Structure-Activity Relationships for the Design of Small-Molecule Inhibitors

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Abstract: One of the most important stages of the drug discovery process is the generation of lead compounds. Structure-activity relationships (SAR) are well-integrated in modern drug discovery and have been largely used for the finding of new leads, scaffold generation, the optimization of receptor or enzyme affinity, as well as of pharmacokinetic and physicochemical properties. This review highlights some SAR approaches that can be used to optimize leads through a continuous, multi-step process based on knowledge gained at each stage, thus exploiting SAR in the design of selective, potent, small-molecule drug candidates.

Keywords: SAR, drug design, enzyme inhibitors, COX-2, protein kinase, QSAR, ADME.

INTRODUCTION

The drug discovery process has changed dramatically over the past decade and continues to evolve in response to new discoveries, technologies, and increasing demands for more drug candidates to treat unmet medical needs for important human diseases and disorders. The entire drug discovery and development process takes between 12 and 15 years and costs about US$ 800 million [1-3]. In general, it is believed that each major pharmaceutical company needs to launch three or four new drugs a year to sustain the present level of growth. Interestingly, productivity over the past few years has been well below this level even though the R&D budget across the industry has substantially increased.

The completion of the human genome sequence is having a profound impact on biomedical research in terms of the very large number of potential drug targets available [4-6]. Current and future challenges will be directed to validating new drug targets for drug development. One approach to this problem is to rapidly identify active low-molecular-weight ligands that interact and modify the biological functions of selected targets (e.g., enzymes, membrane proteins, DNA) [7,8]. These bioactive ligands can be used directly to validate the targets in cell-based assays and serve as leads for drug discovery. Once a drug target is identified and validated, the traditional drug development process begins with the discovery of new bioactive molecules, and then travels successfully through the clinical trials to the endpoint of therapeutically useful drugs.

The widespread use of combinatorial chemistry and high-throughput screening (HTS) technologies for the discovery of lead compounds has created a large demand for small organic molecules that act on specific drug targets [9-11]. Hits can be accessed from screening chemical libraries or natural products. Enhancements in the ability to quickly select between lead candidates, improve potency, and identify toxicological and pharmacokinetic properties are needed to address this bottleneck in the drug development pipeline [12,13].

The study of structure-activity relationships (SAR) has maintained its importance throughout the history in pharmaceutical research, especially in the design of new drug candidates. This is supported by an exponential increase in the number of potential hits that need to be optimized for a number of different properties. SAR is a continuous refinement of structural requirements for biological activity [14]. The design of new ligands (lead optimization) is performed in several cycles. Experimental and theoretical approaches can be used to aid the SAR studies and to speed up the drug discovery process [15].

This brief review provides a perspective of the utility of SAR approaches that lead to the development of several new ligands. It should be noted that we will show some examples of small-molecule inhibitors of cyclin-dependent kinase (CDK) and cyclooxigenase-2 (COX-2) only to discuss the use of SAR approaches. There are many excellent reviews available in the literature and the readers will be referred to them for more detailed analysis.

SAR, LEAD OPTIMIZATION AND DRUG DESIGN

Typically, the structures of leads are modified by synthesis to amplify the desired activity and minimize or eliminate the undesirable properties. The newly synthesized analogs are further screened and the subsequent generation of a sufficient amount of data and information is the essential basis for future SAR studies. Provided that selected active compounds have exhibited target affinity or activity, lead compounds with defined structural scaffolds can be envisaged, and from this point focused libraries of new compounds can be generated to add new values to the hit-to-lead and lead optimization stages. In this effort, diagnosis of mechanism, prediction of activity, classification, optimization, and refinement of synthetic targets can be achieved via SAR. In order to appreciate mechanisms of drug action it is important to understand the forces of interaction

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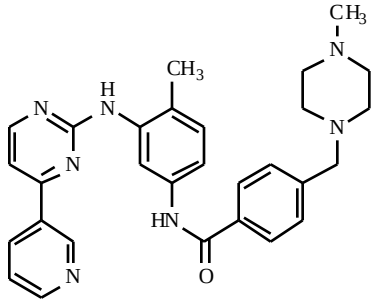
that bind drugs to their receptors. The forces involved in drug-receptor complex include covalent bonding (the strongest bond), ionic (or electrostatic) interactions, ion-dipole and dipole-dipole interactions, hydrogen bonding, charge-transfer interactions, hydrophobic interactions, and van der Waals interactions. In general, the bonds formed between drugs and receptors are weak noncovalent interactions, consequently, the effects produced are reversible. These weak interactions are usually possible only when molecular surfaces are close and complementary. The mechanism of drug-receptor interaction constitutes the pharmacodynamic phase of the process. However, the intensity of a biological response produced by a drug is related to the concentration of the drug at the site of action, which is in turn affected by a variety of processes called pharmacokinetics. The integration of pharmacokinetics/-pharmacodynamics studies has proven to be a powerful tool in drug discovery and development.

