Research Article

# National List of Essential Medicines 2011: A Medicinal Chemistry Perspective

**Ranganathan Balasubramanian*, Hiba Iqbal, Sreerag Gopi**
Department of Pharmaceutical Chemistry, Amrita School of Pharmacy, Amrita Vishwa Vidyapeetham University, Health Sciences Campus, Kochi, Kerala.
***Corresponding author's E-mail:** ranga.balasubramanian@gmail.com

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**ABSTRACT**

The National List of Essential Medicines (NLEM) 2011 represents the third instalment of a continuously evolving document that will immensely benefit healthcare delivery institutions, health insurance bodies, medicine price control bodies, health economists and other relevant healthcare stakeholders in the country. It was painstakingly put together using two important national reference documents viz. Indian Pharmacopeia 2010 and the National Formulary of India 2010. If followed in letter and spirit, the list shall enable the rational use of medicines through better prescribing practices. It serves as a reference for assessing the healthcare access of the population with the solo aim of improving the health outcomes. More significantly, it is supposed to be a handy tool for public education and training of healthcare providers. The philosophy behind our study lies in viewing NLEM 2011 precisely as an educational tool. Consequently this work presents our efforts in adding value to the document via a medicinal chemistry perspective that includes classic approaches like chemically classifying the drug substances, analyzing their drug- and lead-likeness as well as exploring the possibility of orally administering them.

**Keywords:** Drug-likeness, Healthcare, Lead-likeness, National List of Essential Medicines.

## INTRODUCTION

The Ministry of Health & Family Welfare (MoHFW) within the Government of India (GOI) is mandated to promote rational use of medicines with respect to cost, efficacy and safety. Following the introduction of the concept of essential medicines by World Health Organization (WHO), the efforts in India to comprehensively identify and classify such medicines, which are used in satisfying the priority healthcare needs of the majority of our population, culminated in a dynamic document referred to as the National List of Essential Medicines (NLEM) in 1996.

Currently in its third instalment that was released in 2011, the list was painstakingly compiled after wide-ranging consultations with stakeholders of different disciplines within the healthcare umbrella of the country including regulatory officials, pharmacologists, toxicologists, clinicians, microbiologists, pharmacists, community medicine experts and hospital administrators. With the objective of adding value to the list by viewing it in medicinal chemistry terms, we undertook a systematic study of these medicines using NLEM 2011 as the base document.

Medicinal chemists commonly employ the Lipinski's rule of five (Ro5)[1] as a filter to differentiate drug-like chemical entities from the others.[2] Analogously, there are Oprea lead-likeness rules[3] widely applied nowadays in the industry to weed out undesirable compounds based purely on physicochemical properties. These two empirical screens when performed early help trim the compound libraries to be screened[4] and enhance the probability of success in later stages of the drug development process.[5] In the current work, we present a handy medicinal chemistry classification of the medicines in NLEM 2011. Furthermore, we have chosen specific subsets of chemical moieties from this database and screened them against the aforementioned filters.

## MATERIALS AND METHODS

The list is available for free download in the Central Drugs Standard Control Organization website (www.cdsco.nic.in). After careful inspection of their structures depicted unambiguously in the fourteenth edition of the Merck Index, these 348 unique medicines were grouped into seven broad classes: small molecules, salts, inorganics, combination medicines, biologicals, enzymes and miscellaneous. There is bound to be a degree of overlap amongst some of the medicines and such instances were overcome by chemical intuition and literature precedence. The medicines in all the 27 therapeutic categories mentioned in the base document were subsequently reclassified into the seven chemical classes as noted above.

Computation of Lipinski Ro5 parameters was carried out using the high-speed molecular properties calculator which is a free module in the MolSoft software package. While this drug-likeness assessment was performed on two chemical subsets of the NLEM 2011 viz. 184 small molecules and 72 salts, estimation of lead-likeness was performed on only the 184-member small molecule subset. Four out of the six parameters including molecular weight, partition coefficient (log P), hydrogen bond donors (HBDs) and hydrogen bond acceptors (HBAs) for assessing lead-likeness were same as those used for drug-likeness and were simply utilized as such. The other two parameters – number of rings and number of non-terminal single bonds – were counted manually. All the

data was analyzed and processed using Microsoft Office Excel 2007.

