example, the compound predicted to be most active is tri(3-heptyl)methanol with a value of 7.50.

The DARC/PELCO proference includes 339 structures, which are located in the hyperstructure with respect to the experimental structures (Figure 5). Retrospective proference includes two structures, 5 and 11, not used for establishing the correlation. Their predicted values agree with those observed (Figure 1).

All the structures of the proference are predictable with a minimal reliability, four star at level 1, $PR_{min}$ = 339. Since the available key population is not the theoretical one, this proference is completely reliable for only eight structures, $PR_{max}$ = 8 (Figure 5).

Among the intermediate proferences, only those at level 2 are determined here (Figure 5). For each structure, the degree of reliability is automatically determined by considering the reliability degrees of the perturbations associated with its binary cosites (Table I). They are maximal, four star, if the cosites exist in the treated population. Untested binary cosites are considered to be zero with three-star reliability, if they include a site situated beyond the activity frontier $F_A$ or a site s and a site beyond the inhibiting frontier $F_I(s)$. They are considered to be zero with two-star reliability, if they include sites belonging to the active environment and are not required to specify the inhibiting frontiers. They are considered to be the negative value of the sixth or fifth carbon with one-star reliability when introduced in primary or secondary and tertiary alcohols, respectively. Grouping structures whose activity prediction is carried out with similar reliability leads to four level 2 reliability areas (Table III).

The predictive capacity of the DARC/PELCO method is thus both more reliable and more extensive than that of fragmentary models. Topology leads to a greater number of predictions than does cutting up molecules into fragments (Table I). For nonordered models, the number of predictions is 11 453 (11 480 - 27), if the description is topological, and only 337, if the description is fragmentary. Such predictions are risky because the equivalence hypothesis is not verified. For ordered models, the predictive capacity is 340, if it is a topological one, and 91 if it is a fragmentary one. Moreover, the DARC/PELCO method allows one to isolate, within the set of predictions, those which are reliable.

The power of the DARC/CALPHI system and the fundamental character of the structural variable, pertaining to ordered topological sites, enable one to express nuances for global, fragmentary or topological methods. Its use in constructing topohydrophobic or electronic models will be presented in a forthcoming paper.

**Registry No.** 1, 64-17-5; 2, 67-63-0; 3, 75-65-0; 4, 71-23-8; 5, 78-92-2; 6, 75-85-4; 7, 78-83-1; 8, 584-02-1; 9, 600-36-2; 10, 71-36-3; 11, 6032-29-7; 12, 590-36-3; 13, 137-32-6; 14, 123-51-3; 15, 108-11-2; 16, 97-95-0; 17, 589-55-9; 18, 71-41-0; 19, 626-93-7; 20, 589-82-2; 21, 111-27-3; 22, 543-49-7; 23, 104-76-7; 24, 111-70-6; 25, 123-96-6; 26, 111-87-5; 27, 143-08-8.

# Specific Bradycardic Agents. 2. Heteroaromatic Modifications in the Side Chain of Specific Bradycardic Benzazepinones: Chemistry, Pharmacology, and Structure–Activity Relationships

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Compound 1 (UL-FS 49) has recently been described as the representative of a novel class of antiischemic compounds termed "specific bradycardic agents". In search of specific bradycardic agents with different pharmacokinetic profiles, heteroaromatic analogues of 1 have been synthesized and evaluated for their bradycardic activity, selectivity, and duration of action. The chain length *n* and the nature of the heteroaromatic system of compounds 2 strongly determine the biological activities. Unsubstituted benzothiophenes and benzofurans in combination with a chain length of *n* = 2 give the most active bradycardic compounds. Some of the new compounds combine high bradycardic potency and selectivity with a short duration of action and may thus be useful for the development of short-acting specific bradycardic drugs.

The prevention of myocardial hypoxia by reducing the cardiac oxygen consumption is one of the main principles in the treatment of coronary heart disease.[1] Whereas this can be achieved by the administration of cardiodepressive agents like β-adrenoceptor antagonists[2,3] or calcium channel blockers,[4] these drugs may exert detrimental negative inotropic and hypotensive effects. Therefore a specific reduction of sinus heart rate, which is a major determinant of myocardial oxygen demand,[5] appears to be a desirable therapeutic approach.