The emergence of new chemical entities (NCEs) with potential therapeutic application for the treatment of a large number of human diseases requires the optimization of several properties at early stages in the lead discovery process. Ideally, the characteristics of future compounds must be drug-like. ADME/Tox (Absorption, Distribution, Metabolism, Excretion, and Toxicology) properties have to be considered at the design process to decrease the late-stage failure rate traditionally associated with the discovery process [10,16,17]. The main objective is thus to focus on only the



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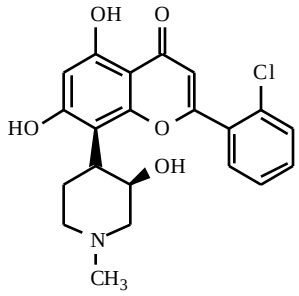

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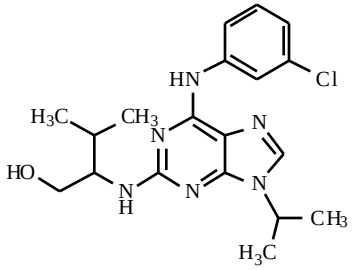

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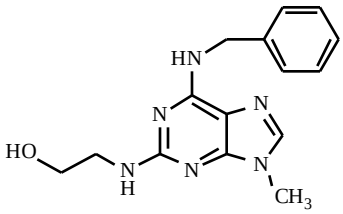

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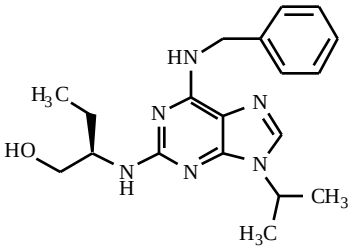

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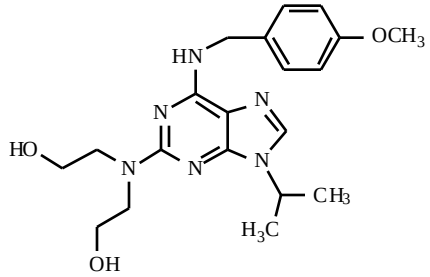

6 CVT-313
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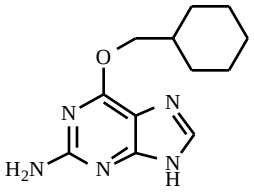

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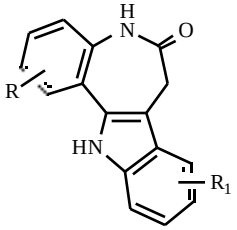
University of Newcastle



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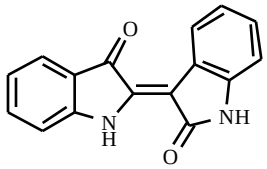

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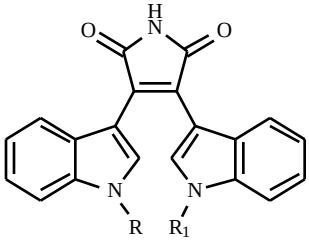

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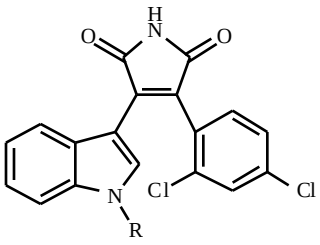

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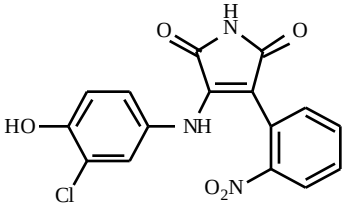


12 SB-415286

Fig. (1). CDK/GSK-3 inhibitors.

most promising compounds, increasing the likelihood of producing better clinical candidates.

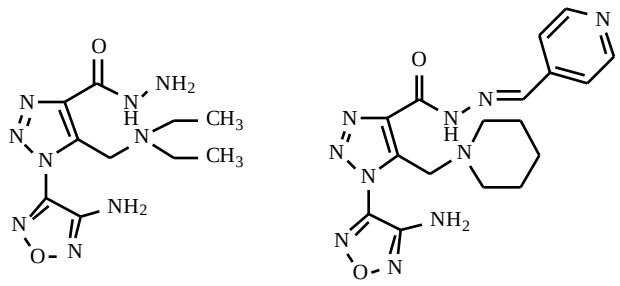
SAR are also required to be knowledge-oriented in order to derive correlations between molecular properties and biological effects [18]. It involves a balance of bio-physicochemical requirements for the molecules to reach its site of action at concentrations sufficient to promote the therapeutic response. In general, SAR approaches take account of the basic physicochemical properties that have been shown to be most useful for predicting pharmacokinetic properties. These include, for example: i. Lipophilicity - often expressed as a partition or distribution coefficient (log *P* or log *D*) between octanol and aqueous phases. Lipophilicity significantly impacts ADME/TOX properties and is widely used in drug discovery for SAR studies. It is related to membrane permeability, absorption, distribution and clearance; ii. Solubility – affects both *in vitro* assay results and *in vivo* oral bioavailability. Poor aqueous solubility is one of the major causes for low systemic exposure and, consequently, lack of *in vivo* activity; iii. pK_a – affects solubility, lipophilicity, permeability and absorption. Acidic compounds tend to be more soluble and less permeable at high pH and basic compounds tend to be more soluble and less permeable at low pH. pK_a impacts biological activity and metabolism through electrostatic interaction; and, iv. Hydrogen bonding — affects both membrane permeability and overall water solubility of the compound. Permeability is an important factor for passage through physiological membranes, absorption through the gastric intestine (GI) tract, penetration through the blood–brain barrier (BBB) and so on. Many highly permeable compounds have low solubility and vice versa. The key for optimal pharmacokinetic properties is to find a balance between the different physicochemical properties.

