



COMPREHENSIVE : DRUG DISCOVERY AND ITS PROCESS

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ABSTRACT :-

This prepare includes the recognizable proof of candidates, union, characterization, approval, optimization, screening and tests for helpful viability. Once a compound has shown its significance in these examinations, it'll start the method of sedate advancement prior to clinical trials. Unused drug development handle must proceed through a few stages in arrange to form a medication that's secure, viable, and has affirmed all administrative necessities. The travel commences with Pre Revelation, a stage characterized by thorough target recognizable proof and approval, underscoring the need of vigorous preclinical inquire about. In this way, the Hit to Lead Disclosure arrange develops, centering on the distinguishing proof and optimization of lead compounds with promising pharmacological properties. At long last, the Medicate Improvement stage encapsulates the regulatory strategies and clinical trials essential for changing promising atoms into market-ready pharmaceuticals.

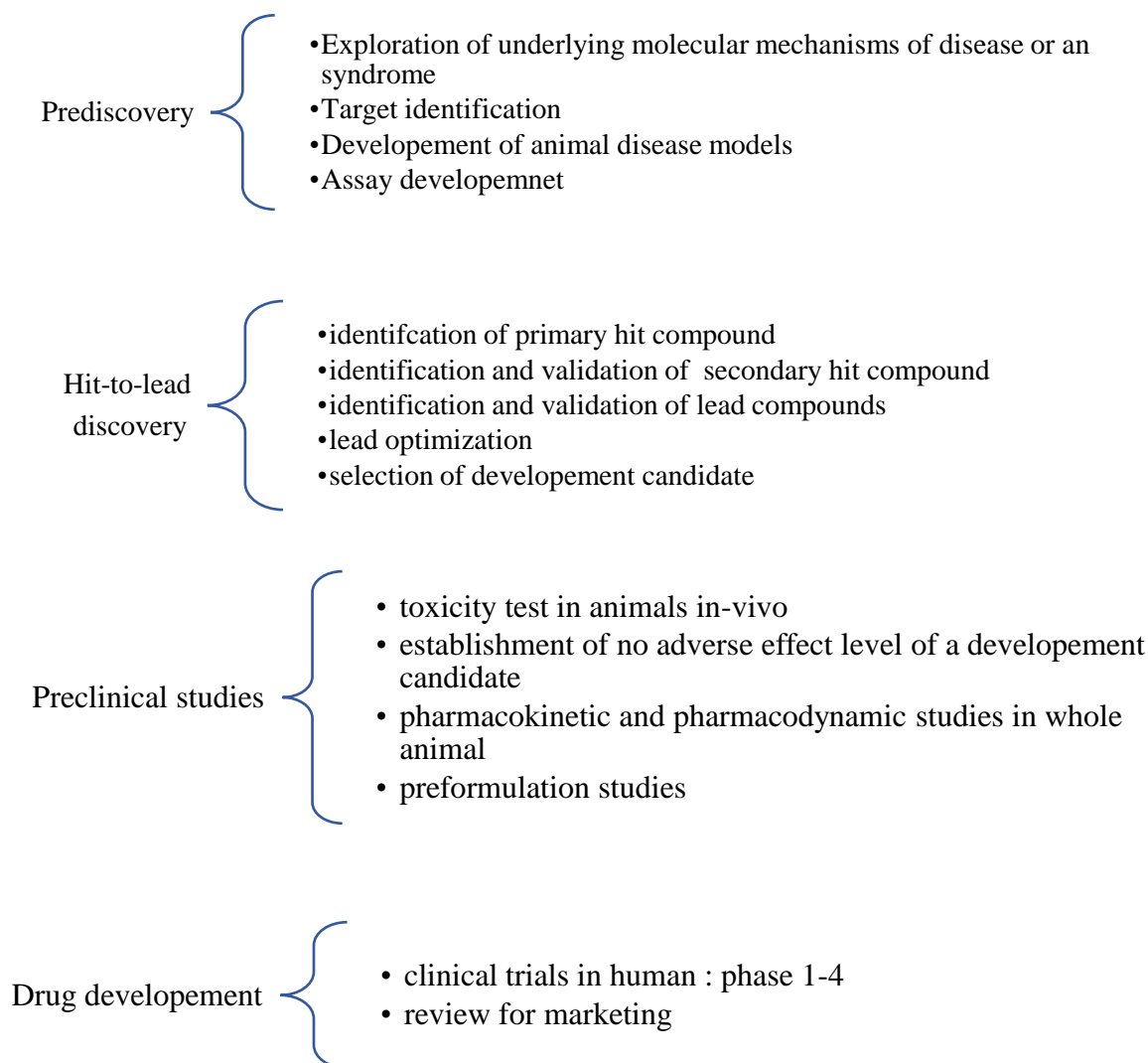
KEYWORDS: Drug discovery, Clinical trials, Pre Discovery, Target identification, Preclinical Studies, Drug Development phase, QSAR, Drug design.