Compound 1 has recently been described as the representative of a novel pharmacological class termed "specific bradycardic agents".[6-8] It reduces heart rate without concomitant negative inotropic or hypotensive effects.[9] Searching for potential follow-up compounds of 1, we directed our attention not only to agents with high activity

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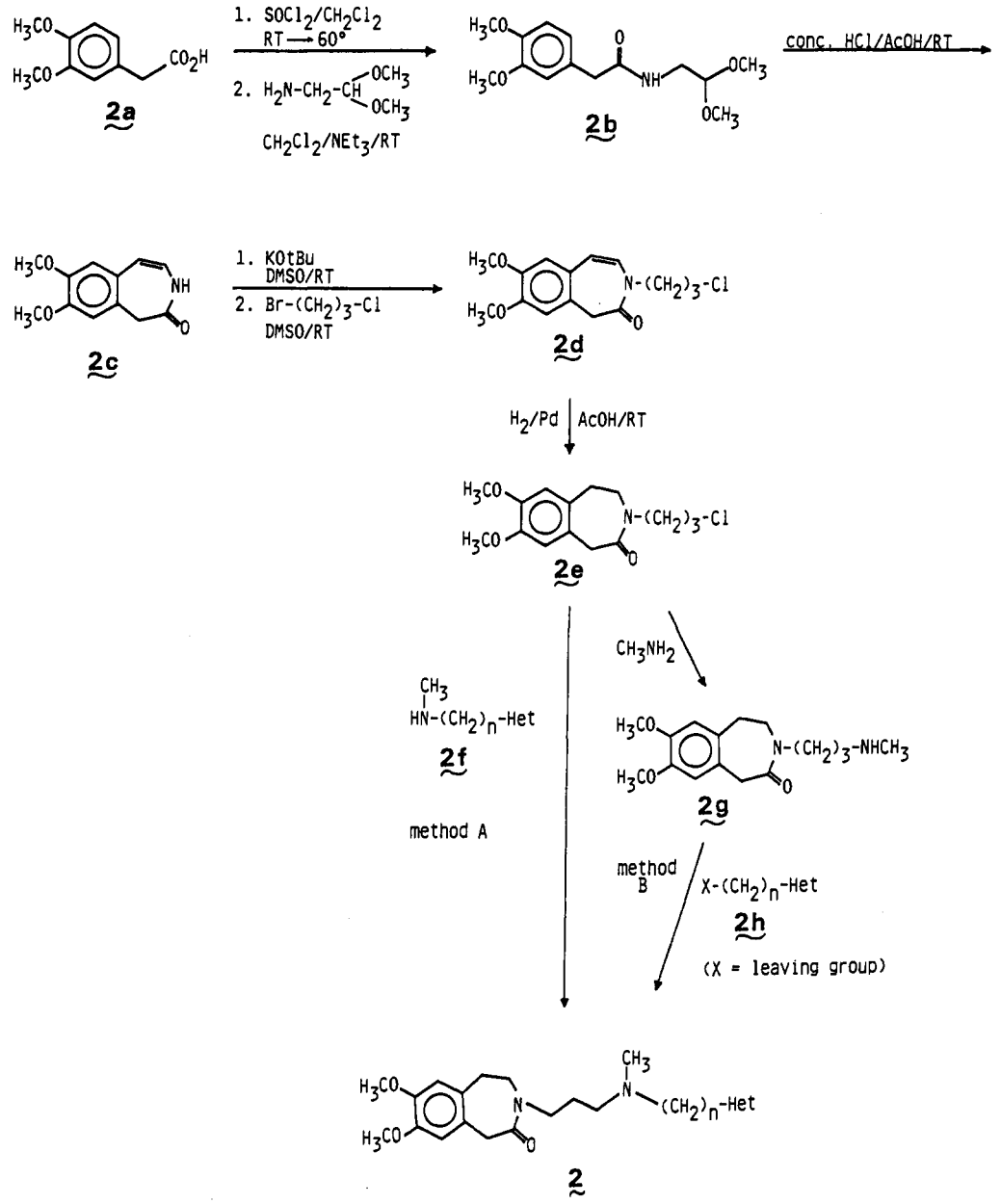
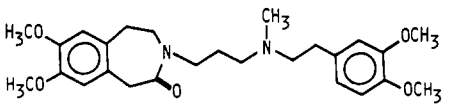
(1) Sonnenblick, E. H.; Skelton, C. L. *Mod. Concepts Cardiovasc. Dis.* 1971, *40*, 9.
(2) Conolly, M. E.; Kersting, F.; Dollery, C. T. *Prog. Cardiovasc. Dis.* 1976, *19*, 203.
(3) Warltier, D. C.; Gross, G. J.; Jesmok, G. J.; Brooks, H. L.; Hardman, H. F. *Cardiology* 1980, *66*, 133.
(4) Meils, C. M.; Gross, G. J.; Brooks, H. L.; Warltier, D. C. *Cardiology* 1981, *68*, 146.
(5) Sonnenblick, E. H.; Ross, J., Jr.; Braunwald, E. *Am. J. Cardiol.* 1968, *32*, 328.
(6) Kobinger, W.; Lillie, C. *Eur. J. Pharmacol.* 1984, *104*, 9.
(7) Kobinger, W.; Lillie, C. *Eur. Heart J.* 1987, *8* (*Suppl. L*), 7.
(8) *Drugs Future* 1985, *10*, 639; (updates) 1986, *11*, 718; 1987, *12*, 825; 1988, *13*, 804.
(9) Franke, H.; Su, C. A. P. F.; Schumacher, K.; Seiberling, M. *Eur. Heart J.* 1987, *8* (*Suppl. L*), 91.

