Progress in Drug Research

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Vol. 53

Edited by Ernst Jucker, Basel

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khäuser Verlag
sel · Boston · Berlin

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Visit our PDR homepage: http://www.birkhauser/books/biosc/pdr

Printed on acid-free paper produced from chlorine-free pulp. TCF ∞
Cover design and layout: Gröflin Graphic Design, Basel
Printed in Germany

ISBN 3-7643-6028-3
ISBN 0-8176-6028-3
9 8 7 6 5 4 3 2 1

Foreword by the Editor

Volume 53 of *Progress in Drug Research* contains five review articles and the various indexes which facilitate the use of monograph and also help to establish PDR as an encyclopedic source of information in the complex and fast growing field of drug research.The first article in this volume is devoted to κ-agonists, an important group of compounds which are being tested as agents with diuretic, analgesic and neuroprotective properties.The remaining contributions deal with quantitative structure-activity relationships of various classes of antihypertensive agents, with combinatorial chemistry as a powerful tool for accelerating the drug discovery process, with the complete characterisation of an organism's gene expression leading to optimisation of the search for new drugs. The last contribution reviews the role of phosphodiesterase inhibitors in the developments of novel therapies for asthma and chronic obstructive pulmonary disease.

All of these reviews contain extensive bibliographies, thus enabling the interested reader to have easy access to the original literature.

In the 40 years of PDR's existence, drug research has undergone drastic changes; the original purpose of this series of monographs, however, remained unchanged: dissemination of information about the actual trends and crucial points of drug research. The Editor is anxious to maintain the high standard of these monographs and is grateful to the contributing authors for their willingness to undertake the hard work of writing comprehensive review articles for the benefit of all involved with drug research.

In ending this foreword, I would like to thank the authors for their contributions, the Members of the Board of Advisors for their advice and the reviewers for their help in improving these monographs. Last but not least, I am grateful to Birkhäuser Publishers, and in particular to Ruedi Jappert, Janine Kern, Bernd Luchner, Eduard Mazenauer, Claus Puhlmann and Gregor Messmer, with whom I have a cooperative relationship that is harmonious and rewarding. My very special thanks go to Mr. Hans-Peter Thür, the CEO of Birkhäuser Publishers. Over many years I did and still do enjoy Mr. Thür's constant support and encouragement to continue with the editorship of PDR.

Basel, September 1999 Dr. E. Jucker

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Progress in Drug Research, Vol. 53 (E. Jucker, Ed.)

U-50,488 and the κ receptor Part II*: 1991–1998

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*Part I was published in vol. 52 of this series.

Jacob Szmuszkovicz

was born in Lódz, Poland. He received a B.Sc. degree at the American University of Beirut and a Ph.D. degree at the Hebrew University and the Weizmann Institute. After postdoctoral appointments at Harvard University, the University of Wisconsin and Columbia, he joined the Upjohn Company. He retired from Upjohn as a distinguished scientist and joined the Department of Chemistry and Biochemistry at the University of Notre Dame.

Summary

This review, Part II, follows an earlier article, Part I, published in volume 52 of this series. Part II is a discussion of centrally and peripherally acting κ agonists which can be considered analogs of U-50,488. Included also are three classes of κ agonists which fall outside of the scope of the general structure of U-50,488. These are benzodiazepines, phenothiazines and diazobicyclononanones. The discussion also covers other pertinent topics including labelled ligands and sigma receptor.

Contents

Keywords
Analgesics, κ agonists, U-50,488, κ receptor, sigma receptor, centrally acting analgesics, peripherally acting analgesics, dysphoria.

Glossary of abbreviations
SC, subcutaneous; NMDA, N-methyl-D-aspartate; nM, nanomolar; IC_{50}, inhibitory concentration$_{50}$; LVD, rabbit vas deferens essay; DUP, DuPont; U, Upjohn; ICI, Imperial Chemical Industries; RP, Rhone-Poulenc; i.v., intravenous; i.p., intraperitoneal; icv, intracerebroventricular; EMD, E. Merck Darmstadt; MAC, mouse abdominal constriction test.

