The Impact of Lipophilicity in Drug Research: A Case Report on ß-Blockers

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Abstract: The key importance of lipophilicity in bio-studies is discussed for ß-blockers. Examples of their lipophilicity-dependent pharmacological properties including pharmacokinetic, pharmacodynamic and clinical aspects are reviewed. Comprehensive lipophilicity compilations of ß-blockers are lacking so far. LogP calculations with 10 programs for 30 clinically relevant ß-blockers are presented for the first time in this review.

Keywords: ß-blockers, pharmacokinetic, pharmacodynamic and clinical properties, lipophilicity, logP calculation programs, logP compilation for ß-blockers.

1. INTRODUCTION

The importance of lipophilicity as a descriptive parameter in bio-studies [1-3] is nowadays acknowledged by its frequent use in an increasing number of research fields including environmental and pharmaceutical sciences, medicinal chemistry and toxicology. The hydrophobic interactions of drugs with their receptors, the pharmacokinetic behaviour of drug molecules, as well as the toxicological properties of drugs are examples for the large number of topics in which lipophilicity plays a major role. An emerging field of application is in combinatorial chemistry. In the design of compound libraries, lipophilicity data can be used as estimates for oral absorption as an important contribution to bioavailability. Consequently, logP is included as a parameter in the well-known, rule of five" work of Lipinski *et al*. [4], dedicated to define the drug-likeness of compounds.

The relevance of lipophilicity for many aspects of biological activity is well-known to everybody involved in drug research. The spectrum of lipophilicity-dependent properties of ß-blockers, however, is particularly broad and even new aspects are added. In patients with myocardial infarction and congestive heart failure some ß-blockers have been found to reduce mortality and morbidity. These beneficial properties are only observed with ß-blockers exhibiting moderate to high lipophilicity [5-7].

Examples of lipophilicity-dependent pharmacological properties of ß-blockers are reviewed in this paper. In contrast to the biological relevance, comprehensive lipophilicity compilations of ß-blockers are lacking so far. Thus, such calculations were performed here with 10 different logP programs for a set of 30 clinically relevant ß-blockers; for chemical structures see (Fig. **1**).

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2. RELEVANCE OF LIPOPHILICITY FOR THE PHARMACOLOGICAL PROFILE OF ß-BLOCKERS

2.1. Pharmacokinetic Properties

Lipophilicity is a key factor in drug disposition. Increased lipophilicity has been shown to correlate with poorer aqueous solubility, increased rate of skin penetration, increased plasma protein binding, increased storage in tissues, as well as more rapid metabolism and elimination, to mention a few.

Controlled administration of ß-blockers via a transdermal delivery system could improve their systemic bioavailability and therapeutic efficacy by avoiding first-pass effect, as well as decreasing the dosing frequency required for the treatment. Accordingly, Ghosh *et al*. [8] studied the *in-vitro* permeation of nine ß-blockers across the hairless mouse skin and found a highly significant correlation between the skin permeability coefficients and ß-blocker lipophilicity, expressed as octanol/buffer distribution coefficients at pH 7.4.

Modamio *et al*. [9] carried out *in vitro* diffusion experiments with propranolol, oxprenolol, metoprolol, and atenolol using excised human abdominal skin. Including the results with celiprolol and bisoprolol, obtained in previous studies under identical experimental conditions, these authors could show that the variation in human skin permeability coefficients could be best explained by a parabolic relation to the partition coefficients of the six ß-blockers included. Corresponding plots indicate a plateau phase reached with propranolol. Thus, the inclusion of more lipophilic ß-blockers would be necessary to verify that really an optimum logP can be found for percutaneous permeation across human skin.

Kawazu *et al*. [10] measured ß-blocker permeation across cultured rabbit corneal epithelial cells grown on permeable supports. They could establish that the permeation data, obtained in their cell culture model, mimic those described in intact corneal epithelium [11] and thus facilitate characterization of ocular permeation mechanisms. A sigmoidal relation could be found between permeability coefficients and lipophilicity, expressed as partition coefficients, of eight ß-blockers including alprenolol, atenolol, metoprolol, nadolol, oxprenolol, pindolol, propranolol, and timolol.