0022-2623/91/1834-0942$02.50/0 

**Scheme I**




and selectivity but also those with different pharmacokinetic profiles. Whereas the long duration of action of compound 1 makes it especially suitable for chronic therapy, interest has recently arisen in the development of short-acting derivatives for acute settings such as the management of sinus tachycardias and acute myocardial ischemia.[10,11]



1

In the course of the optimization work which eventually led to compound 1, extensive information on structure–activity relationships was obtained.[12] With regard to the bradycardic activity the benzazepinone ring, the three-carbon alkyl chain and the basic nitrogen atom are very sensitive to structural modifications. On the other hand, the arylalkyl moiety exhibits considerable potential for structural variations.

It seemed reasonable to assume that this structural element might influence heart rate and blood pressure and the duration of biological activity. Since heteroaromatic systems offer a great deal of variability with regard to lipophilic, electronic, and steric properties, we investigated heteroaromatic analogues 2 of compound 1 in order to find new specific bradycardic compounds with high activity and, preferably, short duration of action.

## Chemistry

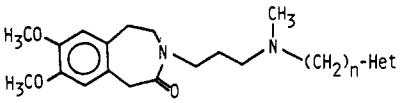
The synthesis of compounds 2 follows essentially the same pathway as that reported for 1 (Scheme I).[12]

(10) Swerdlow, C. D.; Peterson, J.; Turlapaty, P. *Am. Heart J.* 1986, *111*, 49.

(11) Sung, R. J.; Blanski, L.; Kirshenbaum, J.; MacCosbe, P.; Turlapaty, P.; Laddu, A. R.; the Esmolol Research Group *J. Clin. Pharmacol.* 1986, *26* (*Suppl. A*), A15.

(12) Reiffen, M.; Eberlein, W.; Müller, P.; Psiorz, M.; Noll, K.; Heider, J.; Lillie, C.; Kobinger, W.; Luger, P. *J. Med. Chem.* 1990, *33*, 1496.