Using SAR for several properties creates a different situation than its use with a single property. Although the same SAR principles can be applied, having multiple properties under analysis means that experimental data should be available for these properties. Moreover, this is not as simple as breaking down the problem into the optimization/prediction of individual biological or physicochemical properties, although this is a necessary step. It also involves the understanding that the summation of the properties is greater than the contribution of each part. Individual properties interact with each other to form the characteristics of a single molecule, which can become a drug. When SAR can be quantitatively measured, they become quantitative structure-activity relationships (QSAR) [19,20]. QSAR [or quantitative structure-property relationships (QSPR)] is an important technique that applies statistical analysis of potential relationships between chemical structure and biological activity and has been employed, both to correlate information in data sets and as a tool to facilitate drug design and development [21,22].

SAR STUDIES OF PROTEIN KINASE INHIBITORS

Protein kinases (PKs) [23] catalyze the phosphorylation of serine, threonine, and tyrosine residues of proteins. PKs, along with protein phosphatases [24-26], appear to play a key role in several human diseases [27]. Cyclin-dependent kinases (CDKs) [28-30] are involved in controlling the cell cycle [31,32], apoptosis, neurodegeneration, transcription, and exocytosis. Glycogen synthase kinase-3 (GSK-3) [33,34] is an essential element of the WNT signaling pathway [35]. A number of structurally diverse CDK/GSK-3 inhibitors have recently been identified (e.g., maleimide, diaminothiazole, oxalylpyridine, and adenine derivatives). Some selected examples of inhibitors are provided in Fig. (**1**) [27,36]. A new class of small-molecule (hydrazide derivatives) GSK-3 inhibitors with favorable pharmacokinetic properties was identified by HTS of the Novo Nordisk compound library followed by SAR optimization and bioisosteric replacements (Fig. (**2**)). Among these are compounds showing IC_{50} values in the range from 0.1 to 17 μM [37].

With the advent of the U.S. Food and Drug Administration (FDA) approved imatinib mesylate (**1**, Gleevec - Novartis; Fig. (**1**)), the first oral tyrosine kinase inhibitor for the treatment of chronic myeloid leukemia (CML), recent attention has been focused on the therapeutic usefulness of small-molecule inhibitors of other kinase targets [31], a protein family whose members contain a highly conserved active site. The success of Gleevec has shown that it is possible for kinase inhibitors that bind near the ATP binding site to possess sufficient selectivity to become useful drugs. However, the close structural similarity between the active sites of multiple family members remains a serious concern for drug discovery efforts.



13 **14**

IC_{50} = 17 μM IC_{50} = 0.10 μM

Fig. (2). Hydrazide derivatives as GSK-3 inhibitors.

Purine analogs as CDK enzyme inhibitors, originally discovered from screening collections of compounds that were meant to mimic ATP, are especially attractive because they are a large group of organic compounds that are easy to synthesize. Non-peptidic libraries have received the most attention in combinatorial approaches aimed at synthesizing compounds designed around such specific scaffolds. The structural and mechanistic information about the target (competitive-type inhibition of the ATP-binding pocket) is used in the design process to develop enhanced focused libraries. The ability to use the knowledge of the protein structure coupled with SAR analysis was a key endeavor in the identification and design of new CDK/GSK-3 inhibitors, which have been named aloisines [27]. Aloisines (pyrrolo[2,3-*b*]pyrazines), conveniently substituted at positions 2, 3, 5, 6 and 7 (Fig. (**3**)), have yielded valuable SAR information leading to the establishment of relationships between structure and activity displayed against various PKs.

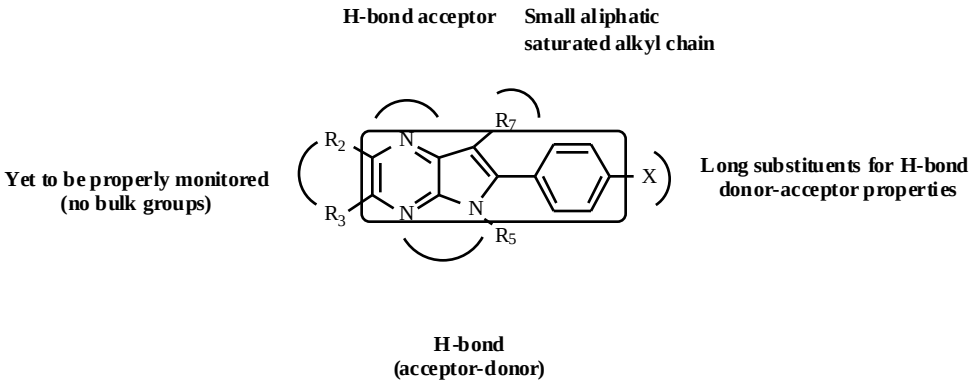


Fig. (3). Aloisine scaffold and SAR analysis.