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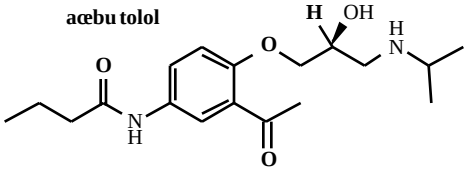
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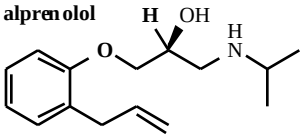
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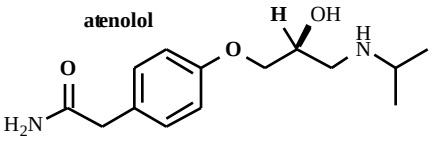
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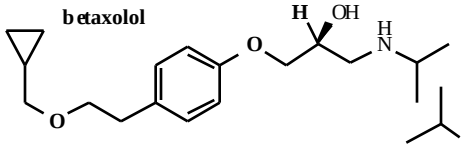
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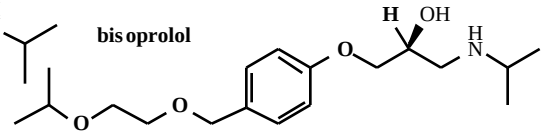
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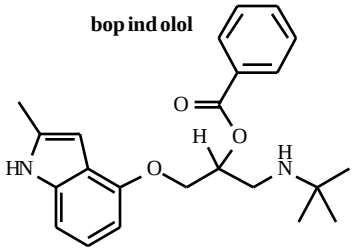
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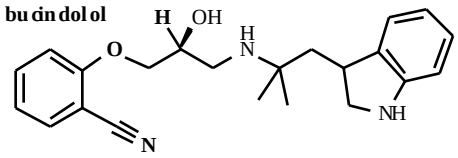
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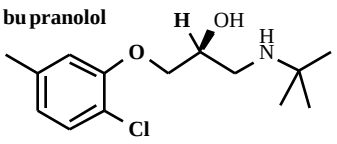
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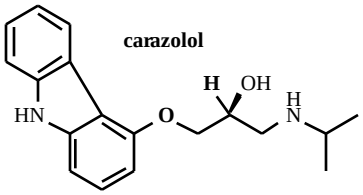
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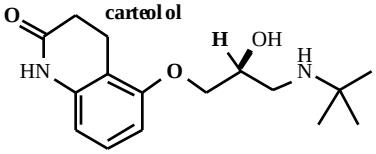
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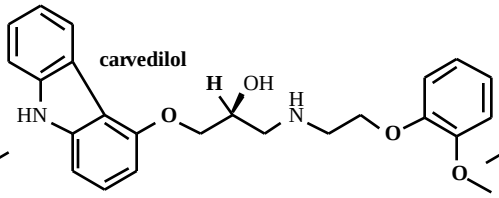
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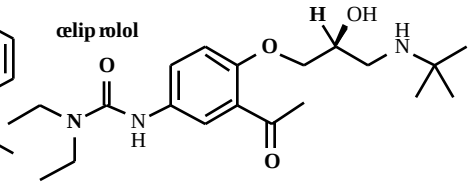
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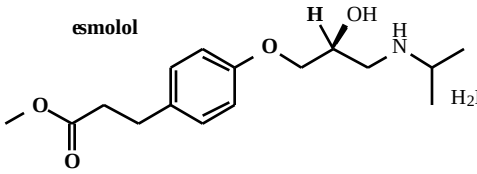
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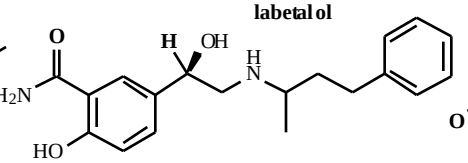
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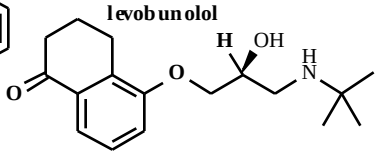
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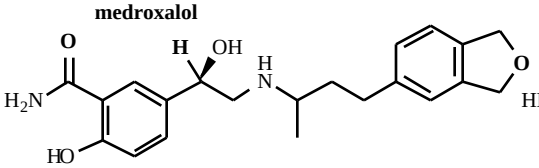
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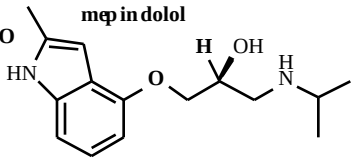
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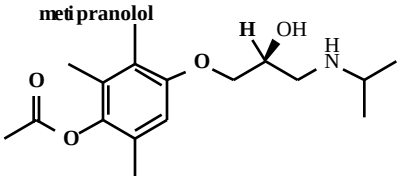
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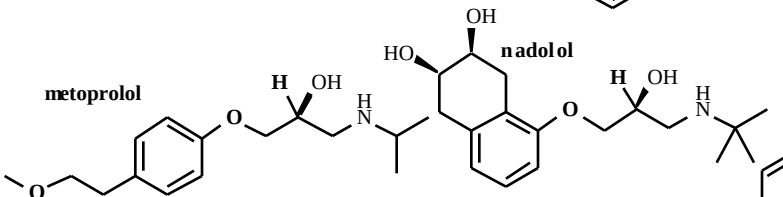
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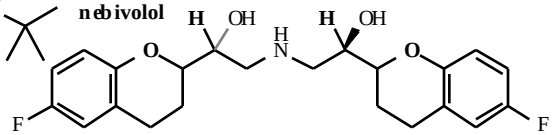
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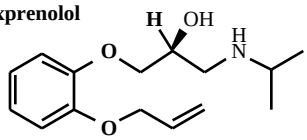
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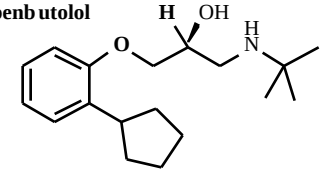
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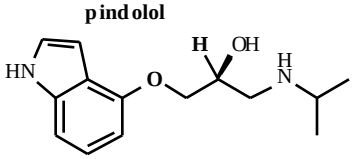
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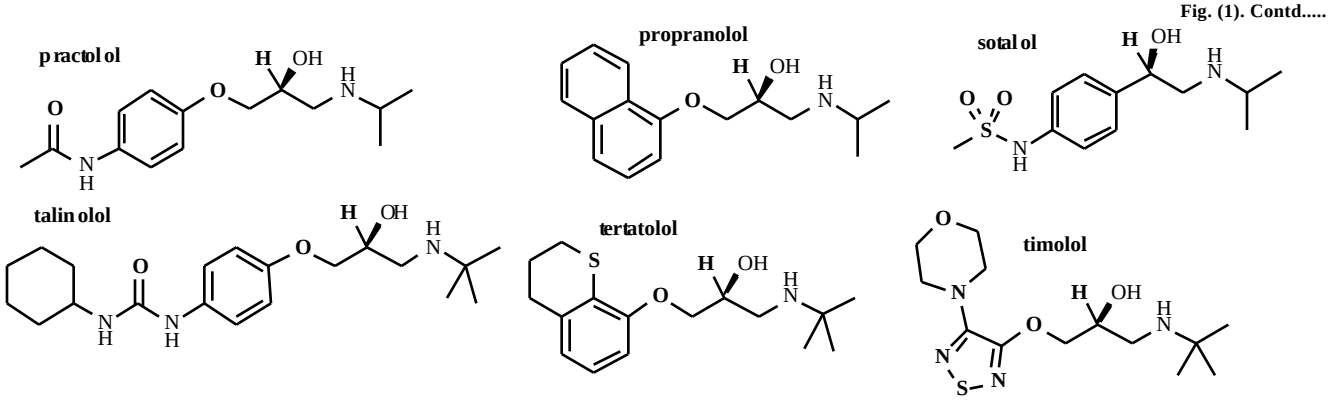

Fig. (1). Structures of the 30 ß-blockers included in this study.