**Table I.** Biological Activities and Physical Properties of Compounds of General Formula 2



2

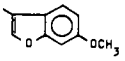
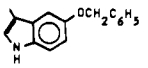
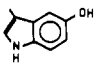
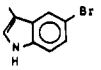
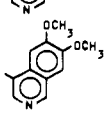
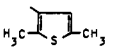
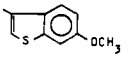
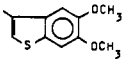
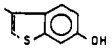
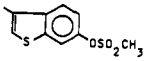
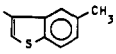
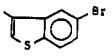
| no. | *n* | Het | ΔHR(5 min)[a] (5 mg/kg iv), % ± SEM | ΔHR(20 min)[a] (5 mg/kg iv), % ± SEM | ΔMAP(5 min)[a] (5 mg/kg iv), % ± SEM | ΔHR(20 min) / ΔHR(5 min) | *S* | formula[b] | mp, °C | TLC[c] |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | | | -56 ± 5 | -46 ± 7 | -21 ± 3 | 0.83 | 2.6 | | | |
| 3 | 2 |  | -12 ± 6 | -11 ± 8 | -52 ± 10 | 0.92 | 0.23 | $C_{22}H_{30}N_2O_4$·HCl | 212 | |
| 4 | 3 | | -19 ± 1 | -18 ± 5 | -61 ± 6 | 0.95 | 0.31 | $C_{23}H_{32}N_2O_4$ | oil | 0.44 (A) |
| 5 | 2 |  | -67 ± 4 | -45 ± 3 | -39 ± 1 | 0.67 | 1.7 | $C_{26}H_{32}N_2O_4$·HCl | 137–139 | |
| 6 | 2 |  | -54 ± 8 | -39 ± 6 | -39 ± 9 | 0.72 | 1.4 | $C_{26}H_{32}N_2O_4$ | oil | 0.35 (A) |
| 7 | 2 |  | -31 ± 4 | -14 ± 4 | -8 ± 5 | 0.45 | 3.9 | $C_{27}H_{34}N_2O_5$ | oil | 0.21 (A) |
| 8 | 2 |  | -59 ± 1 | -34 ± 5 | -35 ± 5 | 0.58 | 1.7 | $C_{27}H_{34}N_2O_5$·HCl | 194–195 | |
| 9 | 2 |  | -30 ± 4 | -18 ± 3 | -18 ± 3 | 0.59 | 1.7 | $C_{23}H_{33}N_3O_3$ | oil | 0.76 (B) |
| 10 | 2 |  | na[d] | na | -11 ± 1 | - | - | $C_{21}H_{30}N_4O_3$ | oil | 0.60 (C) |
| 11 | 2 |  | na | na | na | - | - | $C_{21}H_{30}N_4O_3$ | oil | 0.55 (D) |
| 12 | 4 | | na | na | na | - | - | $C_{23}H_{34}N_4O_3$ | oil | 0.53 (A) |
| 13 | 2 |  | -10 ± 2 | -11 ± 3 | -10 ± 4 | 1.1 | 1.0 | $C_{22}H_{32}N_4O_3$ | oil | 0.70 (D) |
| 14 | 2 |  | -10 ± 1 | -15 ± 1 | na | 1.5 | - | $C_{25}H_{32}N_4O_3$ | oil | 0.57 (A) |
| 15 | 1 |  | -5 ± 2 | -14 ± 3 | na | 2.8 | - | $C_{22}H_{31}N_3O_4$ | 93–95 | |
| 16 | 2 |  | na | na | na | - | - | $C_{22}H_{31}N_3O_3S$·2HCl | 196–197.5 | |
| 17 | 2 |  | -50 ± 7 | -36 ± 3 | -23 ± 1 | 0.73 | 2.2 | $C_{26}H_{33}N_3O_3$ | 136–140 | |
| 18 | 3 | | -62 ± 5 | -47 ± 9 | -34 ± 5 | 0.76 | 1.8 | $C_{27}H_{35}N_3O_3$ | 49–54 | |
| 19 | 2 |  | -50 ± 5 | -37 ± 12 | -22 ± 4 | 0.74 | 2.3 | $C_{27}H_{35}N_3O_3$ | oil | 0.37 (E) |
| 20 | 2 |  | -32 ± 6 | -29 ± 3 | -18 ± 1 | 0.92 | 1.8 | $C_{27}H_{35}N_3O_4$ | 55–59 | |
| 21 | 2 |  | -49 ± 6 | -46 ± 2 | -45 ± 2 | 0.93 | 1.1 | $C_{33}H_{39}N_3O_4$ | oil | 0.46 (F) |
| 22 | 2 |  | -49 ± 6 | -24 ± 2 | -27 ± 4 | 0.49 | 1.8 | $C_{26}H_{33}N_3O_4$ | 68–75 | |
| 23 | 2 |  | -33 ± 7 | -27 ± 3 | -34 ± 4 | 0.82 | 0.98 | $C_{26}H_{32}BrN_3O_3$ | 74–80 | |
| 24 | 2 |  | -50 ± 3 | -44 ± 7 | -26 ± 4 | 0.88 | 1.9 | $C_{27}H_{35}N_3O_3$ | 62–66 | |
| 25 | 1 |  | na | na | na | - | - | $C_{22}H_{29}N_3O_3$·2HCl | 96–102 | |
| 26 | 2 | | -15 ± 7 | -16 ± 5 | na | 1.1 | - | $C_{23}H_{31}N_3O_3$·2HCl | 165–167 | |
| 27 | 1 |  | na | na | na | - | - | $C_{22}H_{29}N_3O_3$·2HCl | 176–178 | |
| 28 | 2 | | -12 ± 5 | -18 ± 2 | -11 ± 6 | 1.5 | 1.1 | $C_{23}H_{31}N_3O_3$·2HCl | 110–112 | |
| 29 | 2 |  | -10 ± 5 | -21 ± 1 | na | 2.1 | - | $C_{23}H_{31}N_3O_3$·2HCl | 116–118 | |
| 30 | 2 |  | -5 ± 4 | -5 ± 6 | na | 1.0 | - | $C_{29}H_{37}N_3O_5$·2HCl | 148–153 | |