INTRODUCTION:

The drug discovery process is complex, involving the identification and development of effective medications for treating diseases. The impact of successful drug discoveries significantly enhances life quality and longevity [1]. Since the 1980s, there has been a decline in novel therapeutic compounds entering research pipelines [2]. Key challenges include the inadequacy of the "one drug-one target" approach [3] and unexpected toxicities due to biological system complexities [4-8]. Advancements in technology, such as in-silico methods [9], bioinformatics, high-throughput crystallography, and improved NMR techniques [10-13], have streamlined the identification of drug targets and accelerated structure determination. Structure-based drug design is critical in developing effective drug leads [14]. CADD (Computer-Aided Drug Design) is a computational approach used for discovering, creating, and assessing pharmaceuticals and bioactive compounds. It analyzes and models interactions between compounds and biological targets, such as proteins and nucleic acids. CADD enhances drug development by streamlining manufacturing processes and addressing challenges like costs and competition. It employs targeted search methods to elucidate therapeutic mechanisms and predict potential derivatives for improved activity. Since the 1980s, CADD has played a significant role in drug discovery, allowing for high-throughput screening of compounds while maintaining efficacy. Key steps in drug discovery include disease selection, target identification, lead compound identification, lead optimization, and lead validation. Preclinical and clinical trials utilize peptide testing, with future efforts focusing on finding novel ligands for new targets. The field combines computer science, bioinformatics, and experimental methods to facilitate drug design, encompassing both computational and experimental CADD techniques [15,16][17].

PRINCIPLE:

Amid lead revelation, an comprehensive look is conducted to recognize a drug-like little atom or organic treatment, commonly alluded to as a advancement candidate, that will progress onto preclinical testing and, in the event that fruitful, clinical improvement, and inevitably ended up a sold pharmaceutical. The distinguishing proof of screening hits, restorative chemistry, and optimization of those hitsto boost liking, selectivity (to lower the hazard for unfavorable impacts), efficacy/potency, metabolic soundness (to extend the half-life), and verbal bioavailability are all portion of advanced sedate disclosure. Once a particle that meets all of these criteria has been recognized, the medicate improvement process will commence earlier to clinical trials [18]

STAGES OF DRUG DISCOVERY :**Target Endorsement:**

Target endorsement includes certifying the particular atomic target of a little atom, such as a quality, protein, or nucleic corrosive. This handle incorporates deciding the structure-activity relationship (SAR) of little particle analogs, making drug-resistant mutants of the target, controlling its expression, and screening known downstream signaling pathways [19].