Mettey *et al.* [27] synthesized a series of low-molecular-weight CDK-1, 2, 5 and GSK-3 inhibitors, carried out SAR studies, and determined the different contributions of individual moieties allocated in the aloisine scaffold (Fig. (**3**)). Polar groups were added to the phenyl moiety at position 6 of the pyrrolo ring (H-bond donors and acceptors, and high-density electron atoms), whereas apolar groups were added at position 7 of the pyrrolo ring (some homologation, alkyl-halogenation, double bond insaturation, ring-chain inclusion and transformation, and branching were applied). A small number of substitutions was made at positions 2, 3, and 5 of the aloisines. The positions 1, 4, and 5 of the pyrrolo-pyrazine fused ring were left unchanged due to the needed H-bonding processes (acceptor-donor) that take place in the binding site through the three nitrogen atoms, as revealed by the co-complex between aloisine B ($R_2 = R_3 = R_5 = H$, $R_7 = CH(CH_3)_2$, X = Cl; Fig. (**3**)) and CDK-2. Accordingly, replacement of nitrogen atoms by carbon atoms abolishes or diminishes inhibitory activities. The SAR studies produced a series of inhibitors with IC_{50} values ranging from >100 μM to 0.12 μM. The results led the authors to further investigate position 6. Although many aryl and hetero-aryl moieties were studied, none of the new compounds exhibited improved potency. The generalizations that can be derived from these findings are hypothesized in Fig. (**3**). On the other hand, selectivity of the aloisine A ($R_2 = R_3 = R_5 = H$, $R_7 = (CH_2)_3CH_3$, X = OH; Fig. (**3**)), the most potent inhibitor in the series (IC_{50} value ≈ 0.3 μM for CDK1/cyclin B, CDK5/p25, and GSK-3), was determined by assaying it against 26 highly purified kinases. GSK-3α/β and CDKs (IC_{50} values of 0.65 and 0.15 μM, respectively) were found to be the two kinase families of greater sensitivity to aloisines. Most protein kinase inhibitors bind to the ATP-binding site, thereby competing directly with ATP binding. There is, however, some evidence that non-ATP competitive GSK-3β inhibitors can be found for thiadiazolidinones (TDZD) (Fig. (**4**)) [38]. From preliminary SAR studies, bulky groups at *N*-2 are detrimental for binding affinities towards GSK-3β, whereas lipophilic moieties at *N*-4 maybe envisaged for a hydrophobic interaction site. Incorporation of a thiocarbonyl fragment at C-3 of the TDZD heterocyclic ring had little effect on IC_{50} values. Nevertheless, the H-bonding pattern should certainly be modified by the lack of such interactions with this thiocarbonyl moiety. The exchange of carbonyl to amino moieties at C-5 would prevent optimal binding. A molecular modeling study carried out with X-ray crystallographic structure of GSK-3β, corroborates these SAR findings well.

Overall, the scaffolds discovered and their respective substitutions imparted a quite reasonable application of the SAR efforts in the well-integrated drug design process: synthesis, pattern recognition SAR, enzyme inhibition, X-ray crystallography, and molecular modeling. The SAR for kinase inhibitors agreed with complementary sites in protein kinases, (i.e., if a compound is known to bind to a certain receptor) some of the regions defined in its site should actually overlap groups of the real receptor site. As a result, at least a subset of regions would be relevant for representing the binding properties of the ligand. Therefore, extensive SAR studies and active site characterization are important achievements encompassing enzyme inhibition and selectivity, as well as cellular effects.

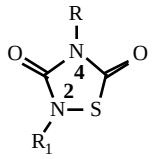


Fig. (4). Scaffold of the GSK-3 non-ATP competitive TDZD inhibitors.

SAR STUDIES OF SELECTIVE COX-2 INHIBITORS

Nonsteroidal anti-inflammatory drugs (NSAIDs) display their pharmacological action through inhibition of cyclooxigenase (COX). Two isoenzymes of COX enzyme have been identified: COX-1 and COX-2. Today, it is well-established that selective inhibition of COX-2 accounts for the anti-inflammatory and analgesic properties while inhibition of COX-1 accounts for the gastric and renal side effects of NSAIDs [39]. The rational design of selective COX-2 inhibitors provided a new class of anti-inflammatory, analgesic and antipyretic drugs. These include the diarylheterocycles celecoxib (**18**, Celebrex-Pharmacia/Pfizer) and rofecoxib (**19**, Vioxx-Merck), which successfully reached the market in 1999. Selective COX-2 inhibitors are designed to reduce or eliminate the gastrointestinal (GI) toxicity that can be found in traditional NSAIDs, such as aspirin (**15**) and ibuprofen (**17**). The second generation COX-2 inhibitors Pharmacia/Pfizer's valdecoxib (**20**, Bextra®) and Merck's etoricoxib (**21**, Arcoxia) aim for enhanced efficacy and further decreased GI toxicity. Arcoxia has been launched in 38 countries worldwide in Europe, Latin America and the Asia-Pacific region. Merck still seeks FDA approval to market the drug in the US. The chemical structures of some classical NSAIDs and those of COX-2 inhibitors are shown in Fig.