**Table I** (Continued)

| no. | n | Het | ΔHR(5 min)[a] (5 mg/kg iv), % ± SEM | ΔHR(20 min)[a] (5 mg/kg iv), % ± SEM | ΔMAP(5 min)[a] (5 mg/kg iv), % ± SEM | ΔHR(20 min)/ΔHR(5 min) | S | formula[b] | mp, °C | TLC[c] |
|---|---|---|---|---|---|---|---|---|---|---|
| **31** | 2 | | -28 ± 1 | -16 ± 5 | -34 ± 10 | 0.56 | 0.82 | $C_{22}H_{30}N_2O_3S\cdot 2HCl$ | 215 | |
| **32** | 3 | | -40 ± 6 | -19 ± 2 | -20 ± 8 | 0.48 | 2.0 | $C_{23}H_{32}N_2O_3S\cdot HCl$ | 176–177 | |
| **33** | 4 |  | -61 ± 4 | -24 ± 4 | -2 ± 5 | 0.39 | 2.3 | $C_{24}H_{34}N_2O_3S\cdot 2HCl$ | 110–113 | |
| **34** | 5 | | -68 ± 5 | -36 ± 11 | -15 ± 4 | 0.53 | 4.4 | $C_{25}H_{36}N_2O_3S\cdot HCl$ | 149–151 | |
| **35** | 6 | | -53 ± 4 | -21 ± 1 | -26 ± 7 | 0.40 | 2.0 | $C_{26}H_{38}N_2O_3S\cdot 2HCl$ | 123–125 | |
| **36** | 2 |  | -24 ± 6 | -19 ± 1 | na | 0.79 | - | $C_{22}H_{30}N_2O_3S\cdot HCl$ | 185 | |
| **37** | 2 |  | -61 ± 1 | -40 ± 4 | -36 ± 4 | 0.65 | 1.7 | $C_{24}H_{34}N_2O_3S\cdot 2HCl$ | 180–181 | |
| **38** | 2 |  | -69 ± 3 | -55 ± 5 | -43 ± 3 | 0.80 | 1.6 | $C_{26}H_{36}N_2O_3S\cdot HCl$ | 110–112 | |
| **39** | 1 | | -18 ± 3 | -7 ± 4 | -27 ± 4 | 0.40 | 0.66 | $C_{25}H_{30}N_2O_3S\cdot 2HCl$ | 218–220 | |
| **40** | 2 |  | -66 ± 4 | -51 ± 3 | -55 ± 5 | 0.78 | 1.2 | $C_{26}H_{32}N_2O_3S\cdot HCl$ | 195 | |
| **41** | 3 | | -65 ± 1 | -45 ± 1 | -46 ± 3 | 0.69 | 1.4 | $C_{27}H_{34}N_2O_3S\cdot HCl$ | 219 | |
| **42** | 2 |  | -34 ± 5 | -24 ± 4 | -21 ± 1 | 0.72 | 1.6 | $C_{27}H_{34}N_2O_4S$ | oil | 0.41 (A) |
| **43** | 2 |  | -67 ± 1 | -60 ± 1 | -52 ± 4 | 0.89 | 1.3 | $C_{27}H_{34}N_2O_4S\cdot 2HCl$ | 177–179 | |
| **44** | 2 |  | -24 ± 5 | -17 ± 2 | -17 ± 1 | 0.71 | 1.4 | $C_{28}H_{36}N_2O_5S$ | oil | 0.27 (A) |
| **45** | 2 |  | -50 ± 8 | -37 ± 4 | -29 ± 6 | 0.74 | 1.7 | $C_{26}H_{32}N_2O_4S$ | oil | 0.45 (C) |
| **46** | 2 |  | -50 ± 6 | -40 ± 12 | -21 ± 16 | 0.80 | 2.4 | $C_{27}H_{34}N_2O_6S_2\cdot HCl$ | 120–123 | |
| **47** | 2 |  | -51 ± 1 | -38 ± 5 | -36 ± 5 | 0.75 | 1.4 | $C_{27}H_{34}N_2O_3S\cdot 2HCl$ | 138–142 | |
| **48** | 2 |  | -50 ± 3 | -17 ± 4 | -41 ± 2 | 0.34 | 1.2 | $C_{26}H_{31}BrN_2O_3S$ | oil | 0.50 (A) |