Measure Advancement:

Most biochemical measures within the industry depend on making steady mammalian cell lines that overexpress the target of intrigued or creating and filtering recombinant proteins. In spite of the fact that the utilize of essential cell frameworks for screening has expanded, a few components influence measure plan, counting the target protein's characteristics, research facility capabilities, analyst ability, the sort of particle being looked for (inhibitor or activator), and the scale of the test. [20]

Key contemplations incorporate:

- Pharmacological Utility:

Tests ought to utilize known ligands that connected with the target to approve their prescient control for illness states and illustrate viability in identifying compounds with the required strength and component of activity.

- Reproducibility:

The test must abdicate steady comes about over diverse exploratory conditions and all through the medicate revelation program.

- Taken a toll Effectiveness:

Microtiter plates are commonly utilized for compound screening. Scholarly considers regularly utilize 96-well or 384-well plates, whereas high-throughput screening (HTS) utilizes 384-well or 1536-well plates with negligible test volumes to decrease costs.

Test Exactness: The Z' figure is commonly utilized to survey measure quality [21].

HIT-TO-LEAD-PHASE:

The objective of this step of the work is to refine each hit arrangement in arrange to create more capable and particular compounds with worthy PK characteristics to test their adequacy in any available in vivo models. Structure-based medicate plan approaches based on atomic demonstrating and advances like as X-ray crystallography and NMR can be utilized to construct SARs more rapidly and accurately. Once a part of hits have been found utilizing virtual screening or HTS, the drug revelation team's to begin with assignment is to select which particles are the finest to work on. The another step within the initial refining strategy is to produce dose-response bends for each hit within the essential test, ideally employing a new test of the chemical. Getting a dose-response bend empowers the calculation of a half greatest inhibitory concentration, which is then used to compare the potencies of imminent drugs. Once substantial dose-response bends for the target have been gotten within the to begin with test, the organize is set to examine the surviving hits in a auxiliary measure, in case one is accessible, for the target of choice. This does not need to be a high-throughput test, but it'll include analyzing the impact of the chemicals on a utilitarian reaction, such as in a moment flag-bearer measure or a tissue- or cell-based bioassay. Key compounds that are starting to approach objective strength and selectivity, as well as the larger part of physicochemical and ADME targets, ought to be tried for PK in rats.

Distinguishing proof of Lead:

A artificially steady, practical, and drug-like particle dynamic in essential and auxiliary measures with satisfactory specificity, fondness, and selectivity for the target receptor is alluded to as a chemical lead. This requires the foundation of the structure-activity relationship, as well as the recognizable proof of synthetic achievability and preparatory verification of in vivo viability and target engagement [22].

LEAD OPTIMIZATION:

To advance from a lead to a helpful candidate, the lead is utilized as a beginning point for the union of hundreds, in the event that not thousands, of subsidiaries in a handle known as "Lead Optimization." In case the lead fixing comes from a ample normal source, it may be simpler to separate and decontaminate the component for consequent restorative improvement. A engineered chemical strategy is as often as possible utilized for novel medicate disclosure in arrange to moderate common assets and oversee immaculateness and surrender. In the event that full blend isn't conceivable, a key forerunner may be extricated and decontaminated for future use [23,24]. To form a pre-clinical restorative candidate, the chemical structures of lead compounds (little molecules or biologics) must be modified in arrange to extend target specificity and selectivity. Pharmacodynamic and pharmacokinetic characteristics, as wellas toxicological properties, are all evaluated [25].

Preclinical considers:

Pre-clinical inquire about within the medicate improvement prepare involves surveying a medicine's security and adequacy in creature models, which leads to a potential human result. Pre-clinical tests must moreover be endorsed by the suitable administrative specialists. The administrative specialists must guarantee that thinks about are conducted in a secure and moral way, and they must as it were favor pharmaceuticals that have been demonstrated to be secure and compelling. The Worldwide Conference on Harmonization (ICH) has made a crucial rule for the specialized necessities of satisfactory preclinical medicate improvement. Undesirable pharmacological impacts must be examined in fitting creature models and checked in toxicological studies[26].

