Research Laboratory of Gedeon Richter Ltd., Budapest, Hungary

Timing of analog research in medicinal chemistry

J. FISCHER and A. GERE

Analog research plays an important role in medicinal chemistry. Having identified a new target in molecular biology many similar lead compounds are synthesized resulting in closely related products on the market. Another approach is the further optimising of an existing drug in order to improve on the original. In some cases these two approaches overlap. The question of timing and the importance of analog research are analyzed in this paper.

1. Introduction

The term is used, according to IUPAC recommendations [1], where an incremental innovation [2] differentiates a drug from the original. This overview focussed on analogs, but bioisosteres [3] were also mentioned if it was appropriate. They do not fit into a general formula of analogs, therefore, we depict all the formulas individually. We aim to demonstrate that analog research can be successful both at an early phase, when no product has yet been introduced on the market, and also after a drug has been launched successfully. In most cases analogs afford an incremental innovation, but in some cases an essential one. We propose a classification of drug discoveries according to their timing: *early phase analogs* and *drug analogs*. With the help of some significant examples from recent decades we wish to show, how analogs of both classes can contribute to drug discovery.

2. Early-phase analogs

Early-phase analogs are structurally similar drugs discovered more or less early, before the original drug is launched. As a result of early-phase parallel research the discovery dates of such derivatives are very close to each other.

2.1. ACE inhibitors

The first successful angiotensin converting enzyme (ACE) inhibitor was captopril [4]. The pioneer discovery by Ondetti and Cushman was achieved by replacing the carboxyl group of the analogous carboxyalkanoyl-L-proline by an SH group. In order to obtain analogs that were more active and mercaptofree, Patchett started from an homologeous carboxyalkanoyl-L-proline and among *N*-carboxyalkyl dipeptides enalapril [5] and lisinopril proved to be long-acting ACE inhibitors. In parallel research activity many analogous ACE inhibitors were discovered before enalapril appeared on the market to create a class of drugs which can be used in the treatment of hypertension and congestive heart disease.

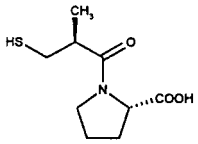
2.2 AT_1 antagonists

In 1982 hypotensive imidazole-5-acetic acid derivatives which antagonized angiotensin II evoked vasoconstriction were reported [6]. The clinical breakthrough came with losartan [7] and its analogs, which – except for eprosartan – have a biphenyl-tetrazole moiety (Table 2). The angiotensin II antagonists are competitive with the ACE-inhibitors and further clinical trials will decide which class is more effective.

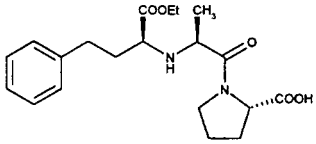
2.3. Proton pump inhibitors

Omeprazole [8], which was the first successfully introduced H^+/K^+-ATPase inhibitor, was followed by novel analogs (Table 3). They are irreversible blockers of the proton pump that is responsible for acid secretion by the gastric parietal cells. According to the mechanism of action [9] omeprazole itself is inactive, but it is transformed into a sulfenamide, which is the active inhibitor in vivo. A comparison of omeprazole, lansoprazole and pantoprazole demonstrated differences in pharmacokinetics and drug interaction profile [10].

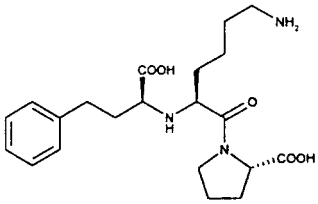
Table 1: ACE-inhibitors



captopril



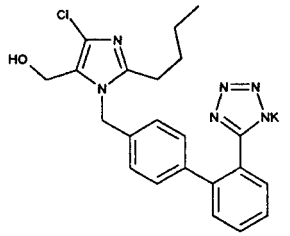
enalapril



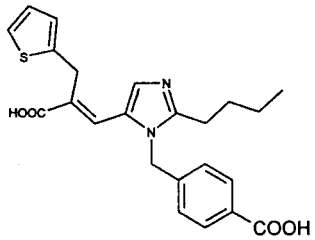
lisinopril

Name	Originator	Basic patent (year)	First launch (year)
Captopril	Bristol-Myers Squibb	1976	1980
Enalapril	Merck and Co. (USA)	1978	1984
Lisinopril	Merck and Co. (USA)	1978	1987