1 Introduction

1.1 General remarks

This review is a sequel to the article published in volume 52 of this series which was entitled "U-50,488 and the κ receptor: A personalized account covering the period 1973 to 1990". The reader is encouraged to peruse the abovementioned Part I of this series as background for Part II. Several concise reviews on this subject have appeared during 1981 to 1998 [1–8]. A comprehensive review of the chemistry of 1,2-diamines has recently been published [9]. Part II of this review does not include morphine and peptide related κ agonists.

1.2 Therapeutic potential of κ agonists

The main therapeutic potential for centrally acting κ agonists (see section 2) is the treatment of severe to moderate pain. This class of drugs possesses several advantages over mu agonists. κ agonists do not cause respiratory depression, constipation and physical dependence liability. Centrally acting κ agonists also have neuroprotective effects and may be useful for the treatment of stroke [10]. They produce water diuresis and have an antitussive effect (for references see [6]); they also have potential as agents for hypertension [11, 12].

Another major interest in κ agonists relates to their potential as peripherally acting analgesics (see section 6), useful for the treatment of inflammatory conditions.

1.3 Ongoing basic research

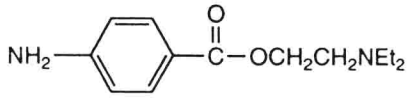
Basic research on κ receptor related science is progressing. Some of the areas of interest include the relationship between μ and κ receptor [13, 14], κ receptor subtypes (see section 9), interaction with the cholinergic system [15–19] site-directed mutagenesis studies [20, 21] studies with knockout mice [22], immunomodulation [23], renal function [24], cocaine addiction [25], anticonvulsant effects possibly involving glycine/NMDA receptor complex [26], feeding and neuroendocrine regulation [27].

1.4 The cocaine-procaine and the morphine-U-50,488 events

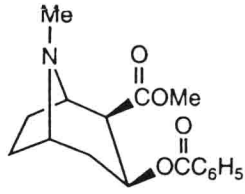
During a lecture in 1977 [28], Dr. Harris Isbell summarized the search for a non-addicting analgesic organized by the Committee on Drug Addiction and Narcotics in 1929. The committee was strongly influenced by the finding that procaine, a synthetic drug, did not have the euphoric properties of cocaine and took the place of cocaine as a local anesthetic in medical practice (Fig. 1).

Morphine has served as a template for several generations of medicinal chemists. Modifications of the morphine molecule produced a vast range of compounds with the mild propoxyphene at one end, potent drugs like methadone in the middle and, finally, extremely potent drugs such as etorphine (Immobilon) and sufentanil at the other end. Despite a wide variation in structures, the pharmacology of these morphine related compounds is similar. Thus, Isbell concluded in 1977 that the discovery of the perfect analgesic had not been realized yet.

Today, the cocaine-procaine experience may be compared to the morphine-U-50,488 development. A major step towards the goal of finding a non-addicting strong analgesic has been accomplished by the Upjohn discovery of U-50,488 [29]. Hopefully, in the near future the dysphoric side-effects of U-50,488 series will be better understood and resolved and, thus, pave the way for the κ agonist to become a pain remedy.



procaine



cocaine

Fig. 1
Structures of procaine and cocaine.

2 Centrally acting U-50,488 analogs

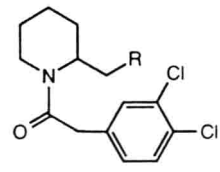
2.1 Glaxo piperidine and piperazine analogs

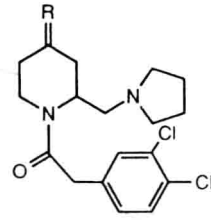
The Glaxo scientists concentrated their efforts on U-50,488 analogs in which one nitrogen is either part of the piperdine ring (Fig. 25) [30, 31] or piperazine ring (Fig. 26) [32]. This effort produced some very active κ agonists. In the piperidine series (Fig. 2) the 3-oxopyrrolidinyl compound A and the ketal compound B were most active. In the piperazine series (Fig. 3) the carbomethoxy pyrrolidine compound A is most active and the activity resided in (R)-enantiomer. The above compounds displayed high selectivity for the κ opioid receptors over both μ and δ receptors. They were also potent antinociceptive agents as determined by the mouse acetylcholine-induced abdominal constriction test (sc).