In-vivo Thinks about:

Since in vitro considers cannot totally expect the drug's impact on organs and organ frameworks, or indeed its combination with other drugs, in vivo examinations are required to clarify realities concerning helpful drugs before clinical trials are conducted. In vivo considers permit for the long-term checking and perception of the drug's impacts, as well as surveying bioequivalency, security, dosing regimen, positive and negative impacts, and drug-drug intelligent in a living system.

In vitro considers give important data on medicate instrument of activity, which is usefulfor making hazard-based choices and educating decision-making within the sedate advancement prepare; in any case, thesignificance to human presentation scenarios and chance evaluation is limitedwithout connecting in vitro toxicodynamic estimations to in vivo toxicokinetics [27].

PHARMACOKINETIC STUDIES:

Animal models have been very advantageous in portraying the joins between tissue concentrations and serum or plasma concentrations. The interstitial compartment and the intracellular compartment are diverse districts, and pharmaceutical dispersion in these two compartments regularly varies. Another pharmacokinetic viewpoint that can influence antibacterial action is serum protein authoritative. Various examinations have appeared that as it were the free or unbound component of the pharmaceutical is accessible for antibacterial action.

Protein authoritative has small impact on the half-life of medications expelled by means of tubular emission, but it can essentially diminish the clearance of drugs killed fundamentally through glomerular filtration [28]. One of the foremost critical contrasts in pharmacokinetics between creatures and people is the rate of medicine clearance in creatures [29,30]. In vitro and creature considers can both be utilized to examine the impact of medicate presentation on life form development taking after sedate presentation. As it were in vivo creature models, be that as it may, can evaluate the worldly course of movement at the location of contamination, as well as the conceivable affect of have immunological factors on antimicrobial movement. Both models

have been broadly utilized for the lion's share of antibacterial classes and numerous antifungals. The perseverance of these post-antibiotic impacts is regularly longer than when surveyed in vitro [31].

Preformulation Studies:

Preformulation is the examination of the chemical and physical properties of medicate components some time recently the definition handle. Its objective is to optimize fabricating conditions and get it the nature of each component. Preformulation information is fundamental for encouraging definition advancement and incorporates examining component intelligent, preparatory debasement profiles, and explanatory highlights. This investigate helps in building up observing methods all through detailing improvement.

Require for a Preformulation Think about:

The logical and administrative inspirations for collecting preformulation information incorporate:

1. Improvement of medicate necessities for toxicological testing and clinical supply arrangements.
2. Setting up clinical supplies and preparatory prerequisites.
3. Giving logical information to help in measurement shape detailing and assessing item viability, quality, soundness, and bioavailability.
4. Conducting steadiness testing of early measurement shapes.
5. Guaranteeing compliance with the CMC area of the IND and ensuing NDA or ANDA.

Preformulation Consider for Drugs and Health-Care Items:

The rules for preformulation considers apply to different health-care items, counting routine solutions, biotechnology items, and dietary supplements. Adjustments may be fundamental to get pertinent information for particular items.

Pharmaceutical Item Classifications:

1. Ethical (Medicine) Items:

R&D-based organizations create these items, requiring FDA endorsement for showcase passage through a long NDA handle, administered by cGMP.

2. Non specific (Multisource) Items:

Numerous companies may showcase the same item post-ANDA endorsement beneath the Waxman-Hatch Act, utilizing the initial product's chemical title. Bioequivalence to the trailblazer must be illustrated, permitting for advertise competition and lower costs.

3. Biotechnology Items:

These items are created utilizing natural frameworks, requiring cautious steadiness contemplations. They may require a Organic Permit Application (BLA) for showcase conveyance.

4. Over-the-Counter (OTC) Items:

These self-treatment medicines are accessible without a medicine, for the most part not requiring preformulation studies as they are expansions of existing items.

5. Dietary Supplement Items:

These incorporate vitamins, minerals, and herbs. In spite of missing exacting FDA endorsement prerequisites, they must be labeled concurring to rules. Preformulation considers ought to take after comparative conventions to customary pharmaceuticals.