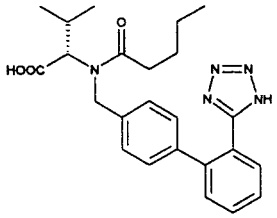
Table 2: Angiotensin II antagonists



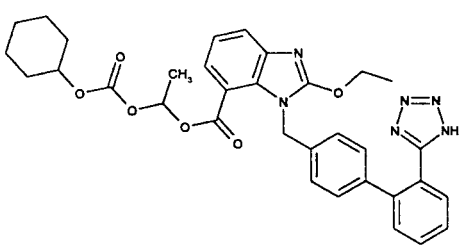
losartan



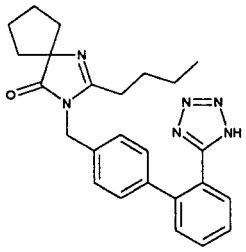
eprosartan



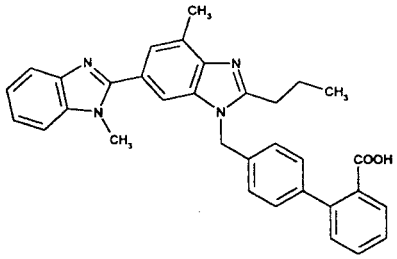
valsartan



candesartan



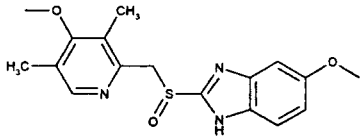
irbesartan



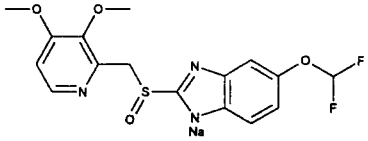
telmisartan

Name	Originator	Basic patent (year)	First launch (year)
Losartan	DuPont	1986	1994
Eprosatran	Smith Kline Beecham	1989	1997
Valsartan	Novartis	1990	1996
Candesartan	Takeda	1990	1999
Irbesartan	Sanofi Synthélabo	1990	1997
Telmisartan	Boehringer Ingelheim	1991	1999

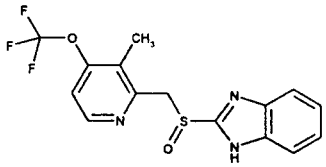
Table 3: Omeprazole and its analogs



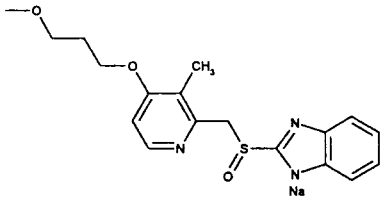
omeprazole



pantoprazole



lansoprazole



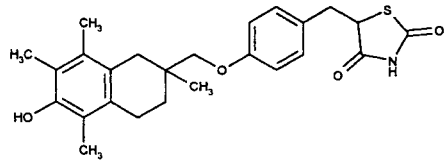
rabeprazole

Name	Originator	Basic patent (year)	First launch (year)
Omeprazole	AstraZeneca	1978	1988
Pantoprazole	Byk-Gulden	1983	1994
Lansoprazole	Takeda	1984	1991
Rabeprazole	Eisai	1986	1997

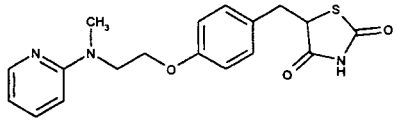
2.4 Insulin sensitizers: "glitazones"

The first member of the thiazolidine-2,4-diones, ciglitazone [11] reduced plasma glucose after oral administration in several insulin-resistant animal models, but a more potent compound was needed. The clinical breakthrough was troglitazone [12], which was introduced in 1997 (Table 4). In contrast to the above three classes of drugs,