In a comprehensive, sophisticated study, Caron *et al*. [12] validated experimental techniques for measuring the logP of protonated and neutral ß-blockers and investigated the inter- and intra-molecular forces influencing the partitioning behaviour in isotropic biphasic solvent systems including octanol/water, 1, 2-dichloroethane (DCE)/water, and dibutyl ether/water. The different information encoded in each system has pharmacokinetic implications. This could be demonstrated reinvestigating the data of Schoenwald and Huang [11]. In the latter paper, permeability coefficients of seven ß-blockers were parabolically related with their distribution coefficients in octanol/water; acebutolol behaved as an outlier. The frequent use of $\Delta\log P_{oct\text{-}alk}$ as a predictor of permeation led Caron *et al*. [12] to look for a relation between the corneal permeation data of Schoenwald and Huang [11] and $\Delta\log P_{oct\text{-}DCE}$ (which encodes the same H-bond donor contribution as $\Delta\log P_{oct\text{-}alk}$). Compounds having low ΔlogP values were shown to exhibit high permeability and vice versa. The corneal permeation data were also examined in relation with distribution coefficients in DCE/water, yielding a sigmoidal relation (r^2=0.96) with no outlier, indicating this descriptor to properly predict corneal permeation.

Taylor *et al*. [13] investigated the impact of lipophilicity on intestinal absorption characteristics of eleven ß-blockers by monitoring their disappearance from in-situ intestinal loops in the anaesthetized rat. Four members of the series (nadolol, atenolol, practolol, sotalol) exhibiting rather low logP values, show quite slow and almost identical absorption rate constants. For the more lipophilic compounds, however, significant correlations are observed between absorption rate constants and log D values, i. e. pH-corrected logP for ileum (pH = 7.3) and jejunum (pH = 6.5).

Ochs *et al*. [14] determined the clearance after oral application of propranolol, metoprolol, atenolol, and sotalol in nine healthy volunteers; clearance was highly correlated (r = 0.99) with the *in vitro* solubility using the liquid chromatographic retention index.

The multiple and interplaying aspects of lipophilicity-controlled pharmacokinetics of ß-blockers were comprehensively reviewed by van de Waterbeemd *et al*. [15]. First of all, these authors emphasise the importance of using unbound (free) pharmacokinetic data for probing the behaviour of drug molecules. This technique is particularly important when comparing properties that describe drug-like behaviour such as *in vitro* potency, rate of metabolism, plasma clearance, dose and duration. Van de Waterbeemd *et al*. [15] exemplify their considerations regarding the impact of physicochemistry including lipophilicity for drug design with a set of ten ß-blockers. One of the pharmacokinetic properties strongly guided by lipophilicity is volume of distribution. The major component of volume of distribution is the drug affinity for cell membranes, which in turn is derived from drug lipophilicity and basicity. Since ß-blockers all possess a similar basic centre, it is mainly the varying degree of lipophilicity which determines their volume of distribution. In another example, correlations of lipophilicity with unbound hepatic intrinsic clearance and with unbound renal clearance are compared. Unbound renal clearance is approximately constant for ß-blockers exhibiting low or moderate lipophilicity and probably declines with highly lipophilic ß-blockers. The amount of renally excreted ß-blockers declines dramatically with lipophilicity due to the increased importance of metabolic clearance; the latter is reflected by a strong positive correlation between the distribution coefficients of the ten ß-blockers and their unbound hepatic intrinsic clearance. Mainly responsible for metabolic clearance of ß-blockers are members of the cytochrome P450 (CYP) family of enzymes such as CYP2C19 and CYP2D6. Ferrari *et al*. [16] determined the affinity of bufuralol, propranolol, betaxolol, oxprenolol, LT18502, acebutolol, pindolol, and atenolol for human CYP2D6 *in vitro* by estimating the inhibition constants in a microsomal system with monitoring the kinetics of dextromorphan-O-demethylation. Lipophilicity was shown to be a key, but not the sole predictor of the affinity of the 8 ß-blockers. Last, but not least van de Waterbeemd *et al*. [15] debate the aspect that chemical drug manipulation can modify potency and key pharmacokinetic properties in a compensating manner. Using the illustrative examples of actual rate of metabolism and pharmacokinetic half-life, the authors underline the importance of concomitantly optimising on pharmacodynamic and –kinetic drug properties.

2.2. Pharmacodynamic Properties

Lipophilicity-dependent pharmacodynamics of ß-blockers refer to binding characteristics such as the dissociation of ß-blockers from their receptors and the ß-blocker selectivity for $ß_1$- and $ß_2$-adrenoceptors. Furthermore, lipophilicity has a major impact on additional pharmacodynamic actions of ß-blockers unrelated to ß-adrenoceptor blockade.

Bopindolol, a ß-blocker with very high lipophilicity (mean logP = 4.86), has been reported to possess a long duration of action with a high ß-adrenoceptor affinity and partial agonist activity. The group of Nagatomo [17, 18] used radioligand binding assays and functional pharmacological experiments to define the underlying mechanism of the long-lasting action of bopindolol in comparison to other ß-blockers. Comparative binding studies with or without preincubation of the test compounds as well as measurements of their residual inhibitory effects after washout on isoprenaline-induced contractions in left and right atria of guinea-pigs indicated a very slow dissociation of bopindolol and its metabolite 18-502 from ß-adrenoceptors, which may explain the long duration of antihypertensive effects of bopindolol [17]. In a later study [18], bopindolol was shown to act as a non-competitive antagonist, when used at higher concentrations. In a further paper [19], the same group could show for a set of ten ß-blockers and the bopindolol metabolite 18-502 that dissociation from ß-adrenoceptors slows down with increasing ß-blocker lipophilicity. These findings nicely correspond to a former study of Doggrell and Henderson [20] on the offset of ß-adrenoceptor antagonism of the responses of the rat right ventricle to isoprenaline. Investigating the effects of ß-blockers with low (atenolol), moderate (celiprolol), high (propranolol), and very high lipophilicity (bopindolol) clearly indicated a significant correlation between offset of action and lipophilicity.