The following specific cases are pertinent to note in the final analysis of the data: (a) the small molecule entry "Isosorbide-5-mononitrate/dinitrate" under the therapeutic category of cardiovascular medicines was treated as two chemical entities "Isosorbide-5-mononitrate" and "Isosorbide dinitrate" respectively; (b) reliable log P values of the cytotoxic platinum-based small molecules "Cisplatin, Carboplatin and Oxaliplatin" used as antineoplastic medicines could not be obtained and were therefore excluded; (c) the entries "Chloroquine phosphate" under anti-infective medicines and "Hydroxychloroquine phosphate", a disease-modifying antirheumatic drug (DMARD), were considered as the corresponding diphosphate salts respectively; (d) the quaternary ammonium salt and the reversible cholinesterase inhibitor "Neostigmine" is to be made available as tablets (bromide) as well as injection (methyl sulfate) and hence counted as two entries; (e) the physicochemical properties of the salts "Cyanocobalamin, Meglumine iotroxate and Vancomycin hydrochloride" remained inaccessible forcing these entries to be left out.

## RESULTS AND DISCUSSION

NLEM 2011 represents a significant improvement over its predecessor that was released in the year 2003. A survey of the document reveals that while 47 medicines were deleted from the previous compilation, 43 relevant ones have been added. Besides, one-letter codes P, S and T have been used to denote the essentiality of requirement at the primary, secondary and tertiary levels of healthcare respectively. Out of the total 348 unique medicines in the list, 181 fall under the category of P, S, T; 106 under S, T and the remaining 61 are categorized as T only.

In our preliminary analysis, we attempted to classify all these unique medicines into seven chemical categories delineated in the experimental section above. The precise structures of the active ingredient(s) in each medicine were carefully considered and classification was rigorously carried out. Those entries which did not fit into any of the chemical classes were grouped as miscellaneous medicines. The results of this exercise are depicted in the form of a pie-chart (Figure 1) which displays both the absolute numbers as well as the percentage contributed by each chemical class towards populating the list. A closer look at this data indicates that small molecules constitute the major chemical category with more than half the entries while the three enzymes "L-Asparaginase, Streptokinase and Urokinase" comprise the least populated category representing less than 1% of the compounds.

The core committee that prepared NLEM 2011 has primarily categorized the medicines according to therapeutic area and grouped them under 27 sections. Naturally, in such a scenario, it is possible that a medicine with more than one indication appears in more than one category. In fact, there are 34 such repetitions taking the total count of the medicines in the list to 382. We have taken this pharmacology-based classification of the list one step further and expanded its scope as well as utility by including the break-up of each therapeutic category into the seven chemical classes introduced herein (table 1).

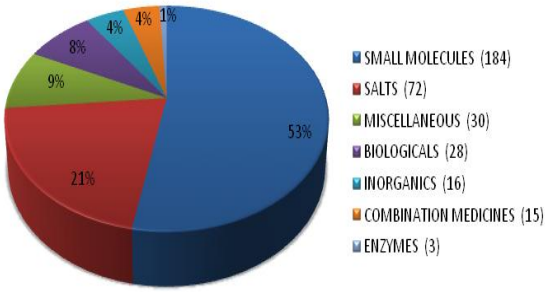


**Figure 1:** Relative distribution of essential medicines into the chemical classes conceived

One of the key features in a medicine that ensures patient compliance is its ability to be orally administered. Therefore, significant efforts have been taken by medicinal chemists and formulation experts to fine-tune the physicochemical properties of chemical entities to make them amenable to oral administration.[6] In our analysis of NLEM 2011, we have precisely zeroed in on this issue and manually counted the number of drugs within each chemical class that have at least one oral dosage form listed as being essential. These results presented in Table 2 are along expected lines. 120 of the 184 small molecules constituting a shade above 65% can be orally administered while none of the medicines under the biologicals (including vaccines, immunologicals and hormones) and enzymes category are suitable for oral administration. Given the importance of this aspect in pharmaceutical sciences, the core committee of NLEM 2011, after elaborate deliberations, decided to include the following features in the document: route of administration, dosage forms and their respective strengths that are to be made available in the various levels of healthcare centres across the country. Accordingly, the 382 medicines (including repetitions) in the list encompassing a total of about 650 formulations are to be mandatorily sold at or below the ceiling price fixed by the GOI.

