | 4.400 | 1.020 | 4.680 | 0.792 | 4.691 | 0.495 | 4.426 |
| *Breast cancer* | | | | | | | | | | | | | | |
| MCF7 | 1.690 | 90.60 | 1.950 | >100 | 0.431 | 4.770 | 0.356 | 3.780 | 0.728 | 4.500 | 1.000 | 5.520 | 0.309 | 4.690 |
| NCI/ADR-RES | 55.00 | >100 | 39.70 | >100 | 2.100 | >100 | 1.660 | >100 | 1.450 | >100 | 1.240 | 9.407 | 0.412 | 12.50 |
| MDA-MB-231ATCC | 3.390 | 63.60 | 4.680 | 64.20 | 0.616 | 4.550 | 0.449 | 4.857 | 1.030 | 5.110 | 1.040 | 5.930 | 0.378 | 4.820 |
| HS 578T | 3.130 | >100 | 6.110 | >100 | 0.538 | 6.110 | 0.335 | 6.310 | 0.536 | 6.151 | 0.546 | 8.483 | 0.287 | 5.431 |
| MDA-MB-435 | 1.790 | 69.10 | 2.150 | 77.50 | 0.482 | 6.978 | 0.684 | 7.961 | 0.851 | 6.637 | 1.080 | 6.689 | 0.344 | 2.930 |
| BT-549 | 1.840 | 50.80 | 2.380 | 51.90 | 1.04 | 5.925 | 0.557 | 5.327 | 1.290 | 6.909 | 1.060 | 5.948 | 0.334 | 4.200 |
| T-47D | 4.290 | >100 | 4.310 | >100 | 0.564 | >100 | 0.546 | >100 | 0.719 | >100 | 0.600 | >100 | 0.282 | 63.70 |
| MDA-MB-468 | 0.384 | 15.30 | 0.556 | >100 | 0.092 | 2.980 | 0.066 | 7.252 | 0.159 | 5.110 | 0.196 | >100 | 0.173 | >100 |

nd: not determined.
[a] $GI_{50}$: 50% growth inhibition, concentration of drug resulting in a 50% reduction in net protein increase compared with control cells.
[b] $LC_{50}$: lethal concentration, concentration of drug lethal to 50% of cells.

higher $LC_{50}$ values. Compound **8** was also highly active against non-small cell lung cancer cell lines EKVX and NCI-H23 and prostate cancer cell line DU-145 with $GI_{50}$ 0.873, 0.885 and 0.688 μM, respectively (cytotoxicity expressed in $LC_{50}$ was >100 μM for these cell lines). Compound **9** exhibited $GI_{50}$ of 0.792 μM ($LC_{50}$ >100 μM) for EKVX (non-small cell lung cancer panel) and 0.533 μM ($LC_{50}$ >100 μM) for IGROV1 (ovarian cancer panel). As the chain length of N-3 alkyl substitution increased to C-16 and then to C-18, the compounds become more sensitive towards tumor cell lines (Table 2). Compound **10** with C-16 alkyl chain length was highly active against all the tumor cell lines with overall potency of $GI_{50}$ in the range of 0.092–2.10 μM. Compound **11** exhibited the $GI_{50}$ 0.027–1.660 μM for all cell lines, both having chloride as anion. However, with the increased alkyl chain length cytotoxicity also increased as can be seen by low $LC_{50}$ values in most of the cases for compounds **10** ($LC_{50}$ 0.764 to >100 μM) and 11 ($LC_{50}$ 0.720 to >100 μM). Similar results were observed with **12** (having $PF_6^-$ anion), **13** (having $(CF_3SO_2)_2N^-$ anion) and **14** (having $(C_2F_5)_3F_3P^-$ anion) all having 1-methyl-3-octadecylimidazolium cation showing overall potency with $GI_{50}$ 0.017–1.850 μM ($LC_{50}$ 0.811 to >100 μM), 0.062–2.090 μM ($LC_{50}$ 3.970 to >100 μM) and 0.086–3.370 μM ($LC_{50}$ 0.778 to >100 μM), respectively for all the tumor cell lines (Table 2). These results also show that in the ionic liquid pair cation plays important role on the activity (compounds **11**–**14**) while anion does not have similar effects; however more studies and screening should to be done to certain this fact. Interestingly, active compounds **8**–**14** were highly active against leukemia cell lines, especially compounds **13** and **14** where the cytotoxicity was also very low as given by $LC_{50}$ >100 μM in all six leukemia cell lines. This can also be seen from their drug response curves (Fig. 1). The drug response curves of all active compounds **8**–**14** for all tumor cell lines are given in the Supplementary data.