Bree *et al*. [21] investigated the thermodynamics of ß-adrenoceptor binding of twenty agonists and antagonists and attributed a main discriminator role to ligand lipophilicity. Binding of the rather weakly lipophilic ß-adrenoceptor agonists is enthalpy driven; binding of the more lipophilic antagonists is entropy driven. However, binding of the lipophilic agonist dobutamine is thermodynamically similar to that of antagonists and underlines the guiding role of this physicochemical property.

El Tayar *et al*. [22] investigated the influence of lipophilicity and chirality on the selectivity of ligands for $ß_1$- and $ß_2$-adrenoceptors; the affinities of ten enantiomeric pairs of ß-adrenoceptor ligands in heart and lung tissues served as biological data. Their investigations showed that the affinity for $ß_2$-adrenoceptors is slightly more lipophilicity-dependent than that for $ß_1$-adrenoceptors. As a result, the $ß_1$-selectivity of the investigated $ß_1$-adrenoceptor ligands strongly and negatively correlated with their lipophilicity. Beyond it, El Tayar *et al*. [23] calculated molecular electrostatic potentials for 32 ß-blockers by quantum chemical methods and identified some stereoelectronic features responsible for their $ß_1$-/$ß_2$-selectivity.

Several additional pharmacodynamic actions of ß-blockers are unrelated to ß-adrenoceptor blockade. Many of these actions are predominantly controlled by lipophilicity. In an early study, Rauls and Baker [24] attempted to separate the non-specific antiarrhythmic effects from the specific, ß-adrenoceptor related negative inotropic effects, using propranolol analogues containing a naphthyl ring and N substituents with varying degrees of lipophilicity. Maximum driving frequency of isolated atria of the rabbit were used as screening procedure for antiarrhythmic and negative inotropic potency. Corresponding data showed a strong and very similar correlation with lipophilicity both for the antiarrhythmic and negative inotropic effects excluding a separation between the two effects, at least with the dataset used here.

Another membraneous effect of lipophilic ß-blockers – not related to ß-blockade – is the membrane stabilising activity (MSA), the molecular basis of which is a matter of debate. It has been suggested that ß-blockers interact with membrane phospholipids. On the other hand, as MSA is often explained in terms of blockade of the voltage-dependent sodium channel in neurons, it is conceivable that ß-blockers are capable of interacting with this channel, resulting in membrane stabilization. Thus, the MSA of 12 ß-blockers was studied by Ijzerman *et al*. [25] via their interaction with the [^{3}H]batrachotoxinin A 20-β-benzoate binding site on voltage-sensitive sodium channels in rat brain. All derivatives displaced the radioligand from its specific binding site; penbutolol exhibited the highest affinity. Multiple regression analyses, correlating biological activity with physicochemical properties, revealed a prime importance of lipophilicity, but steric factors are relevant as well. Accordingly, these authors suggest that the molecular basis of MSA of ß-blockers is their lipophilicity-controlled interaction with the voltage-dependent sodium channel.

Beneficial cardioprotective effects widen the therapeutic potential of ß-blockers. Mak and Weglicki [26] examined the effects of ß-blockers on free radical-mediated sarcolemmal lipid peroxidation. Highly purified canine myocytic sarcolemmal membranes were pretreated with 10 – 800 µM of propranolol, pindolol, metoprolol, atenolol, or sotalol at 37°C for 10 min. Subsequently, a superoxide radical driven, Fe^{3+}-ADP catalyzed free radical generating system was added and incubated for up to 45 min. Lipid peroxidation of sarcolemma was determined by malondialdehyde formation. Pretreatment of the membranes with the five ß-blockers resulted in various degrees of inhibition of sarcolemmal peroxidation in a concentration- and time-dependent manner. The order of potency of the ß-blockers was propranolol > pindolol > metoprolol > atenolol > sotalol and correlated to their degree of lipophilicity. Since increased free radical production occurs during myocardial ischemia/reperfusion injury, the above findings suggest that lipophilic ß-blockers provide additional antiperoxidative protection of ischemic tissue.

In a comparable study, Jenkins *et al*. [27] studied the effects of five ß-blockers on lipid peroxidation. Homogenates or liposomes of adult rat hearts were incubated in the presence of increasing concentrations of propranolol, labetalol, dilevolol, metoprolol, and atenolol. Lipid peroxidation was stimulated with 50 µM $FeSO_4$, 5 µM *t*-butyl hydroperoxide (homogenates) or 0.2 mM citrate $FeSO_4$ (liposomes) plus O_2 and assessed by both the thiobarbituric acid reaction and chemoluminescence. The five ß-blockers reduced lipid peroxidation both in crude homogenates and in liposomes; their effectiveness was lipophilicity-dependent.

Cardioprotective actions of ß-blockers against Ca^{2+}-overload induced by lysophosphatidylcholine (LPC) were the subject of a study by Chen *et al*. [28]. Using fura-2 for the measurement of $[Ca]_i$, these authors could show that

preincubation with lipophilic ß-blockers such as penbutolol and propranolol significantly inhibited the increase in $[Ca]_i$ induced by 15 µM LPC. On the other hand, pretreatment with less lipophilic ß-blockers like timolol or atenolol was ineffective. Investigation of the enantiomers of propranolol proved this protective effect to be unrelated to ß-adrenoceptor blockade. Inhibitory effects on Ca^{2+}-overload induced by LPC might represent an additional mechanism of the antiischemic effects of ß-blockers.