6. Animal Wellbeing Items:

These incorporate pharmaceuticals for non-human creatures, requiring a Modern Creature Medicate Application (NADA) for commercialization.

7. Extraordinary or Novel Drug-Delivery Frameworks:

These utilize modern fabricating innovations to make strides quiet comfort and address conveyance challenges of conventional items.

8. Other Health-Care Items:

This category incorporates demonstrative things, therapeutic gadgets, and radiopharmaceuticals, which require particular preformulation considers [32].

DRUG IMPROVEMENT:

CLINICAL TRIALS

Clinical trials are conducted in volunteers to evaluate the security and adequacy of drugs, immunizations, and treatments. Designers must layout destinations for each of the four Clinical Inquire about Stages and start the Investigational Modern Medicate (IND) handle some time recently beginning clinical inquire about.

Stage 0:

These are first-in-human trials (regularly called human microdosing considers) conducted beneath FDA rules, including single sub-therapeutic dosages given to 10 to 15 volunteers. They give pharmacokinetic information and help in imaging targets without actuating pharmacological impacts [33].

Stage 1:

Security and Dose:

Stage I trials include 20 to 80 solid volunteers (or patients when essential) to assess the drug's security, dose, and instrument of activity. This stage assembles basic information on side impacts and makes a difference educate Stage II think about plan. Almost 70% of drugs advance to the another stage.

Stage 2:

Adequacy and Side Effects:

Conducted on a number of hundred patients, Stage II trials test the drug's adequacy whereas affirming security from Stage I. In spite of the fact that these trials cannot completely decide adequacy, they give important security information and offer assistance refine ponder plans for Stage III. Around 33% of drugs move forward after this organize.

Stage 3:

Viability and Unfavorable Medicate Responses Observing:

This stage creates the larger part of security information and points to recognize any unprecedented unfavorable impacts. Essential thinks about include 300 to 3,000 members and center on whether the item offers a noteworthy advantage to particular bunches. The FDA audits all information some time recently choosing on endorsement.

Stage 4:

Post-Market Sedate Security Observing:

Conducted after FDA endorsement, Stage IV trials center on post-marketing reconnaissance, counting pharmacovigilance and continuous back. These ponders may be required by administrative organizations or started by the supporting company for competitive reasons. They offer assistance guarantee progressing evaluation of a drug's security all through its commercial lifecycle [34].

What is CADD?

CADD stands for Computer-Aided Medicate Plan, which utilizes computational strategies to upgrade medicate revelation and plan, advertising inventive treatment alternatives. Key components incorporate:

1. Virtual Screening: Recognizing hits through structure- and ligand-based plan.

2. Hit-to-Lead Optimization:

Progressing liking and selectivity based on structure and quantitative structure-activity connections (QSAR).

3. Lead Optimization: Improving pharmacological characteristics whereas holding fundamental properties [35].

Focal points : Less chemicals are chosen from huge compound libraries for test testing.

Optimizing lead compounds upgrades digestion system and pharmacokinetics (ADME), such as retention.

Decreases the probability of sedate resistance, cultivating improvement of compounds that address fundamental causes. Gives point by point data approximately infections.

Minimizes screening endeavors and decreases labor [36].

SAR Definition and Improvement:

Quantitative Structure-Activity Relationship (QSAR) may be a key approach in ligand-based sedate plan. QSAR/QSPR thinks about quantitatively relate changes in chemical structure with organic action, recognizing which chemical properties impact natural capacities [37].

QSAR IMPROVEMENT:

QSAR includes a computerized factual strategy that clarifies varieties in natural movement based on basic changes. It sets that the organic action of related compounds depends on particular physicochemical properties, which can be optimized through cautious determination of substituents. The objective of QSAR/QSPR ponders is to set up numerical connections between organic action or properties and atomic descriptors, guaranteeing that the atomic structure includes the highlights dependable for its action [38,39].