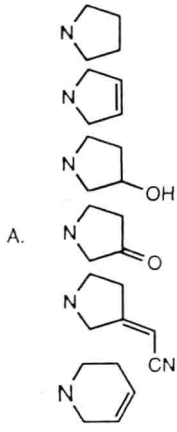
Compoundd GR 89696 (Fig. 3) was found to be neuroprotective in both global and cerebral ischaemia animal models [10].

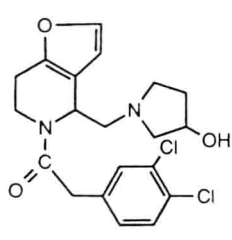
GR 89696 was found to an agonist at κ-2 receptor and antagonist at κ-1 receptors in the guinea pig hippocampus. κ-2 receptors may represent an important route to the regulation of NMDA receptor function in certain neuropathologies [33].

The Adolor group reported orally on the analog of GR 89696 with improved peripheral selectivity but no details were published [34].

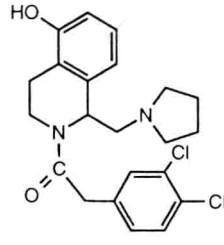




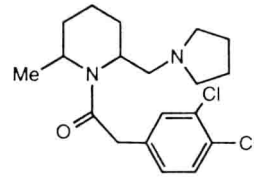
R	κ agonist potency rabbit vas deferens (LVD) IC_{50}, nM	R	κ LVD IC_{50}, nM
A. 	11	B. OCH_2CH_2O	0.1
	3.5	O	46
	0.88	SCH_2CH_2S	5
	0.2		
	0.12		
	6.3		



κ LVD = 2.7
IC_{50}, nM



κ LVD = 0.6
IC_{50}, nM



κ LVD = 1.7
IC_{50}, nM

Fig. 2
Glaxo analogs of U-50,488 in which one nitrogen is part of a piperidine ring.

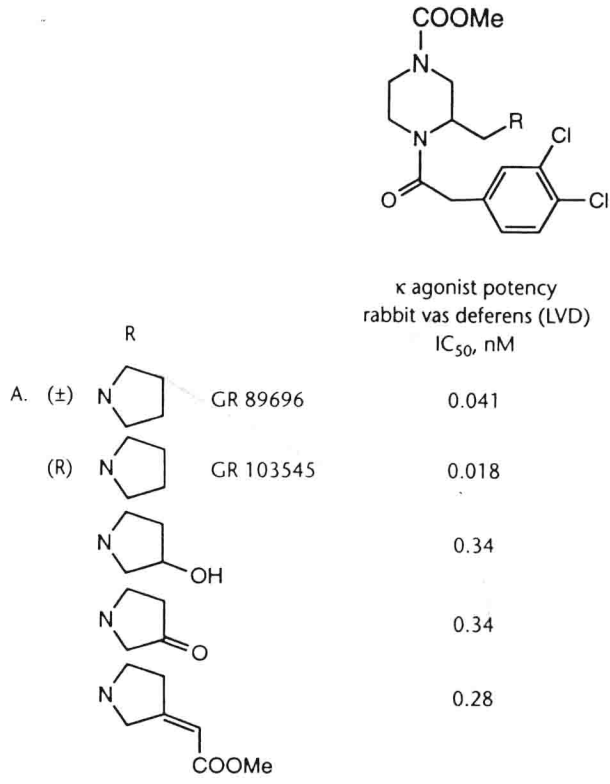
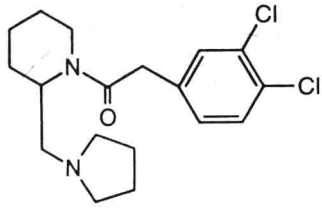


Fig. 3
Glaxo analogs of U-50,488 in which one nitrogen is part of a piperazine ring.