(**5**). The discovery of COX enzyme and development of selective COX-2 inhibitors have recently been the subject of extensive reviews [39-41]. SAR studies have shown that for optimum inhibitory potency and selectivity, a SO_2CH_3 or SO_2NH_2 substituent is required at the *para* position of phenyl ring (Fig. (**5**)).

A common strategy in pharmaceutical research consists in the use of well-established drugs as lead compounds to design new drug candidates with improved therapeutic properties. Analogs of selected leads are synthesized and evaluated to optimize their activity and minimize undesirable characteristics. Previously, Kalgutkar *et al*. [42] have reported detailed SAR studies on the identification of novel COX-2 selective inhibitors from the NSAID indomethacin (**16**; Fig. (**5**)), a well-known COX inhibitor. This involved the conversion of indomethacin into esters and amide derivatives via a single chemical derivation of the carboxylate moiety, using a biochemically based strategy [43]. Recently, Kalgutkar *et al*. [44] described SAR studies that led to the identification of meclofenamic acid derivatives as selective COX-2 inhibitors (Fig. (**6**)). Ester or amide derivatives of the nonselective COX inhibitor meclofenamic acid (**22**; Fig. (**6**)) were prepared by the treatment of the acid with the appropriate alcohol or amine in the presence of bis(2-oxo-3-oxazolidinyl)phosphonic chloride (BOP-Cl) and triethylamine, according to the general method described earlier [42,43]. Unlike indomethacin esters, alkyl or aryl esters of meclofenamic acid displayed low potency for both isoenzymes, whereas the primary amide derivatives of meclofenamic acid (**23**, **24**) displayed low-micromolar, but nonselective COX inhibition. Following their initial findings, further SAR studies were carried out only with *N*-(substituted) amide derivatives.

As noted in the Fig. (**6**), extension of the alkyl chain length in the alkylamide derivatives (**23**, methyl → **24**, octyl) significantly enhanced inhibitory potency against both COX-1 and COX-2, while improved selectivity was achieved by the incorporation of terminal halogens in the alkyl chain (**25**, **26**). Some *O*-substituted hydroxamate analogs (**27**, **28**, and **29**) also displayed high selectivity. For example, the introduction of a strong electron-withdrawing nitro group in the position 4 of the phenyl ring of **28** afforded **29** with improved selectivity for COX-2 over COX-1 of about 5-fold. SAR analysis on the selective COX-2 inhibitory profile was also undertaken *via* esterification of the carboxylate moiety in the amino acid portion of a small series of meclofenamic acid-amino acid conjugates. For example, two potent COX-2 inhibitors were identified (**31**,

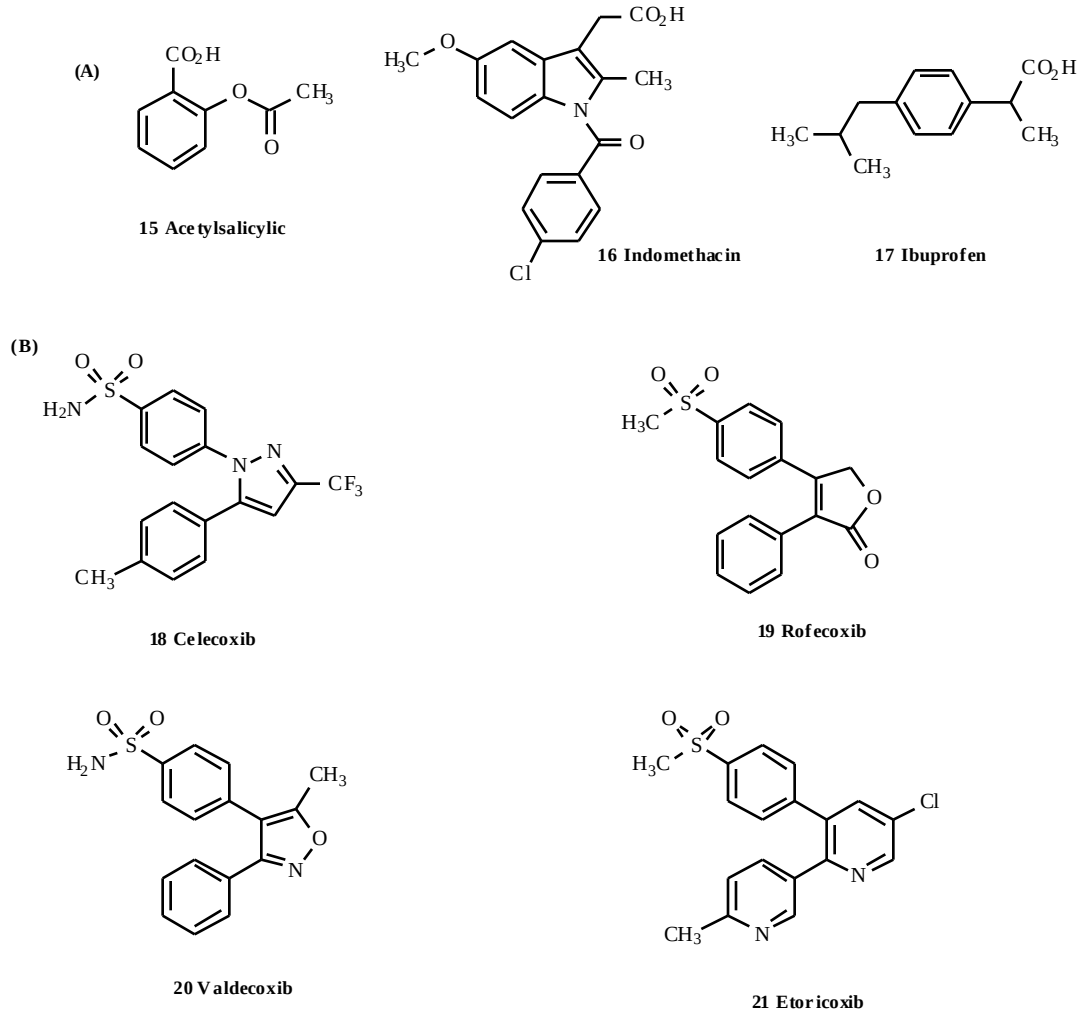
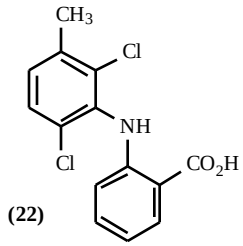
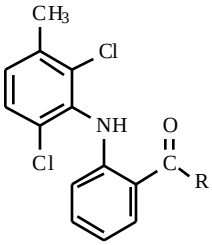