REASON OF QSAR:

QSAR (Quantitative Structure-Activity Relationship) points to create ideal sedate models to play down trial-and-error strategies, in this way lessening costs and time in sedate amalgamation whereas upgrading natural activity. The method analyzes connections to form models whose legitimacy can be tried utilizing factual instruments.

Key targets incorporate:

1. 1. Diminishing trial and mistake in medicate amalgamation, bringing down research facility amalgamation time and costs.
2. 2. Advancing greener chemistry by diminishing squander and utilizing less poisonous compounds.
3. 3. Minimizing time and exertion in clinical and preclinical trials, especially creature testing.
4. 4. Creating progressed sedate instruments focusing on particular proteins and proteins for more strong medicines.
5. Understanding and rationalizing instruments of activity over different compounds.

APPLICATION FOR DRUG DESIGN:

Since Hansch's distribution, there has been an increment in writing with respect to QSAR's applications in therapeutic chemistry, counting its prescient capabilities and part in understanding sedate instruments. Key applications incorporate:

1. Captured Values:

The captured in QSAR conditions reflects the movement of unsubstituted compounds, with tall intervention and moo inclines demonstrating tall natural movement and negligible commitment from substituents.

2. Bioisosterism:

QSAR permits for the evaluation of bioisosterism, encouraging the substitution of bunches based on comparative physicochemical properties. An illustration is the discovery of cyanoguanidine as a bioisosterism for thiourea in H₂ opponents.

3. Receptor Location Data:

QSAR thinks about upgrade understanding of receptor destinations, as seen within the restraint of dihydrofolate reductase (DHFR) by benzyl pyrimidines. Considers have given experiences into hydrophobic pockets in both mammalian and bacterial DHFR.

4. Significance in Medicate Investigate:

QSAR investigation has appeared that anti-inflammatory specialists have come to crest movement, demonstrating no require for advance analogs. Thinks about on nitroimidazole's carcinogenic potential have appeared endeavors for non-nitro subordinators to be pointless. Moreover, QSAR considers on diphenhydramine analogs recommend expanded hydrophilicity improves antihistaminic action without CNS side impacts.

5. Success Story of PCA Inhibitor:

A consider at Smith Kline and French Research facilities utilized QSAR to create anti-allergic pyranen-amines. Beginning endeavors utilizing the Topliss conspire did not essentially improve action, driving to the blend of bioisosters, with the 4-OH derivative distinguished as the foremost dynamic compound.

6. Application of Free-Wilson Demonstrate:

The Free-Wilson strategy could be a quantitative examination procedure utilizing pointer factors without physico-chemical parameters. It has been connected in different settings, such as anticipating the antimicrobial movement of Quinoxaline 1,4-dioxider and analyzing the pain relieving action of semi-synthetic opioid opiates like morphinan-6. The investigation shown that phenolic and nonphenolic compounds tie at diverse locales or by means of elective components. For erythromycin esters, the Free-Wilson strategy outflanked the Hansch strategy, yielding an condition withof 0.986 and s of 0.072, recommending a stronger relationship with action. This strategy is additionally successful for peptide investigation, centering on person amino acids without obstructions from others. Applications incorporate ACTH-related peptides and bradykinin potentiating peptides. In spite of confinements, the Free-Wilson strategy gives important experiences in different scenarios.

7. Quantitative Structure-Pharmacokinetic Relationship:

QSAR strategies broadly explore physical-chemical properties related to assimilation, dispersion, digestion system, and excretion (ADME). Expanding log P is related with improved retention and liver digestion system, whereas urinary excretion diminishes. Be that as it may, QSAR uncovers deviations from anticipated direct connections. Lipophilicity is crucial for protein authoritative, but auxiliary highlights moreover play a noteworthy part, as appeared in plots of binding constants against log P for diverse drugs.