2.3. Clinical Aspects and Side Effects

Last, but not least the impact of lipophilicity on clinical aspects or in determining certain side effects of ß-blockers should be discussed in some detail. Cruickshank [29] comprehensively reviewed the clinical implications of the pharmacokinetic profile of ß-blockers differing with their degree of lipophilicity. Weakly lipophilic ß-blockers exhibit rather narrow inter-patient peak blood levels affording a certain predictability of drug action as reflected by the narrow dose range for both hypertension and angina. This contrasts with the large variation in peak blood levels of moderately and highly lipophilic, liver metabolised ß-blockers necessitating individualisation of dosage.

Weakly lipophilic ß-blockers tend to have long plasma half-lives; e.g. atenolol has a half-life of 6 to 9 h after a single dose, which does not change after chronic administration. Half-life of the highly lipophilic ß-blocker propranolol is only 2-3 h and it appears to lengthen after chronic administration. The long biological action of weakly lipophilic ß-blockers enables a low dose to be given once daily, resulting in 24h-cover for both hypertension and angina.

Weakly lipophilic ß-blockers are excreted virtually unmetabolised by the kidney. Normally, there is no significant drug accumulation, which occurs, however, in moderate to severe renal failure. In order to achieve optimal therapeutic blood levels, in that cases daily dosaging has to be accommodated accordingly. With highly lipophilic, liver metabolised ß-blockers there is likewise a tendency for increased blood levels in severe renal failure due to the accompanying liver dysfunction. Higher blood levels plus a marked accumulation of metabolites indicate dosage reduction.

Some ß-blockers with moderate to high lipophilicity such as timolol, metoprolol, and propranolol have been shown to decrease mortality in coronary heart disease, particularly sudden cardiac death. In the MAPHY (Metoprolol Atherosclerosis Prevention in HYpertension) study, a significant impact of metoprolol in reducing the rates of total mortality [30] and sudden cardiac death [31] could be shown. An overview of the findings of key studies illustrates that cardioprotective efficacy is associated with moderate to high lipophilicity [6]. In a study from Hjalmarson [7], ß-blockers with a proven effect on prognosis comprise carvedilol (mean logP = 3.91), propranolol (3.00), bisoprolol (2.27), metoprolol (1.89), and timolol (1.06). In contrast, ß-blockers with a lacking effect on prognosis like sotalol (0.44) and atenolol (0.33) are less lipophilic. The impact of lipophilic ß-blockers in secondary prevention trials was particularly evident in relation to sudden cardiac death [32]. Following findings might explain the efficacy of lipophilic ß-blockers to reduce risk for sudden cardiac death; ventricular fibrillation as the prime pathological precursor of sudden cardiac death is associated with acute myocardial ischemia, increased sympathetic drive, and most importantly decreased vagal tone [33-35]. Lipophilic ß-blockers that easily penetrate into the brain have been shown to increase vagal tone [34-37]. Enhancement of vagal tone was shown by instilling propranolol into porcine brain and the capability of ß-blockers to prevent ventricular fibrillation was correlated with lipophilicity and changes in vagal tone in rabbits [36].

Finally, some attention should be dedicated to side effects. Lipophilic ß-blockers readily penetrate into the brain and for that reason might cause more frequently central nervous side effects, like halluzination, vivid dreams, and sleep disturbance [38]. Data from Street and Walsh [39] are in line with these considerations. They examined ten ß-blockers for inhibitory effects on synaptosomal [^{3}H]noradrenaline uptake in synaptosomes of male Wistar rats. All compounds produced a concentration-dependent uptake inhibition. Inhibition was unrelated to ß-adrenoceptor blocking potency, but was highly correlated with lipophilicity. Street and Walsh [39] suggest that noradrenaline uptake inhibition may be mediated by an action on membrane phospholipids and that it may underlie certain central side effects observed with some ß-blockers.

Table 1. Classification Scheme for LogP Calculation Programs

Substructure Approaches	Whole Molecule Approaches
fragmental methods	*molecular lipophilicity potential*
CLOGP	CLIP
Σ*f* – SYBYL	HINT
AB/logP	MOLFESD
ACD/LogP	*topological indices*
KOWWIN	MLOGP
KLOGP	AUTOLOGP
CHEMICALC	VLOGP
atom contribution methods	T-LOGP
MOLCAD, TSAR	SciLogP ULTRA
PROLOGP	*molecular properties*
ALOGP98	BLOGP
SMILOGP	QLOGP
XLOGP	

Substructure and whole molecule approaches are the main subclasses of logP calculation programs: substructure approaches cut molecules into groups (fragmental methods) or atoms (atom contribution methods). Fragmental methods use corrections except CHEMICALC. Atom contribution methods work without correction factors except XLOGP. Whole molecule approaches inspect the entire molecule; they use either molecular lipophilicity potentials, topological indices or molecular properties to quantify logP.

However, the frequency of CNS adverse reactions does not seem to be exclusively dependent on relative ß-blocker lipophilicity [40]. CNS side effects such as tiredness and fatigue were found with the low lipophilic atenolol. Pindolol, a moderately lipophilic ß-blocker, has been