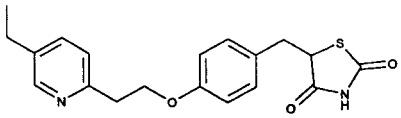
Table 4: "Glitazones"



troglitazone



rosiglitazone



pioglitazone

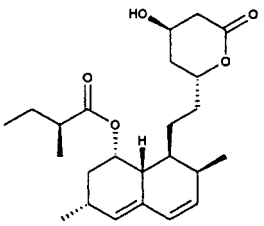
Name	Originator	Basic patent (year)	First launch (year)
Troglitazone	Sankyo	1983	1997
Pioglitazone	Takeda	1985	1999
Rosiglitazone	Glaxo Smith Kline	1987	1999

where the first member of the class remained successful even after the introduction of analogs, the case of the "glitazones" shows a different situation. Troglitazone was withdrawn [13] from the market in 2000 because of liver toxicity in man. The clinical use of rosiglitazone and pioglitazone follows the FDA labelling, including the need for liver enzyme monitoring before the start of therapy and periodically during treatment. The "glitazones" exert their insulin sensitizer activity via stimulation of peroxisome proliferator-activated receptor gamma subtype (PPAR-γ) [14].

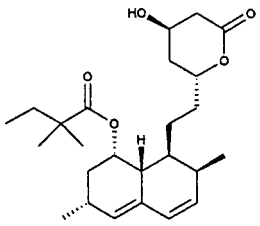
2.5. HMG-CoA reductase inhibitors

Mevastatin (compactin), a fungal metabolite [15], and a potent inhibitor of hydroxymethylglutaryl (HMG) CoA reductase, initiated a series of "statins" for treatment of lipoprotein disorders (Table 5). The clinical breakthrough was lovastatin [16], followed by simvastatin and pravastatin. Their therapeutic field is the treatment of hypercholesterolemia. As a result of intense activity in the design of synthetic analogs of the above "statins" new analogs were obtained, where the decalin moiety was replaced by different

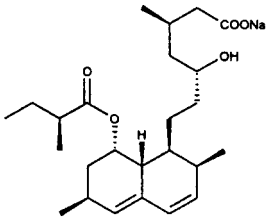
Table 5: "Statins"



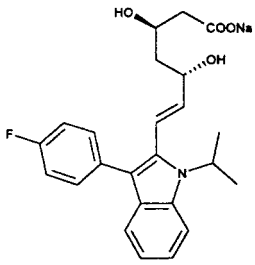
lovastatin



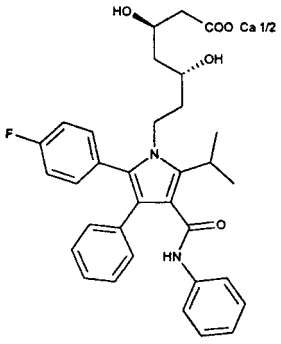
simvastatin



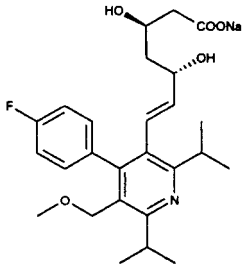
pravastatin



fluvastatin



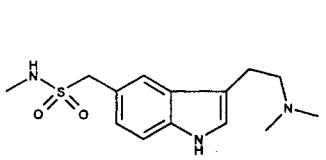
atorvastatin



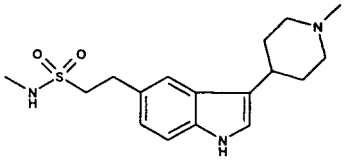
cerivastatin

Name	Originator	Basic patent (year)	First launch (year)
Lovastatin	Merck and Co. (USA)	1979	1987
Simvastatin	Merck and Co. (USA)	1980	1989
Pravastatin	Sankyo	1980	1989
Fluvastatin	Novartis	1982	1994
Atorvastatin	Pfizer	1986	1997
Cerivastatin	Bayer	1988	1997

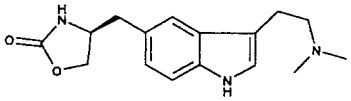
Table 6: Antimigraine drugs



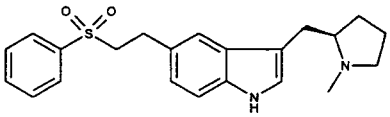
sumatriptan



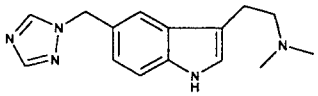
naratriptan



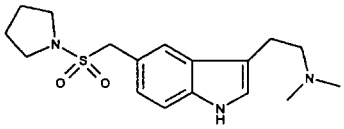
zolmitriptan



eletriptan



rizatriptan



almotriptan

Name	Originator	Basic patent (year)	First launch (year)
Sumatriptan	Glaxo Smith Kline	1982	1991
Naratriptan	Glaxo Smith Kline	1987	1997
Zolmitriptan	Astra Zeneca	1987	1997
Eletriptan	Pfizer	1990	1999*
Rizatriptan	Merck and Co. (USA)	1991	1998
Almotriptan	Almirall	1992	1999