[a] SEM values for entry 1 are based on $n = 45$ for HR and $n = 21$ for MAP. SEM values for entries 3–48 are based on $n = 3$. [b] For all compounds satisfactory C, H, N analyses were obtained (±0.4%). [c] For the TLC system used refer to the Experimental Section. [d] Na = not active (HR or MAP changes less than 5%).

Starting from 3,4-dimethoxyphenylacetic acid (**2a**), reaction with thionyl chloride followed by aminoacetaldehyde dimethyl acetal yields compound **2b**. Subsequent acid cyclization gives dihydroazepinone **2c** and alkylation with 1-bromo-3-chloropropane (**2d**) followed by hydrogenation leads to the key intermediate **2e**. Compound **2e** can be transformed to the final products **2** in two different ways. Either it is directly reacted with heteroaromatic amine **2f** (method A) or it is first converted to amine **2g**, followed by alkylation with **2h** (method B).

The final alkylation steps proceed with moderate to low yields, yet no attempts at optimization have been made. The target compounds **2** were usually isolated as hydrochloride salts, but many exist as dihydrochlorides.

## Pharmacological Results

The target compounds of this study were evaluated for bradycardic and hypotensive activities in an anesthetized rat model.[12] Heart rate (beats/min) and mean aortic blood pressure (mmHg) were recorded before and 5 and 20 min after iv injection of 5 mg/kg of test compounds.

The bradycardic potency of the compounds of general formula **2** is assessed by the percent heart rate reduction 5 min after injection, ΔHR(5 min), which in most cases corresponds to the maximum of the bradycardic effect.

As a measure for the duration of action, the ratio of heart rate reductions after 20 and 5 min, respectively, ΔHR(20 min)/ΔHR(5 min), is used. Low values of this ratio thus characterize short-acting compounds.