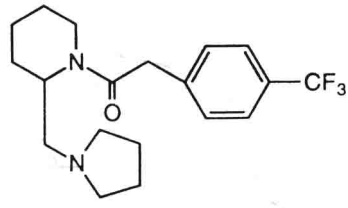
2.2 SmithKline Beecham piperidine analogs

The SmithKline Beecham group synthesized some very active κ agonists related to U-50,488 in which one nitrogen is a part of a piperidine ring (Fig. 4) [35]. Two of the compounds are shown in Figure 4. They are very potent κ ligands and show very good mu/κ selevitivity. They are also potent in the mouse tail flick model of antinociception. Compound B has been subjected to clinical trial as a κ selective analgesic.

Compound C (Fig. 4) was described in a patent [36]. No opioid receptor binding data was reported but in standard rodent analgesic assays potent activity was observed after sc injection (mouse writhing $ED_{50} = 0.005$ mg/kg).

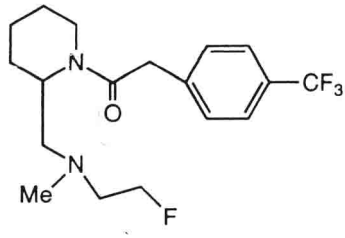


A.



B.

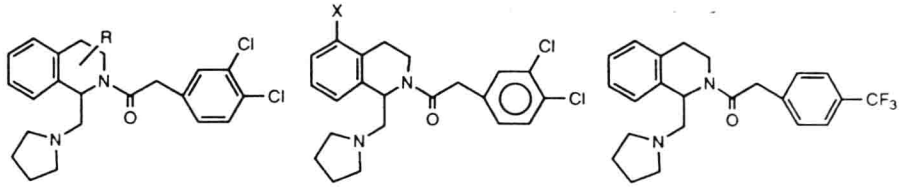
	receptor binding affinity Ki, nM			mouse tail flick
	κ	μ	μ/κ	ED_{50}, mg/kg sc
A.	0.24	1560	6500	50
B.	0.57	2340	4100	110



C.

Fig. 4
SmithKline Beecham analogs of U-50,488 in which one nitrogen is part of a piperidine ring.

The SmithKline Beecham group described a series of U-50,488 analogs in which one nitrogen is part of a tetrahydroisoquinoline ring (Fig. 5) [37, 38]. The general trend of the receptor binding profile in this series tends to be morphine-like; namely, the compounds exhibit affinity to κ as well as to μ and δ receptors. The presence of the fused aromatic ring has caused an increase in μ affinity. This increase is particularly striking in the case of the 5-hydroxy compound E when compared to the unsubstituted compound D. The authors ascribe it to the presence of the phenolic ring, mimicking the tyramine moiety, as in the alkaloid agonists of the morphine series. The best mu/κ ratio is exhibited by compound D which does not have substituents on either ring of the tetrahydroisoquinoline moiety.



A, B, C D, E F

		receptor binding affinity Ki, nM			
	all are (–)	κ	μ	δ	μ/κ
A	R = 3-Me cis	0.43	11.1	43.6	26
B	R = 4-Me trans	0.6	56.5	158	94
C	R = 4.4-Me_2	2.3	239	1010	104
D	X = H	0.2	30.2	113	151
E	X = OH	0.09	0.49	7.09	5.4
F		0.24	10.7	149	44

Fig. 5
SmithKline Beecham analogs of U-50,488 in which one nitrogen is part of a tetrahydroisoquinoline ring.

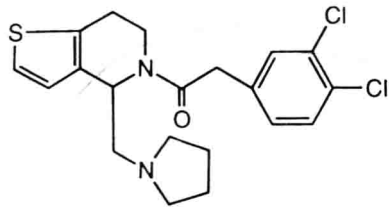
The above group has extended the above SAR to include two compounds in which one nitrogen is part of a thienopiperidine ring (Fig. 6) [38]. Compound A showed the best mu/κ ratio of the compounds shown in Figures 5 and 6.