As per Lipinski's rule of five, poor absorption or permeation is more likely when (a) molecular weight is over 500 Daltons, (b) log P is over 5, (c) there are more than 5 HBDs and (d) there are over 10 HBAs in the molecule. Although additional clauses have since been added[7] to make the guidelines increasingly relevant in the current setting, these four criteria remain the benchmarks for assessing drug-likeness.[8] Therefore, these basic features were used in our first screen that was performed on the subsets of small molecules and salts within NLEM 2011. It was observed that molecular weight was the most violated property while the maximum number of compounds complied with the log P ≤ 5 stipulation.

**Table 1:** Systematic therapeutic area-wise chemical classification (including 34 repetitions)

| Section Number and Name | | SMALL MOLS.[a] | SALTS | INORG.[b] | COMBOS[c] | BIOL.[d] | ENZ.[e] | MISC.[f] | Total |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Anaesthesia | 7 | 6 | 1 | 2 | - | - | 2 | 18 |
| 2 | Analgesics, antipyretics, nonsteroidal anti-inflammatory medicines, medicines used to treat gout and disease modifying agents used in rheumatoid disorders | 12 | 2 | - | - | - | - | - | 14 |
| 3 | Antiallergics and medicines used in anaphylaxis | 4 | 5 | - | - | - | - | - | 9 |
| 4 | Antidotes and other substances used in poisonings | 5 | 5 | 2 | - | - | - | 2 | 14 |
| 5 | Anti- convulsants/epileptics | 4 | 2 | 1 | - | - | - | - | 7 |
| 6 | Anti-infective medicines | 46 | 11 | - | 7 | - | - | - | 64 |
| 7 | Antimigraine medicines | 3 | 1 | - | - | - | - | - | 4 |
| 8 | Antineoplastic, immunosuppressives and medicines used in palliative care | 32 | 5 | - | - | 2 | 1 | - | 40 |
| 9 | Antiparkinsonism medicines | 0 | 2 | - | 1 | - | - | - | 3 |
| 10 | Medicines affecting the blood | 3 | 2 | 1 | - | 3 | - | 1 | 10 |
| 11 | Blood products and plasma substitutes | 0 | - | - | - | 6 | - | 4 | 10 |
| 12 | Cardiovascular medicines | 18 | 5 | 1 | - | 1 | 2 | - | 27 |
| 13 | Dermatological medicines (topical) | 8 | 3 | 2 | 1 | - | - | 2 | 16 |
| 14 | Diagnostic agents | 5 | 5 | 1 | - | - | - | - | 11 |
| 15 | Disinfectants and antiseptics | 4 | 2 | 1 | 1 | - | - | 4 | 12 |
| 16 | Diuretics | 4 | - | - | - | - | - | - | 4 |
| 17 | Gastrointestinal medicines | 10 | 2 | 2 | - | - | - | 2 | 16 |
| 18 | Hormones, other endocrine medicines and contraceptives | 11 | 2 | - | 2 | 4 | - | 5 | 24 |
| 19 | Immunologicals | 0 | - | - | - | 12 | - | 1 | 13 |
| 20 | Muscle relaxants (peripherally acting) and cholinesterase inhibitors | 0 | 5 | - | - | - | - | - | 5 |
| 21 | Ophthalmological preparations | 8 | 7 | - | - | - | - | 2 | 17 |
| 22 | Oxytocics and antioxytocics | 5 | 1 | - | - | 1 | - | - | 7 |
| 23 | Peritoneal dialysis solution | 0 | - | - | - | - | - | 1 | 1 |
| 24 | Psychotherapeutic medicines | 6 | 3 | 1 | - | - | - | - | 10 |
| 25 | Medicines acting on the respiratory tract | 2 | 4 | - | - | - | - | - | 6 |
| 26 | Solutions correcting water, electrolyte and acid-base disturbances | 1 | - | 2 | 1 | - | - | 6 | 10 |
| 27 | Vitamins and minerals | 6 | 2 | 1 | - | - | - | 1 | 10 |
| | TOTAL | 204 | 82 | 16 | 15 | 29 | 3 | 33 | 382 |