In summary, for the first time anti-tumor activity of imidazolium-based ionic liquids has been determined using NCI 60 hu-

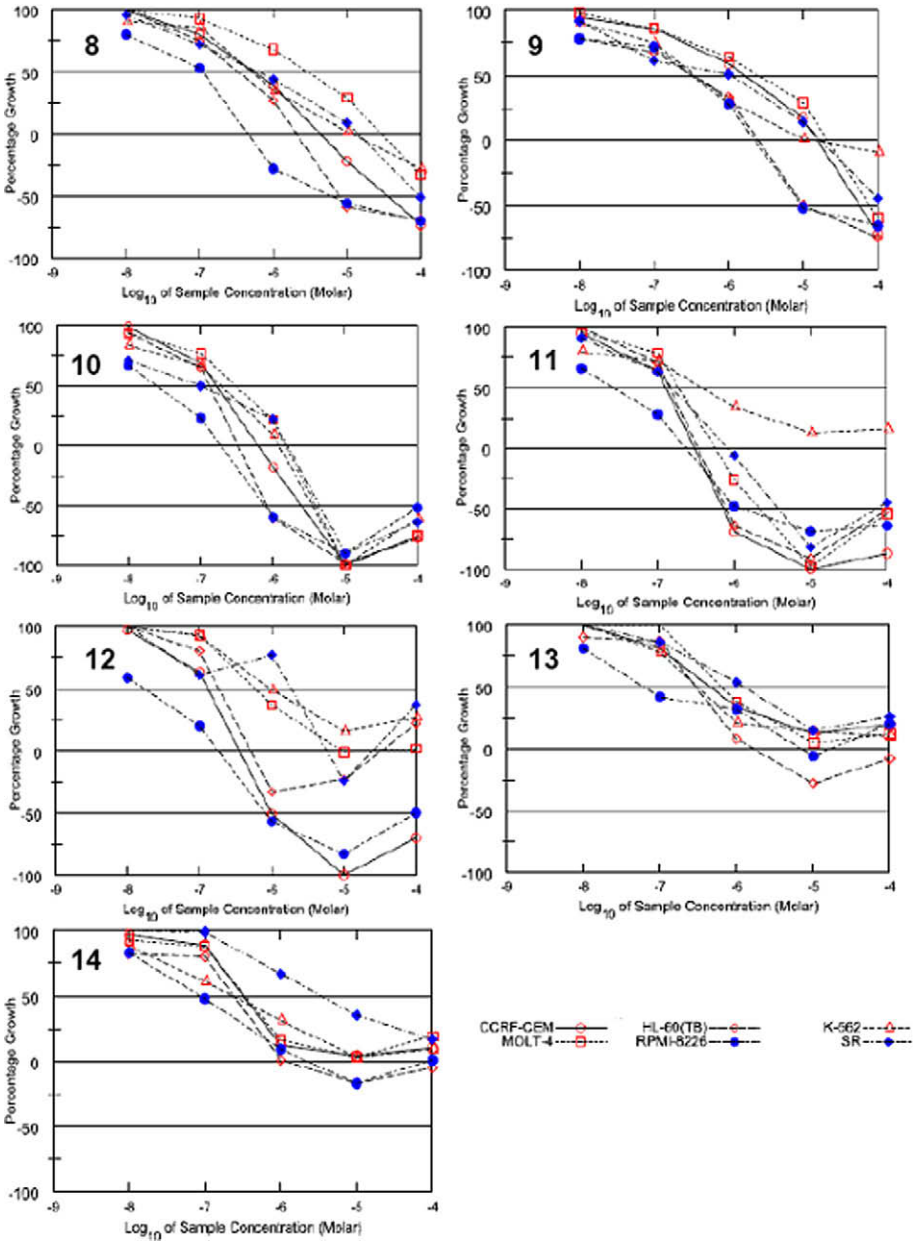



**Figure 1.** Drug–response curves of compounds **8**–**14** for six different leukemia tumor cell lines.

man tumor cell lines. Structure–activity relationship showed that chain length of N-3 alkyl substitution plays a significant role in the anti-tumor activity and cytotoxicity. With increase in alkyl chain length from C-8 to C-12 significant improvement in anti-tumor activity was observed, while cytotoxicity towards the tumor cell lines remained low as evident by higher $LC_{50}$ (>100 μM) values in most of the cases. Further increase in alkyl chain length enhanced both the anti-tumor activity and the cytotoxicity of these compounds towards the tumor cell lines. These results clearly shows that the 'tunability' of ionic liquids (by changing the cation/anion combination and by modifying the cation with different substituents) can control their biological activity and cytotoxicity and could play a major role in their therapeutic applications such as in cancer therapy. Further investigation into the mechanism of action of these compounds with more extensive screening may lead to their potential utility as drugs.

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## Supplementary data

Supplementary data (the one dose data of all the compounds **1**–**17** and drug response curves of active compounds **8**–**14)** associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2009.11.085.

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