* Recommended approval by FDA

heterocyclic rings bearing almost the same substituents, such as 3,5-dihydroxy-heptanoic acid derivative, 4-fluorophenyl and isopropyl-substituents. The first member of this series of heterocyclic "statins" was fluvastatine sodium, followed by atorvastatin and cerivastatin, which lower both cholesterol and triglyceride levels. The lactone forms are prodrugs, which are metabolized to the corresponding active hydroxy-acid form [17].

2.6. Antimigraine drugs

The first representative of the class of drugs with a 5-$HT_{1B/1D}$ agonist mechanism was sumatriptan [18], which proved to be a useful drug for the treatment of acute attacks of migraine. Among the analogs 5-HT_{1D}-selectivity and pharmacokinetic parameters play an important role (Table 6). Rizatriptan showed both an increased oral bioavailability and more rapid absorption compared with oral sumatriptan [19].

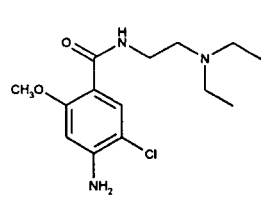
3. Drug analogs

A drug analog is a structurally similar drug, which was discovered later or much later than the launch of the original drug. There are some unique drugs, such as aspirin, levodopa, methyldopa, metformin, PAS, colchicin etc. without analogs, but they represent only a minority of all drugs. In most cases several examples of successful analog research based on pioneer drugs can be observed.

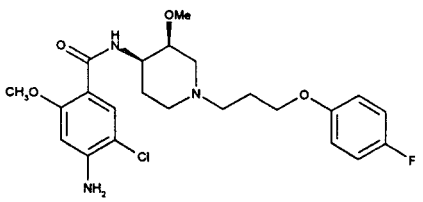
3.1. Metoclopramide analogs

The history of these drugs covers some four decades (Table 7). Metoclopramide was discovered in 1961. It is a centrally acting antiemetic agent [20]. Its mechanism of action has not been fully elucidated. Antidopaminergic properties at both D_1 and D_2 receptor subtypes play an important role in its activity [21], but its extrapyramidal side effects are also associated with this mechanism. Twenty years later the analog cisapride was discovered,

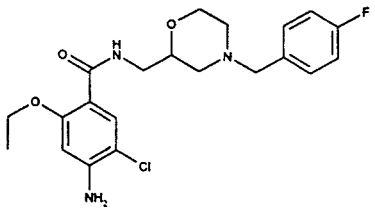
Table 7: Gastroprokinetic drugs



metoclopramide



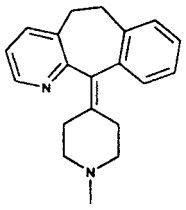
cisapride



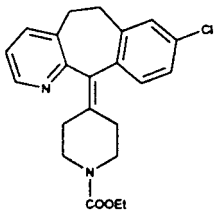
mosapride

Name	Originator	Basic patent (year)	First launch (year)
Metoclopramide	Glaxo Smith Kline	1961	1964
Cisapride	Janssen	1981	1988
Mosapride	Dainippon	1986	1998

Table 8: Azatadine analog



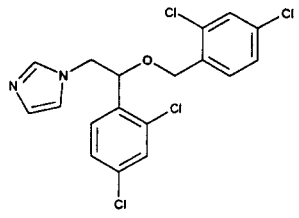
azatadine



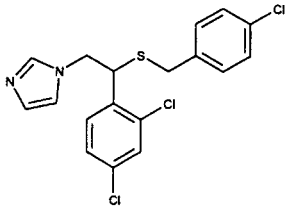
loratadine

Name	Originator	Basic patent (year)	First launch (year)
Azatadine	Schering-Plough	1963	1977
Loratadine	Schering-Plough	1980	1988