[a]SMALL MOLS.: Small molecules; [b] INORG.: Inorganic; [c] COMBOS: Combination medicines; [d] BIOL.: Biologicals; [e] ENZ.: Enzymes; [f] MISC.: Miscellaneous

**Table 2:** Orally administered medicines in each chemical class

| Chemical Class | SMALL MOLS.[a] | Salts | INORG.[b] | COMBOS[c] | BIOL.[d] | ENZ.[e] | MISC.[f] |
|---|---|---|---|---|---|---|---|
| **Orally Administered** | 120 | 30 | 6 | 10 | 0 | 0 | 5 |

[a] SMALL MOLS.: Small molecules; [b] INORG.: Inorganic; [c] COMBOS: Combination medicines; [d] BIOL.: Biologicals; [e] ENZ.: Enzymes; [f] MISC.: Miscellaneous

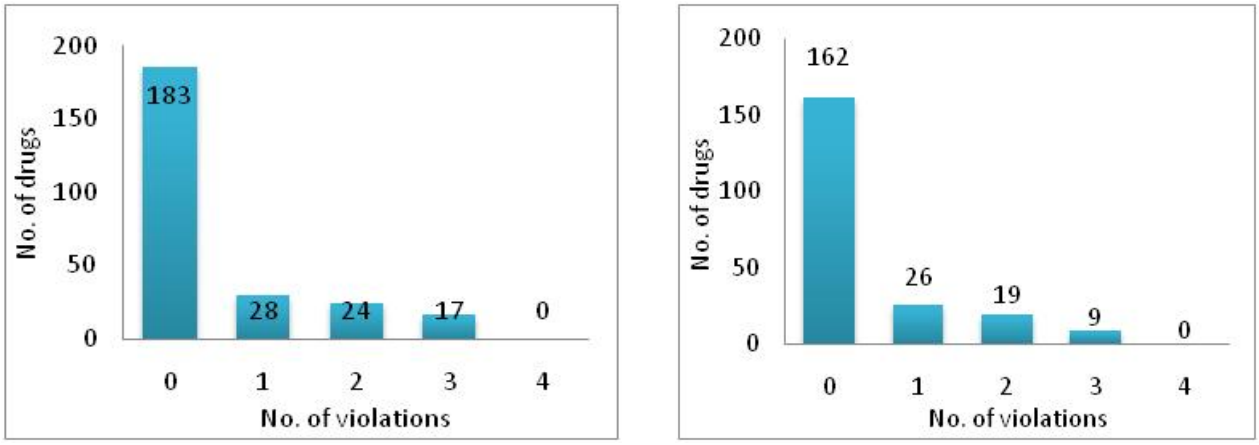


**Figure 2a (left):** Lipinski Ro5 analysis performed on the entire "Small Mols." & "Salts" subsets; **Figure 2b (right):** Identical analysis carried out on the same datasets after removing exceptions.

Obviously, the results from this screen (Figure 2a) ended up overestimating the number of drug-like candidates because of the inclusion of drugs belonging to certain categories that fall outside the Ro5 mnemonic. A closer inspection of the base document led to the identification of a total of 36 medicines (30 small molecules and six salts) covering therapeutic categories like vitamins, fungicides, antibiotics, protozoacides, cardiac glycosides and antiseptics that are traditional exceptions to the Lipinski rules[9,10] on account of them likely being transported rather than undergoing passive diffusion. After removing these exceptions, the subsequent histogram depicting the number of violations (Figure 2b) within this dataset provided a more reasonable estimate of compliance. Interestingly, the number of orally available drugs as predicted by this analysis (162 compounds have no violations as per Figure 2b) correlates quite well with the data shown in Table 2 that was obtained by a manual count of marketed drugs in the list (150 compounds between the two relevant categories comprising small molecules and salts) having an oral dosage form available for sale.