8. Quantitative Structure-Toxicity Relationship:

QSAR strategies are progressively utilized in toxicology and biological sciences to anticipate the mutagenicity of compounds. Hansch's ponders shown that hydrophobicity is the essential calculate affecting mutagenicity, with steric and electronic parameters being auxiliary. QSAR has too been viable in evaluating the carcinogenicity and mutagenicity of different amines, appearing a critical relationship between their potencies. Moreover, lipophilicity influences the bioconcentration of pesticides within the nourishment chain [40].

CONCLUSION :

Medicate plan and conveyance may be a complex and crucial prepare in pharmaceuticals, including a few key stages. The predisccovery stage builds up the foundation through broad inquire about and target distinguishing proof, directing future improvement endeavors. Transitioning from hit revelation to lead disclosure is basic for narrowing down promising compounds, upgrading effectiveness in sedate improvement. Preclinical thinks about play an fundamental part in evaluating security and adequacy, permitting for early elimination of risky candidates and moderating assets. The ultimate medicate advancement organize coordinating past endeavors to deliver market-ready medicines, bridging logical advancement and quiet care. Quantitative Auxiliary Examination (QSAR), particularly Hansch examination, serves as a prescient device with broader applications in medicate plan. Its integration with progressed computer-aided plan procedures, such as atomic design and 3D QSAR, highlights its developing significance. In spite of blended comes about in examining chiral drugs, compelling descriptors give bits of knowledge into utilitarian bunches in compounds, showing that alterations can progress pharmacological action and physicochemical properties. This consider emphasizes understanding the organic exercises of sedate particles through auxiliary examination.

REFERENCE :