The SmithKline Beecham group described U-50,488 analogs in which one nitrogen is part of a piperidine ring and the aromatic ring is extended to tetraline and tetralone. Four of these are shown in Figure 7 [39].

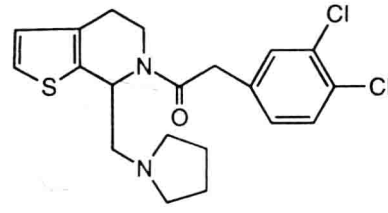
Overall this series showed lack of correlation between κ binding affinity and antinociceptive potency *in vivo* as shown in Figure 7.

The most interesting compound C showed moderate κ affinity (Ki = 47 nM), negligible affinity for mu, delta and sigma receptors (Ki > 1000 nM), *in vivo* subcutaneous antinociceptive activity, reduced propensity to cause sedation and diuresis and, finally, it displayed lesser propensity to aversive side-effects.

A paper also appeared from this group [40] describing the receptor binding and antinociceptive activity of racemates and enantiomers of a large number of compounds in the series discussed above.



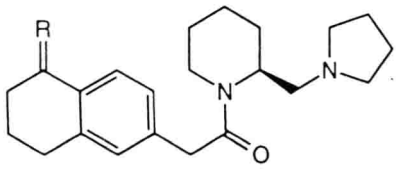
A



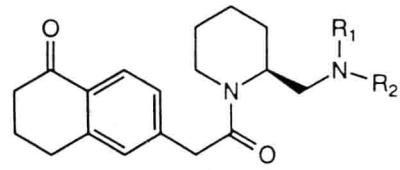
B

	binding affinity Ki, nM			
	κ	μ	δ	μ/κ
A	0.22	47.2	153	215
B	0.46	47	362	102

Fig. 6
SmithKline Beecham analogs of U-50,488 in which one nitrogen is part of a thienopiperidine ring.



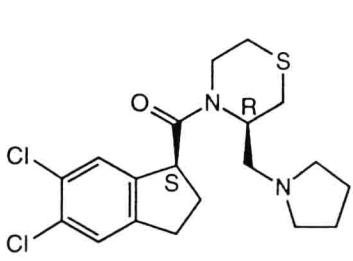
A, R = H_2
B, R = O



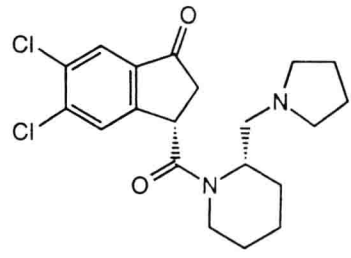
C, $R_1 = R_2$ = Me
D, R_1 = Me, R_2 = i - Pr

	κ Ki, nM	mouse abdominal constriction ED_{50} mmol/kg sc
A.	0.81	0.57
B.	7.60	0.35
C.	47.0	0.47
D.	4.07	0.22

Fig. 7
SmithKline Beecham analogs of U-50,488 in which one nitrogen is part of a piperidine ring.



R-84760



A.

IC_{50}, nM
κ = 0.9
μ = 230

	IC_{50}, nM			
	κ	μ	δ	μ/κ
R-84760	0.436	297	1030	681
U-50,488	7.59	571	10.400	75.2

Fig. 8
Sankyo analogs of U-50,488 in which one nitrogen is part of a six-membered ring and the amide side-chain has restricted rotation.

2.3 Sankyo piperidine analogs

The Sankyo group synthesized analogs of U-50,488 in which one nitrogen is part of a six-membered ring and the amidic side chain has restricted rotation (Fig. 8) [41]. R-84760 is a κ agonist with high affinity, selectivity and functional potency and has been subjected to extensive pharmacology. An earlier Sankyo compound A, which belongs to the same structural class, is also shown in Figure 8 [42].

2.4 Parke-Davis analogs with conformationally restricted aromatic rings

In elaboration of the earlier leads PD 117302 and PD 129290 (CI-977, enadoline) (Fig. 9, compound A and B) [43] Parke-Davis scientists found that com-