Furthermore, the small molecules within NLEM 2011 were investigated for their ability to act as leads. Since these represent marketed medicines, they cannot be treated as "pure" leads in the classic medicinal chemistry sense. Rather, this analysis was aimed at estimating how many of these structures would be amenable to modification as novel drugs. Oprea and co-workers from AstraZeneca formulated a set of guidelines for assessing lead-likeness, a concept analogous to drug-likeness introduced by Lipinski, in which they suggest that the physicochemical parameters of a lead compound should not exceed the following property values: (a) 450 Daltons in molecular weight, (b) $-3.5 < \log P < +4.5$, (c) 4 rings, (d) 10 nonterminal single bonds, (e) 5 HBDs and (f) 8 HBAs.[11] Inspired by a study along similar lines which successfully predicted viability of natural products as lead structures in drug development[12], we employed the Oprea benchmarks as a lead-likeness filter. It was gratifying to observe that about 52% of the chemical moieties do not violate the Oprea mnemonic in the absolute sense. These results that are illustrated in Figure 3 are very encouraging as they suggest that a majority of the small molecules in the list possess good developability. A more detailed inspection of the raw data indicated that most compounds tend to not obey the 10 nonterminal single bonds stipulation whereas the number of rings was the least violated property.

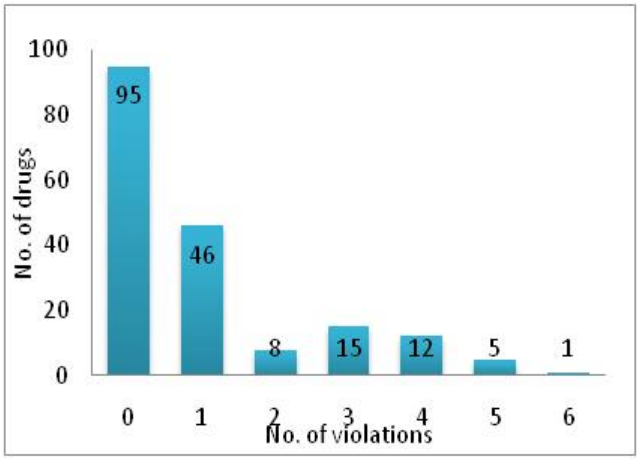


**Figure 3:** Assessment of Oprea lead-likeness compliance

The antineoplastic drug "Bleomycin" presented an interesting scenario by being the sole entry in the entire analysis that violated all six Oprea guidelines. However, there was no single small molecule or salt which was an outlier with respect to the four Lipinksi Ro5 parameters. This is a case in point to the fact that both the above analyses yield different results with each being meaningful in its specific context.

## CONCLUSION

We have attempted herein a rigorous chemical classification of the medicines included in the NLEM 2011. Small molecules and salts which constitute the two most informative chemical classes to a medicinal chemist with respect to drug design have been studied in greater detail by performing drug-likeness and lead-likeness analyses. Since all the medicines in our dataset are already

marketed, the empirical Lipinksi Ro5 analysis yielded results which correlate very well with observed numbers of orally administered drugs. The Oprea analysis suggested that more than half the small molecules in the dataset have the ability to act as leads. The latter finding is quite promising from a discovery/development perspective. Taken along with the strong clinical leaning of the base document, these observations add a structured layer of information to the list that should now be a handy guide for not only the practising pharmacist but also for the chemist. In summary, our primary objective of adding value to the list as an educational tool has been reasonably met through this preliminary communication.

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**Corresponding Author’s Biography: Dr. Ranganathan Balasubramanian.**

After graduating with a B.Pharm (Hons.) degree from BITS Pilani, Dr. Ranganathan left for USA to pursue higher education. Over the next seven years, he obtained M.S. in Pharmaceutical Chemistry & Ph.D. in Medicinal Chemistry from New Jersey and Minnesota respectively. He returned to India after a postdoctoral stint at the prestigious Johns Hopkins Medical School in Baltimore. Currently, he is pursuing his passion in pharmaceutical sciences by teaching as well as mentoring students in Organic, Medicinal & Pharmaceutical Chemistry at Amrita School of Pharmacy, Kochi.