1. Gaynes R, "The discovery of penicillin—new insights after more than 75 years of clinical use" *Emerg Infect Dis*. May 2017:5.
2. Pammolli F, Magazzini L, Riccaboni M "The productivity crisis in pharmaceutical R&D" *Nat Rev Drug Discov* June 2011:10.
3. C. T. Keith et al., "Multicomponent therapeutics for networked systems" *Nat. Rev. Drug Discov* January 2005:4.
4. J. Jia et al., "Mechanisms of drug combinations: Interaction and network perspectives" *Nat. Rev. Drug Discov* February 2009:8.
5. M. J. Keiser et al., "Relating protein pharmacology by ligand chemistry" *Nat. Biotechnol*, February 2007:25.
6. E. Lounkine et al., "Large-scale prediction and testing of drug activity on side-effect targets" *Nature*, June 2012:10.
7. M. Kuhn et al., "Systematic identification of proteins that illicit drug side effects" *Mol. Syst. Biol*, April 2013:9.
8. A. Cami et al., "Predicting adverse drug events using pharmacological network models" *Sci. Transl. Med*, December 2011:3.
9. Rognan D, "Chemogenomic approaches to rational drug design" *Br J Pharmacol*, September 2007:152.
10. Zheng D et al., "Automated protein fold determination using a minimal NMR constraint strategy" *Protein Sci*, June 2003:12.
11. Oezguen N et al., "Automated assignment and 3D structure calculations using combinations of 2D homonuclear and 3D heteronuclear NOESY spectra" *J. Biomol. NMR*, March 2002:22.
12. Bailey-Kellogg C et al., "The NOESY jigsaw: automated protein secondary structure and main-chain assignment from sparse unassigned NMR data" *J. Comput. Biol*, July 2000:7.
13. Riccardo Zanni et al., "Latest advances in molecular topology application for drug discovery" *Expert Opin Drug Discov*, July 2015:10:9.
14. Stephani Joy Y Macalino et al., "Role of computer aided drug design in modern drug discovery" *Arch Pharm Research*, September 2015:38:9.
15. Nikita S. Patil et al., "A Review on Drug Design by the Application of Computer" *Journal of Advanced Pharmaceutical Science and Technology*, April 2022:3:1.
16. Chopra G et al., "Combating Ebola with Repurposed Therapeutics Using the CANDO Platform" *Molecules*, November 2016:21.
17. Lindsay MA, "Target discovery" *Nature Reviews Drug Discovery*, October 2003:2.
18. Terstappen G et al., "Target deconvolution strategies in drug discovery" *Nature Reviews Drug Discovery*, November 2007:6.
19. Imming P et al., "Drugs their targets and the nature and number of drug targets" *Nature Reviews Drug Discovery*, October 2006:5.
20. Dunne A et al., "Use of primary cells in high throughput screens" *Meth Mol Biol*, January 2009:162.
21. Zhang JH et al., "A simple statistical parameter for use in evaluation and validation of high throughput screening assays" *J Biomol Scr*, April 1999:4.
22. Patidar AK et al., "Lead Discovery and lead optimization: A useful strategy in molecular modification of lead compound in analog design" *International Journal of Drug Design and Discovery*, July 2011:2.
23. Steindl T.M et al., "Parallel screening: a novel concept in pharmacophore modelling and virtual screening" *J Chem Inf Model*, September-October 2006:46.
24. Koch M.A et al., "Charting biologically relevant chemical space: a structural classification of natural products (SCONP)" *Proc Natl Acad Sci USA*, November 2005:102.
25. Huber W, "A new strategy for improved secondary screening and lead optimization using high-resolution SPR characterization of compound-target interactions" *J Mol Recogn*, July-August 2005:18.
26. Friedman LM et al., "Fundamentals of clinical trials," 4th ed, New York: Springer Science and Business Media LLC, January 2010:3.
27. Sewell F et al., "The current status of exposure-driven approaches for chemical safety assessment: a cross-sector perspective" *Toxicology*, August 2017:11.
28. Redington J et al., "Role of antimicrobial pharmacokinetics and pharmacodynamics in surgical prophylaxis" *Rev Infect Dis*, September-October 1991:13.
29. Craig WA et al., "Pharmacodynamics of amikacin in vitro and in mouse thigh and lung infections" *J Antimicrob Chemother*, May 1991:27.
30. Leggett JE et al., "Comparative antibiotic dose effect relations at several dosing intervals in murine pneumonitis and thigh-infection models" *J Infect Dis*, February 1989:2.
31. Craig WA et al., "Postantibiotic effect" In: Lorian V, editor. *Antibiotics in laboratory medicine*, Baltimore: Williams and Wilkins, May 1996:5.
32. Satinder Ahuja et al., "Handbook of modern pharmaceutical analysis," Academic Press, 2001, vol 3, pp. 180-186.
33. DiMasi J, "Risks in New Drug Development: Approval Success Rates for Investigational Drugs" *Clinical Pharmacology & Therapeutics*, May 2001:5.
34. Friedhoff L, "New Drugs: An Insider's Guide to the FDA's New Drug Approval Process for Scientists, Investors and Patients" New York, NY: PSPG Publishing, June 2009:1.
35. Dr. Samesh Ahemad M-Abdelghany, "Computer aided drug design, section-1, slide 10-11."
36. Matthew E Welsch et al., "Privileged scaffolds for library design and drug discovery" *Curr Opin Biol*, June 2010:14:3.
37. Jitender Verma et al., "3D-QSAR in drug design" *Current Topics in Medicinal Chemistry*, 2010:10:1.
38. Shanno Pathan et al., "Quantitative Structure Activity Relationship and Drug Design" *International Journal of Research in Biosciences*, September 2016:5:4.
39. Pontiki Eleni et al., "Review in quantitative structure activity relationships on lipoxygenase inhibitors" *Mini Rev Med Chem*, August 2003:3:5.
40. Edward E. Hodgkin et al., "Molecular similarity based on electrostatic potential and electric field" *International Journal Quantum Chemistry*, March 1987:32:14.