Table 2. Lipophilicity Calculations for 30 Clinically Relevant ß-Blockers

	fragmental				atom-based		whole molecule approaches				
compound	**AB/logP**	**ACD/logP**	**KOWWIN**	**CLOGP**	**XLOGP**	**ALOGP**	**HINT**	**CLIP**	**SciLogP**	**QLOGP**	**mean (±SD)**
acebutolol	1. 89	2. 11 ± 0. 36	1. 19	1. 71	1. 68	1. 95	3. 08	1. 75	1. 33	2. 20	1. 89 ± 0. 17
alprenolol	2. 89	2. 88 ± 0. 21	2. 81	2. 65	2. 84	2. 97	3. 35	3. 23	2. 58	3. 19	2. 94 ± 0. 08
atenolol	0. 44	0. 10 ± 0. 25	- 0. 03	- 0. 11	0. 46	1. 00	- 0. 48	0. 83	0. 70	0.35	0. 33 ± 0. 15
betaxolol	2. 77	2. 69 ± 0. 36	2. 98	2. 32	2. 37	2. 91	3. 18	3. 36	2. 84	3. 29	2. 87 ± 0. 11
bisoprolol	1. 94	2. 22 ± 0. 34	1. 84	2. 12	2. 16	2. 36	2. 59	3. 21	2. 04	2. 24	2. 27 ± 0. 12
bopindolol	5. 17	5. 46 ± 0. 77	4. 94	4. 98	5. 02	4. 65	4. 65	4. 83	3. 57	5. 29	4. 86 ± 0. 16
bucindolol	3. 79	3. 19 ± 0. 27	2. 84	3. 29	3. 42	3. 34	2. 66	2. 99	3. 10	4. 11	3. 27 ± 0. 14
bupranolol	3. 14	2. 97 ± 0. 23	3. 07	3. 10	3. 24	3. 32	3. 51	4. 14	3. 02	3. 45	3. 30 ± 0. 11
carazolol	3. 38	3. 37 ± 0. 74	2. 66	3. 06	3. 27	3. 46	2. 96	3. 30	3. 42	3. 22	3. 21 ± 0. 08
carteolol	1. 30	1. 67 ± 0. 24	1. 42	1. 29	1. 11	1. 61	2. 39	1. 96	1. 11	0. 99	1. 49 ± 0. 14
carvedilol	4. 33	4. 23 ± 0. 31	3. 05	4. 04	3. 76	4. 34	4. 10	4. 20	3. 95	3. 08	3. 91 ± 0. 15
celiprolol	2. 36	2. 31 ± 0. 45	1. 93	1. 86	2. 58	1. 93	4. 00	2. 99	1. 49	3. 40	2. 49 ± 0. 25
esmolol	1. 90	1. 91 ± 0. 22	2. 00	1. 72	1. 68	2. 31	2. 29	2. 53	1. 53	2. 59	2. 05 ± 0. 12
labetalol	2. 12	2. 87 ± 0. 40	2. 41	1. 55	2. 52	2. 66	1. 77	1. 88	1. 93	3. 21	2. 29 ± 0. 17
levobunolol	2. 00	2. 86 ± 0. 24	2. 48	2. 26	2. 05	2. 69	2. 74	2. 67	2. 31	2. 59	2. 47 ± 0. 09
medroxalol	1. 19	1. 93 ± 0. 44	2. 14	1. 98	1. 92	2. 22	0. 68	1. 24	1. 62	2. 66	1. 76 ± 0. 18
mepindolol	2. 55	2. 43 ± 0. 22	2. 03	2. 17	2. 15	2. 40	2. 13	1. 59	1. 40	2. 48	2. 13 ± 0. 12
metipranolol	2. 82	2. 67 ± 0. 23	2. 66	2. 55	2. 22	3. 19	4. 78	3. 23	2. 47	3. 04	2. 96 ± 0. 23
metoprolol	1. 80	1. 79 ± 0. 35	1. 69	1. 35	1. 63	2. 09	1. 96	2. 43	2. 03	2. 13	1. 89 ± 0. 10
nadolol	1. 00	1. 29 ± 0. 34	1. 17	0. 38	1. 17	1. 48	1. 38	1. 72	0. 52	1. 54	1. 17 ± 0. 14
nebivolol	4. 05	3. 91 ± 0. 55	3. 71	3. 50	2. 74	3. 89	4. 21	3. 36	3. 63	3. 62	3. 66 ± 0. 13
oxprenolol	2. 17	2. 29 ± 0. 24	1. 83	2. 44	2. 02	2. 56	3. 01	3. 08	2. 04	2. 69	2. 41 ± 0. 13
penbutolol	3. 88	4. 17 ± 0. 21	4. 20	4. 04	4. 17	3. 90	4. 86	4. 70	3. 69	4. 44	4. 21 ± 0. 12
pindolol	2. 11	1. 97 ± 0. 22	1. 48	1. 67	1. 92	1. 70	2. 43	1. 86	1. 45	2. 04	1. 86 ± 0. 09
practolol	0. 80	0. 76 ± 0. 21	0. 53	0. 76	1. 02	1. 08	2. 00	0. 93	1. 04	1. 05	1. 00 ± 0. 12
propranolol	2. 95	3. 10 ± 0. 19	2. 60	2. 75	3. 03	2. 87	3. 44	3. 02	3. 07	3. 17	3. 00 ± 0. 07
sotalol	0. 82	0. 32 ± 0. 37	0. 37	0. 23	0. 79	0. 82	- 0. 42	0. 08	0. 57	0. 80	0. 44 ± 0. 13
talinolol	3. 20	3. 20 ± 0. 30	3. 32	3. 15	2. 90	3. 14	5. 45	3. 57	2. 25	3. 10	3. 33 ± 0. 26
tertatolol	3. 50	3. 42 ± 0. 76	3. 40	3. 12	3. 06	2. 55	4. 24	4. 13	3. 39	4. 06	3. 49 ± 0. 17
timolol	2. 10	-0. 15 ± 0. 49	1. 75	1. 58	1. 16	1. 46	0. 24	0. 91	1. 09	0. 49	1. 06 ± 0. 22

reported to cause greater disturbances on electroencephalograms than propranolol, a highly lipophilic ß-blocker. Bevantolol exhibits a moderate degree of lipophilicity and a low frequency of CNS side effects. Drug-induced increases in plasma catecholamine levels, the possible saturation of CNS receptor sites at relatively low drug levels, and the specific structural details of ß-blocker molecules have been suggested as possible contributory factors in determining the degree of CNS effects.