Fig. (5). Chemical structures of NSAIDs used in the treatment of pain and inflammation. (A) classical NSAIDs. (B) COX-2 inhibitors currently on the market.



(22)

Meclofenamic acid
IC_{50} = 0.05 μM (COX-2)
IC_{50} = 0.04 μM (COX-1)

Lead	No.	R	IC_{50} (μM) Cox-2	IC_{50} (μM) Cox-1	COX-2 / COX-1 *
	23	$NHCH_3$	> 2.0	> 2.0	--
	24	$NH(CH_2)_7CH_3$	0.05	0.06	1.3
	25	$NH(CH_2)_3Cl$	0.05	2.4	40
	26	$NH(CH_2)_2Br$	0.07	2.0	28
	27	$NHOCH_3$	0.5	55	110
	28	$NHOCH_2PH$	1.0	66	66
	29	$NHOCH_2$-(4-NO_2Ph)	0.2	66	300
	30	$NH(CH_2)Ph$	4.5	4.0	0.9
	31	$NHCH_2C(O)OCH_3$	0.07	1.2	17
	32	$NHCH_2C(O)OCH_2CH_3$	0.2	4.0	20
	33	$NH(CH_2)_2OPh$	0.15	66	440

* Selectivity: IC_{50} Cox-1/COX-2 [44].

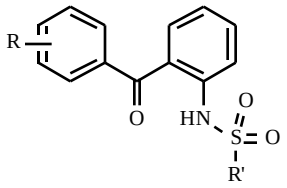
Fig. (6). SAR studies of the conversion of meclofenamic acid into COX-2-selective inhibitors.

32). SAR of the COX-1/COX-2 selectivity ratios for the analogs **28**, **29** and **33,** and for the amino acid conjugates **31** and **32** suggest that bulk aryloxy substituents seem to be detrimental for COX-1 inhibition. Since these derivatives are generated in a single step from the parent NSAID, combinatorial chemistry approaches may provide an easier access to more potent and selective meclofenamic acid analogs.

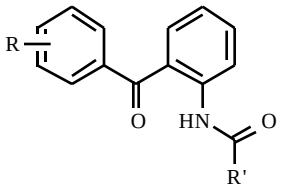
Many other novel structural classes of COX inhibitors have recently emerged as a result of molecular modifications of well-established NSAIDs scaffolds [45-47]. Diarylmethanones such as ketoprofen, tolmetine and ketorolac are known in the therapy of inflammation. Dannhardt *et al*. [48] reported SAR studies of a series of COX inhibitors using the diarylmethanone scaffold. In this study, several *N*-(aroylphenyl)sulphonamides and *N*-(aroylphenyl)benzamides (Fig. (**7**)) were synthesized and screened for their COX-1 and COX-2 inhibitory potency.