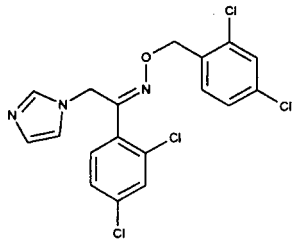
Table 9: Miconazole analogs



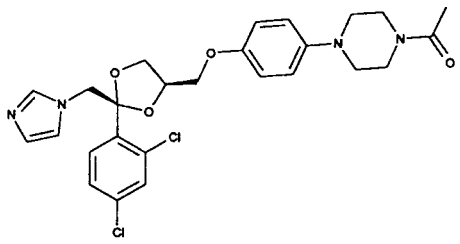
miconazole



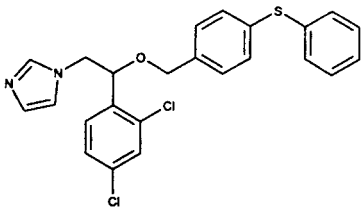
sulconazole



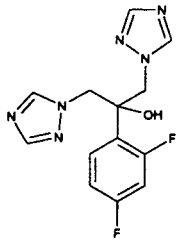
oxiconazole



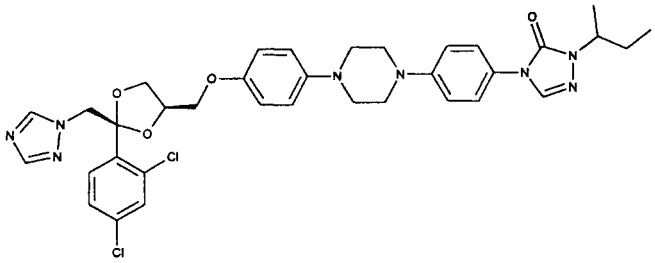
ketoconazole



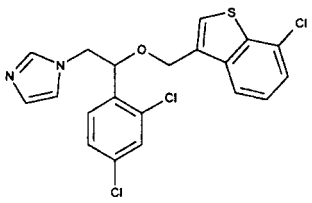
fenticonazole



fluconazole



itraconazole



sertraconazole

Name	Originator	Basic patent (year)	First launch (year)
Miconazole	Janssen	1968	1971
Sulconazole	Syntex	1974	1985
Oxiconazole	Siegfried	1975	1983
Ketoconazole	Janssen	1977	1981
Fenticonazole	Recordati	1978	1987
Fluconazole	Pfizer	1981	1988
Itraconazole	Janssen	1983	1988
Sertraconazole	Ferrer	1984	1992

which does not exhibit potent dopamine-receptor antagonist activity. Its main therapeutic use is the treatment of gastroesophageal reflux disease and it was one of the most successful drugs of the last decade. Agonistic action at 5-HT_4 receptors, and hence facilitation of cholinergic excitatory neurotransmission, has been suggested as the mechanism by which these agents enhance gastric motility [22]. Current data suggest that concomitant administration of cisapride and certain azole-derivatives (e.g. ketoconazole) can result in prolongation of the QT interval. The marketing of cisapride was terminated in the USA in 2000 [23], but further research is going on in this field. Mosapride was discovered in 1986. The mode of action of mosapride on gastrointestinal motor activity was clearly different from that of cisapride, which stimulates motor activity in all sites of the GI tract [24]. Further clinical trials are needed to evaluate the drug interaction profile of mosapride.

3.2. Azatadine analog

It was a popular view a generation ago that a non-sedating H_1-receptor antagonist is unobtainable [25]. There was a lack of validated methods to predict the sedative effects of a new antihistamine. The clinical breakthrough was terfenadine, which proved to be such an agent in 1978 [26]. This encouraged researchers at Schering-Plough to start drug-analog research, the lead-molecules for which were terfenadine and azatadine [27]. A selected battery of CNS tests in guinea pigs and mice using terfenadine and azatadine as references helped to screen analogs. The carbamate-analog of azatidine was without CNS activity while retaining much of its antihistamine potency. Further optimisation of the carbamate-azatadine resulted in its 8-chloro-derivative, loratadine [28], with a longer duration of action.