3. COMPARATIVE LOGP CALCULATIONS

In contrast to its pharmacological impact, comprehensive lipophilicity compilations for ß-blockers are lacking so far. Only few studies with limited structure sets exist [41-43] LogP calculations are given here for 30 ß-blockers (Fig. **1**) with 10 logP programs (version numbers in brackets), including AB/logP (1.0), ACD/logP (4.5), KOWWIN (1.64), CLOGP (4.0), XLOGP (2.0), ALOGP 98, HINT (2.35S), CLIP (1.0), SciLogP (1.1) and QLOGP (2.01); for

details see [44]. In brief, AB/logP, ACD/logP [45], KOWWIN [46], and CLOGP [47] represent fragmental approaches; XLOGP [48] and ALOGP 98 [49] are atom-based. HINT [50], CLIP [51], SciLogP, and QLOGP [52] are whole molecule approaches, using either molecular lipophilicity potentials (CLIP and HINT), topological indices (SciLogP) or molecular properties (QLOGP) to quantify logP. Thus, programs used here cover the entire methodological spectrum as depicted in Table **1**.

LogP calculations for the 30 ß-blockers are given in Table **2** together with mean values of these calculations and their standard deviations. Mean values indicate a spanned logP spectrum of more than four log units ranging from 4.86 for bopindolol to 0.33 in the case of atenolol. Standard deviations reflect the variability of logP calculations, depending on the ß-blocker structure considered. Thus, structures like alprenolol, carazolol, pindolol or propranolol are evenly treated by the program set, whereas celiprolol, metipranolol, talinolol, and timolol exhibit comparably larger variations in calculated logP.

From these calculations one can subclassify ß-blockers into three groups of high, moderate and low lipophilicity, as shown in (Fig. **2**). 13 compounds are highly lipophilic including bopindolol > penbutolol > carvedilol > nebivolol > tertatolol > talinolol = bupranolol = bucindolol > carazolol > propranolol = metipranolol = alprenolol > betaxolol. 11 ß-blockers exhibit moderate lipophilicity: celiprolol = levobunolol = oxprenolol > labetalol = bisoprolol > mepindolol > esmolol > metoprolol = acebutolol = pindolol > medroxalol. A group of only 6 ß-blockers is characterized by low lipophilicity: carteolol > nadolol > timolol = practolol >> sotalol > atenolol. It should be emphasized that all common ß-blockers are lipophilic and even atenolol, frequently and misleadingly labelled a „hydrophilic ß-blocker“ in medicinal literature, is in truth a weakly lipophilic compound.

Experimental logP data for 18 ß-blockers from the logP*-compilation of Leo and Hansch [53] are included in Table **3** to allow a comparative validity check. Differences between experimental and calculated logP were used to derive the averaged absolute residual sums (AARS). These values give an immediate overview on the varying validity of the logP programs used. Before discussing these results, it deserves mentioning that such considerations cannot be generalised given a database of only 30 structures. However, results obtained here, nicely correspond to previous comparisons on the basis of larger datasets [54]. AARS prove a superiority of substructure over whole molecule approaches; no real differences are observed between fragmental and atom-based methods. As far as these ß-blocker calculations are concerned, out of the group of whole molecule approaches only SciLogP can compete with the substructure methods. AARSs of QLOGP (0.41), CLIP (0.58), and HINT (0.79) significantly surmount the values of the majority of substructure approaches with AARSs around 0.30. Regarding the performance of the HINT calculations it should be considered that this program is primarily developed for the calculation of hydrophobic interaction fields, whereas the calculation of logP is only a by-product of the software.

Application of the program set instead of only one individual software allows to detect severe outliers within individual programs. An impressive example is the miscalculation of timolol by ACD/logP with a calculated logP of -0.15 versus an experimental logP value of 1.83.

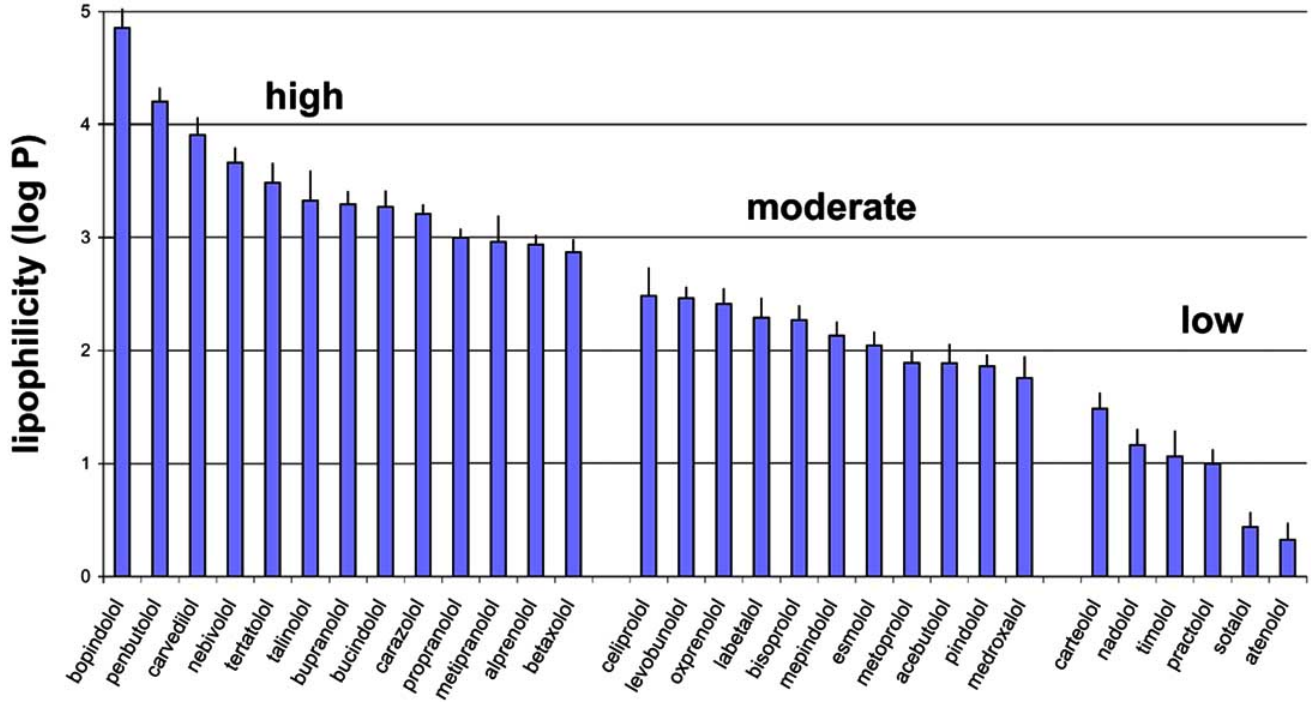

Fig. (2).