Many variations of the benzoyl, aniline and sulphonamide moieties were produced. For example, a small series of *N*-(2-benzoylphenyl)methanesulphonamides substituted only at position 4' of R (R = H, CH_3, CH_3S, Ph, and *tert*-butyl; R' = CH_3) exhibited no noticeable inhibitory activity against COX-2. On the other hand, the *N*-(2-benzoylphenyl)benzamides (R = Ph, R' = Ph, 4-CH_3-Ph, or 4-Cl-Ph) were balanced dual inhibitors of COX-1 and COX-2 (selectivity index COX-1/COX-2: 0.52-0.82), with the activity increasing from the unsubstituted compound to the chloro derivative (IC_{50}^{COX-1} = 0.18 μM, IC_{50}^{COX-2} = 0.24 μM) in both cases. In general, benzamide derivatives were more potent than the corresponding sulphonamides. However, all the investigated compounds preferentially inhibit the COX-1 isoform.

SAR approaches often involve the synthesis of analogs containing a range of substituents on the aromatic or heterocyclic ring or accessible functional groups. There are an infinite number of possible analogs, which can be made if one tries to synthesize analogs with every substituent and all possible combinations. Therefore, it is clearly advantageous to use a rational approach to guide the selection of which substituent or modifications to use. QSAR approaches have been proved extremely useful in tackling this problem. By



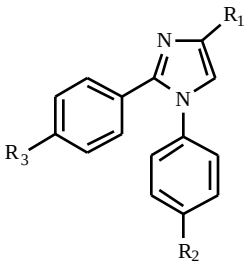
N-(aroylphenyl)sulphonamides



N-(aroylphenyl)benzamides

Fig. (7). SAR studies of Diarylmethanone-derived COX inhibitors.

quantifying physicochemical and biological properties derived from SAR studies, QSAR models can be developed to predict the biological activity of new analogs not synthesized yet. The advantage is that only the most promising compounds will be synthesized and thus cut down the number of analogs that need to be made.



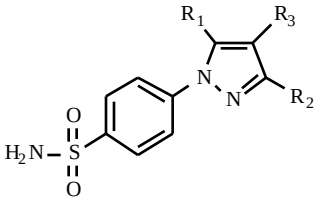
R_1 = mostly CH_3 or CF_3
R_2 and R_3 = variously substituted

Fig. (8). 3D QSAR and docking studies of 1,2-diarylimidazole derivatives.

Desiraju *et al*. [49] reported results of 3D QSAR studies of a large series of substituted 1,2-diarylimidazoles (Fig. (**8**)), structurally related to celecoxib and rofecoxib (Fig. (**5**)), with the goal to optimize their COX-2 selective anti-inflammatory activities. CoMFA (comparative molecular field analysis) and CoMSIA (comparative molecular similarity indices analysis) methodologies [50,51], which includes steric, electrostatic, hydrophobic, and hydrogen bond donor and acceptor fields, were employed to create QSAR models. These studies produced models with very good correlation coefficients (cross-validated r^2 values of 0.568 for the CoMFA 1 - database alignment, and of 0.488 for the CoMFA 2 - field fit alignment), and good predictive abilities. Overall, CoMSIA models had slightly higher predictive abilities than the CoMFA models. The CoMSIA model developed by employing five fields (steric, electrostatic, lipophilic, donor and acceptor) produced a cross-validated r^2 of 0.774 with seven components, indicating the importance of contributions from all fields to the biological activity. In addition, the 1,2-diarylimidazole derivatives were docked into both COX-1 and COX-2 active sites. The docking studies gave good insights into the COX-2 ligand interactions. Interestingly, the correlation of the 3D QSAR data and the docking results mutually validated the intermediacy of a binding step in overall drug action. These models should be useful in the design of new COX-2 selective inhibitors as anti-inflammatory agents with reduced effects.

The combination of molecular docking and 3D QSAR approaches was also reported by Liu *et al*. [52]. The binding models of a series of 40 1,5-diarylpyrazole analogs (Fig. (**9**)) were studied against COX-2 and the COX-2/COX-1 selectivity using automated docking approaches. 3D QSAR models were constructed employing CoMFA and CoMSIA methodologies. The final goal was to obtain predictive QSAR models involving the main intermolecular interactions between inhibitors and COX-2. The use of these approaches resulted in highly predictive and interpretable models showing promising potential in the design of new synthetic COX-2 inhibitor candidates.

Palomer *et al*. [53] reported pharmacophore generation based on the structure of the known selective inhibitors and on the 3D structure of COX-2 inhibitor complexes, followed by ligand design and screening of compounds structurally related to indomethacin (**16**, Fig. (**5**)) to identify novel selective COX-2 inhibitors. The application of the resulting pharmacophore to the design of indomethacin analogs having the basic *N*-benzyl- or *N*-benzoyl-5-sulfonylindoleframework (Fig. (**10**)) allowed the identification of a small set of simple, novel COX-2 selective inhibitors structurally related to indomethacin. For example, the successful modeling results and SAR led to the discovery of compounds **34**-**36** as being



R_1 = variously subtituted phenyl group
R_2 = mostly CF_3 (CHF_2, H, $COOCH_3$, $CONH_2$, CN, or CH_2OCH_2Ph were also used)
R_3 = mostly H (Cl, CH_3, CH_2CH_3, OCH_3, CN, SO_2CH_3, or NH_2 were also used)

Fig. (9). General structures of the 1,5-diarylpyrazoles employed in molecular docking and 3D QSAR studies.