3.3 Miconazole analogs

Miconazole is used primarily as a topical antifungal agent. Ketoconazole and fluconazole can also be given orally. The terminal half-life of fluconazole is approximately three times higher than that of ketoconazole. Oral fluconazole produces clinical cure of uncomplicated vulvovaginal candidiasis with a single dose. All of these agents are fungistatic by inhibing biosynthesis of ergosterol. Clinical failure of antifungal therapy due to resistance to existing agents is spreading rapidly, and is often multifactorial [29] (Table 9).

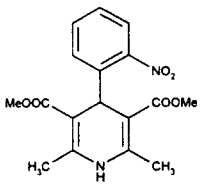
3.4. Nifedipine-analogs

The calcium channel blocking mechanism was discovered by Fleckenstein in 1967 [30]. Nifedipine [31], the first member of this class, has a short duration of action. Many structural analogs were developed with a better pharmacokinetic profile (gradual onset, long duration of action). These drugs are used for the treatment of mild and moderate hypertension (Table 10).

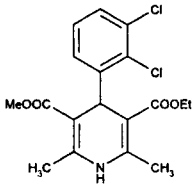
3.5. Propranolol analogs

Propranolol is the first but nonselective beta-adrenergic blocking agent with no intrinsic sympatomimetic activity. It is used for the treatment of arrhythmias, angina pectoris and hypertension. Because of its ability to block beta-receptors in bronchial smooth muscle, the drug is usually not used in individuals with bronchial asthma. As a consequence, there has been a search for beta-adrenergic blocking agents that are cardioselective. Practolol, discovered in 1966, was the first such agent, but it was withdrawn be-

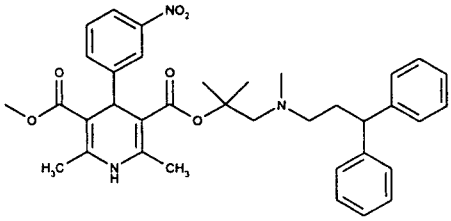
Table 10: Calcium channel blockers



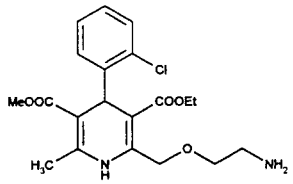
nifedipine



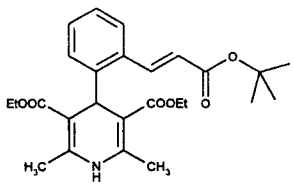
felodipine



lercanidipine



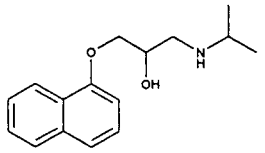
amlodipine



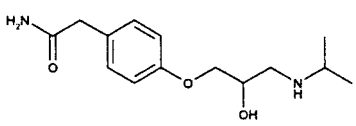
lacidipine

Name	Originator	Basic patent (year)	First launch (year)
Nifedipine	Bayer	1967	1975
Felodipine	Astra Zeneca	1978	1988
Lercanidipine	Recordati	1984	1997
Lacidipine	Glaxo Smith Kline	1985	1991
Amlodipine	Pfizer	1986	1990

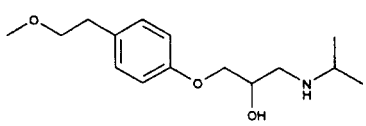
Table 11: Beta$_1$-adrenergic blocking agents