Table 3. Validity of LogP Calculations in Comparison to Experimental LogP

compound	$logP_{exp}$	AB/logP	ACD/logP	KOWWIN	CLOGP	XLOGP	ALOGP	HINT	CLIP	SciLogP	QLOGP
acebutolol	1. 71	1. 89	2. 11 ± 0. 36	1. 19	1. 71	1. 68	1. 95	3. 08	1. 75	1. 33	2. 20
alprenolol	3. 10	2. 89	2. 88 ± 0. 21	2. 81	2. 65	2. 84	2. 97	3. 35	3. 23	2. 58	3. 19
atenolol	0. 16	0. 44	0. 10 ± 0. 25	- 0. 03	- 0. 11	0. 46	1. 00	- 0. 48	0. 83	0. 70	0.35
betaxolol	2. 81	2. 77	2. 69 ± 0. 36	2. 98	2. 32	2. 37	2. 91	3. 18	3. 36	2. 84	3. 29
bisoprolol	1. 87	1. 94	2. 22 ± 0. 34	1. 84	2. 12	2. 16	2. 36	2. 59	3. 21	2. 04	2. 24
bupranolol	2. 80	3. 14	2. 97 ± 0. 23	3. 07	3. 10	3. 24	3. 32	3. 51	4. 14	3. 02	3. 45
carazolol	3. 59	3. 38	3. 37 ± 0. 74	2. 66	3. 06	3. 27	3. 46	2. 96	3. 30	3. 42	3. 22
mepindolol	2. 30	2. 55	2. 43 ± 0. 22	2. 03	2. 17	2. 15	2. 40	2. 13	1. 59	1. 40	2. 48
metipranolol	2. 66	2. 82	2. 67 ± 0. 23	2. 66	2. 55	2. 22	3. 19	4. 78	3. 23	2. 47	3. 04
metoprolol	1. 88	1. 80	1. 79 ± 0. 35	1. 69	1. 35	1. 63	2. 09	1. 96	2. 43	2. 03	2. 13
nadolol	0. 81	1. 00	1. 29 ± 0. 34	1. 17	0. 38	1. 17	1. 48	1. 38	1. 72	0. 52	1. 54
oxprenolol	2. 10	2. 17	2. 29 ± 0. 24	1. 83	2. 44	2. 02	2. 56	3. 01	3. 08	2. 04	2. 69
penbutolol	4. 15	3. 88	4. 17 ± 0. 21	4. 20	4. 04	4. 17	3. 90	4. 86	4. 70	3. 69	4. 44
pindolol	1. 75	2. 11	1. 97 ± 0. 22	1. 48	1. 67	1. 92	1. 70	2. 43	1. 86	1. 45	2. 04
practolol	0. 79	0. 80	0. 76 ± 0. 21	0. 53	0. 76	1. 02	1. 08	2. 00	0. 93	1. 04	1. 05
propranolol	2. 98	2. 95	3. 10 ± 0. 19	2. 60	2. 75	3. 03	2. 87	3. 44	3. 02	3. 07	3. 17
sotalol	0. 59	0. 82	0. 32 ± 0. 37	0. 37	0. 23	0. 79	0. 82	- 0. 42	0. 08	0. 57	0. 80
timolol	1. 83	2. 10	-0. 15 ± 0. 49	1. 75	1. 58	1. 16	1. 46	0. 24	0. 91	1. 09	0. 49
AARS		**0. 18**	**0. 31**	**0. 26**	**0. 27**	**0. 28**	**0. 32**	**0. 79**	**0. 58**	**0. 30**	**0. 41**

Averaged absolute residual sums (AARS) describe the varying validity of the log P programs used. AARS prove a superiority of substructure over whole molecule approaches; no real differences are observed between fragmental and atom-based methods. Out of the group of whole molecule approaches only SciLogP can compete with the substructure methods. AARSs of QLOGP (0.41), CLIP (0.58), and HINT (0.79) significantly surmount the values of the majority of substructure approaches with AARSs around 0.30.

4. CONCLUDING REMARKS

Taken together, ß-blockers exhibit many lipophilicity-controlled pharmacological properties. Skin penetration, intestinal absorption, volume of distribution and unbound hepatic intrinsic clearance represent examples for lipophilicity-guided pharmacokinetics. Among pharmacodynamic properties the dissociation rates from ß-adrenoceptors and the $ß_1$-selectivity demonstrate direct or inverse correlations with lipophilicity, respectively. Furthermore, lipophilicity has an impact on additional pharmacodynamic actions of ß-blockers unrelated to ß-blockade such as membrane stabilizing activity and beneficial cardioprotective effects. Some ß-blockers have been shown to decrease mortality in sudden cardiac death. Accumulating experimental evidence attributes a key determinant role in this respect to lipophilicity and underlines the clinical relevance of this physicochemical descriptor. Finally, lipophilic ß-blockers that readily penetrate into the brain might cause some CNS side effects, like halluzination, vivid dreams, and sleep disturbance.

In contrast to its pharmacological relevance, summarized above, comprehensive compilations of ß-blocker lipophilicity are missing so far. Such a broad lipophilicity listing for 30 clinically relevant ß-blockers is given for the first time in this review; it will much better allow an adequate selection of test compounds for proving the putative impact of lipophilicity on the pharmacological profile of ß-blockers.

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