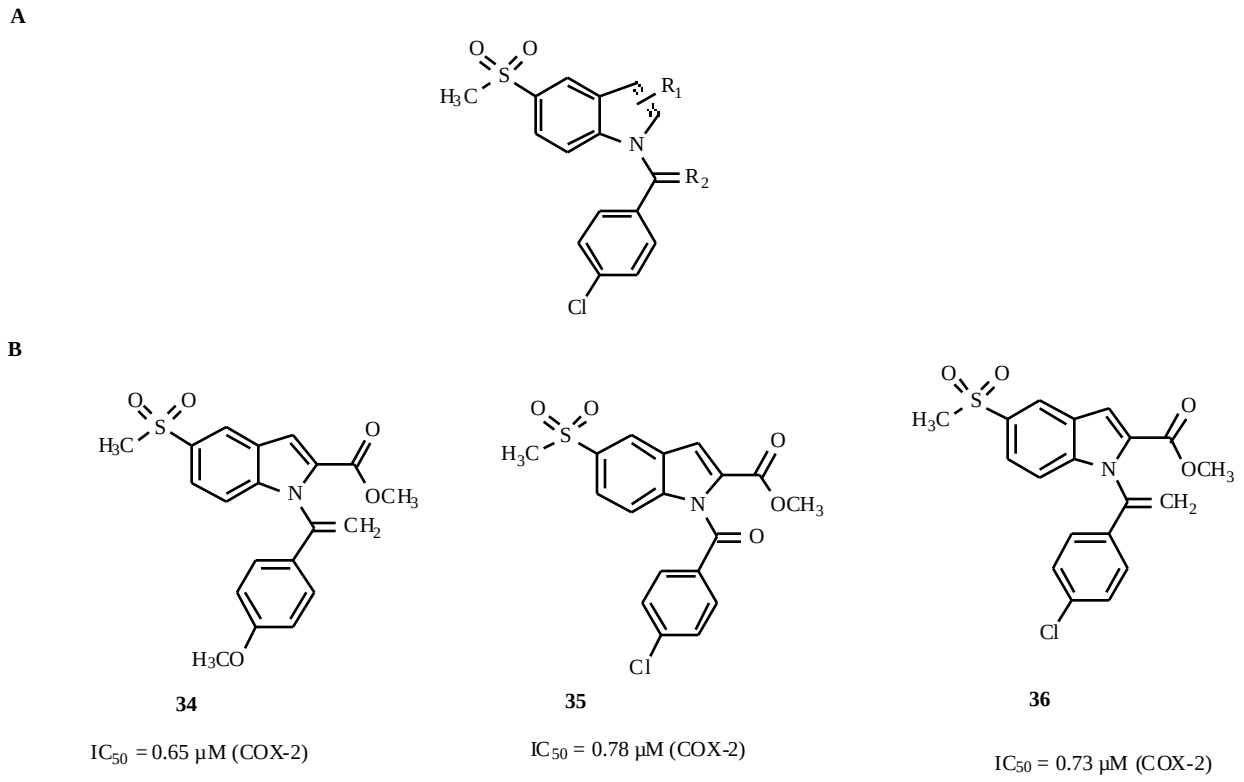


Fig. (10). Inhibitor design. (A) basic indole framework. (B) potent COX-2 inhibitors.

potent inhibitors of the COX-2 from human monocytes, with hardly any effect on the COX-1 ($IC_{50}^{COX\text{-}1} >> 10$ μM) from human platelets. After further investigation of these compounds in the human whole blood assay, compound **34** was confirmed as a promising candidate for further pharmacological studies.

CONCLUSIONS

Success in drug discovery is dependent on the ability to identify novel, patentable NCEs that have the potential to treat human diseases in a safe and efficacious manner. The use of SAR as a tool for drug discovery has seen numerous advances since its first use many decades ago. These advances are not just limited to technological advances in the field of medicinal chemistry, but also include creative and innovative new ways of using SAR and combining it with a variety of technologies (e.g., NMR, X-ray crystallography, molecular modeling, QSAR). Traditional SAR studies are carried out to determine those atoms or functional groups that are important to a drug's activity. This includes variation of substituents, chain extensions or contractions, ring substitutions, ring fusions, isosteres and bioisosteres, simplification of the structure, etc. The application of SAR to lead discovery and development will continue to yield diverse classes of compounds as leads for an equally diverse range of biological targets and properties. The cycle of SAR has evolved to focus not only on potency, efficacy and selectivity but also on drug-like properties that are required to be optimized as well. The optimization of multiple properties (e.g., potency, selectivity, ADME) will require more data on diverse molecules, obtained in an accurate, precise and reproducible fashion. Discovery informatics and data-mining methods will be crucial components to addressing the changing of the pharmaceutical industry. Methods will need to incorporate a rational way to analyze larger and more diverse datasets. The application of SAR approaches in drug discovery is likely to remain prevalent through the continual development of medicinal chemistry. However, it is no longer sufficient to perform SAR studies using data from a single biological assay or physicochemical property. The output of a drug discovery program should be a molecule that possesses as many of the ideal characteristics of a drug as possible.

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