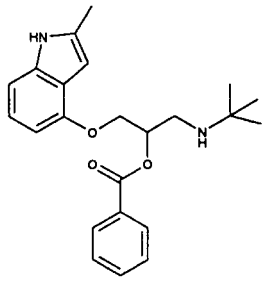
propranolol



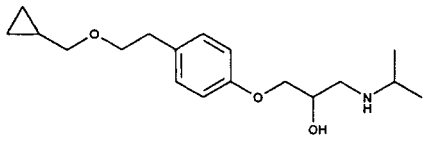
atenolol



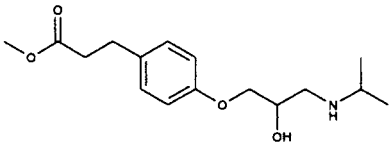
metoprolol



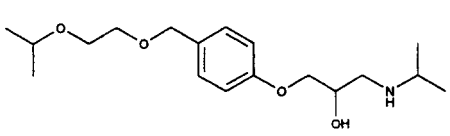
bopindolol



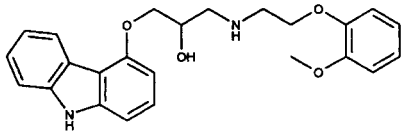
betaxolol



esmolol



bisoprolol



carvedilol

Name	Originator	Basic patent (year)	First launch (year)
Propranolol	Astra Zeneca	1962	1964
Atenolol	Astra Zeneca	1969	1975
Metoprolol	Astra Zeneca (Hässle)	1970	1975
Bopindolol	Novartis	1975	1985
Betaxolol	Synthélabo	1975	1983
Esmolol	DuPont Pharmaceutical	1980	1987
Bisoprolol	Merck (Darmstadt)	1976	1986
Carvedilol	Roche	1978	1991

cause of its toxic side effects. Table 11 summarizes the beta$_1$-selective (cardioselective) antagonists, which made an essential contribution to improving therapy [32].

3.6. Clodronate analogs

Bisphosphonates are powerful bone resorption inhibitors that have been found to be clinically useful in the treatment of osteoporosis. Bisphosphonates are generally very poorly absorbed when given orally, but once absorbed they are taken up preferentially in bones. Clodronate disodium and etidronate sodium were used for the treatment of Paget's disease [33]. The second generation products (alendronate and pamidronate) are much more effective. A third generation agent, risedronate, seems to have fewer esophageal side efffects [34].

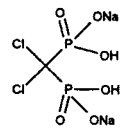
4. Conclusion

This short overview of analog research in medicinal chemistry aimed to define two main approaches on the basis of their timing: the *early-phase analogs* and the *drug analogs*. A breakthrough discovery in medicinal chemistry initiates parallel early-phase research activities in several research centers around the world. The marketing of the new drugs, however, takes on average 10–15 years and during this long period several similar lead compounds are identified which result in several early-phase analogs on the market. In case of drug analogs the situation is different. A drug is the end-product of a long optimising process in research and development; nevertheless, during clinical trials side effects, drug interactions and other weak points can be observed, which initiates research to develop drug analogs which include some remarkable achievements as shown with the above examples.

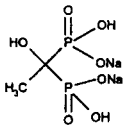
These two approaches overlap in some cases. If parallel research activity starts in a period when the clinical results of a candidate drug are published (Phase III), the products of the analog-research will be regarded as a drug-analog because of the long development process today.

There are no general rules to determine when early-phase or drug-analog research is preferred. It depends on the marketing conditions, the company strategy and the medicinal chemistry possibilities, and last but not least it depends on the inventive capacities of the people involved.

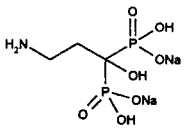
Table 12: Clodronate analogs



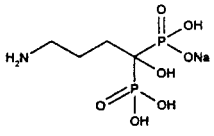
clodronate disodium



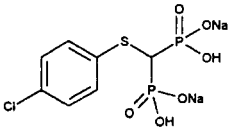
etidronate disodium



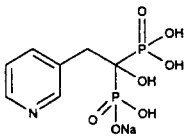
pamidronate disodium



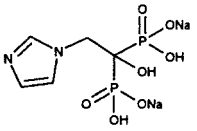
alendronate sodium



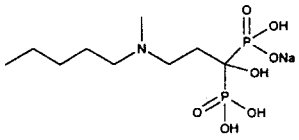
tiludronate disodium



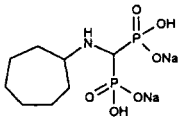
risedronate sodium



zoledronate disodium



ibandronate sodium



incadronate sodium

Name	Originator	Basic patent (year)	First launch (year)
Clodronate	Procter & Gamble	1963	1986
Etidronate	Procter & Gamble	1966	1977
Pamidronate	Gador and Henkel	1971	1987
Alendronate	Gentili/Merck (USA)	1982	1993
Tiludronate	Sanofi-Synthélabo	1982	1993
Risedronate	Procter & Gamble	1984	1998
Zoledronate	Novartis	1986	2000*
Ibandronate	Roche	1986	1996
Incadronate	Yamanouchi	1988	1997

* registered

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Dr. János Fischer
Gedeon Richter
Pf. 27
1475 Budapest
Hungary