As a rough estimate of the selectivity of the bradycardic activity a selectivity parameter $S$ is introduced. $S$ is defined as the ratio of heart rate reduction to mean arterial blood pressure reduction, each determined 5 min after injection and expressed in percent values.

$$S = \frac{\Delta HR(5\ min)}{\Delta MAP(5\ min)}$$

According to this definition, highly selective bradycardic agents are characterized by high values of $S$. Values of $S$ greater than 2 in the rat model represent highly selective compounds. This has been shown for compound **1** in more refined pharmacological models[7] or in human studies.[9]

As shown in Table I, the biological activities of compounds **2** span a broad range concerning potency, duration of action, and selectivity. Imidazole (**10–14**) and pyridine (**25–30**) derivatives show, if at all, very low biological activity. In contrast, the most potent derivatives of **1** reported to date could be found among the furan and thiophene derivatives (**5**, **34**, **38**, **43**). Regarding the duration of action, the vast majority of compounds with at least moderate bradycardic potency (heart rate reduction more than 20%) are shorter acting agents than **1**.

Whereas compounds like **7** and **34** show a very high selectivity for bradycardic versus hypotensive activity, the majority of compounds are less selective than compound **1** in the rat model used here. Some derivatives (e.g. **3**, **4**, **39**) are even more potent as hypotensives than as bradycardics.

## Discussion

Both the chain length $n$ and the nature of the heteroaromatic ring of compounds **2** distinctly influence the biologic activities.[13–15]

**(a) Influence of the Chain Length *n*.** In all cases investigated, compounds with chain lengths $n = 1$ show, if at all, low bradycardic activity (compounds **25**, **27**, **39**), which, however, increases with elongation of the chain (**26**, **28**, **40**). Further increase from $n = 2$ to $n = 3$ in general increases bradycardic potency (**3** → **4**, **17** → **18**, **31** → **32**), whereas in the case of the highly active benzothiophenes **40** and **41** the maximum of the bradycardic potency seems to be already achieved with $n = 2$.

In the thiophene series (**31**–**35**) the heart rate lowering activity steadily increases from $n = 2$ to $n = 5$ (**31** → **34**) and decreases thereafter (**35**). Assuming a common receptor binding site for the dimethoxyphenyl group of **1** and the heteroaromatic ring of analogues **2**, the high activity of compounds **33**–**35** is very remarkable since it requires an appropriate folding of the highly flexible side chain.

The correlation between the chain length $n$ and the selectivity $S$ roughly parallels that between $n$ and the bradycardic potency (**3** → **4**, **31** → **35**, **39** → **41**). In other words, $n$ seems to affect mainly the bradycardic, and less so the hypotensive, activity of compounds **2**. Similarly, the duration of action is essentially unaffected by variations in the chain length $n$ (**3** → **4**, **17** → **18**, **31** → **35**), the only exception being the benzothiophenes (**39** → **40**). Most remarkably, the 2-thienyl compounds (**31**–**35**) constitute the only structurally homogeneous subgroup with a uniformly short duration of action.

**(b) Influence of the Heteroaromatic Moiety Het.** The comparison of compounds **2** with the chain length $n$ being held constant within each subgroup shows that the nature of the heteroaromatic ring and the substituents attached to it exert a strong influence on the biological activity.

In a series of monocyclic systems, polar heterocycles like imidazoles (**10**, **11**, **13**) and pyridines (**26**, **28**, **29**) are very weakly active. The same holds true for the bradycardic activity of thiazole derivative **16** and furan **3**, whereas pyrrole **9** and thiophenes **31** and **36** are significantly more active.

Most remarkable changes in the biological activity are brought about by the addition of aliphatic substituents or benzocondensation of the five-membered heteroaromatic rings. Dimethyl (**37**) or tetramethylene (**38**) substitution as well as benzocondensation (**40**) of the 3-thienyl compound **36** dramatically increase bradycardic potency, whereas the duration of action remains essentially constant. Similarly, the hardly bradycardic furan **3** turns into the highly active benzofuran **5**. Even the completely inactive imidazole **11** gains some activity by benzocondensation (**14**). It might be speculated that an increase in lipophilicity of the heteroarylalkyl moiety of compounds **2** leads to an increase in bradycardic potency.

On the basis of these findings, we further investigated the influence of substituents on the heteroaromatic systems with the highest bradycardic activities, namely the benzofuran, benzothiophen, and indole compounds. With all the substitution patterns investigated, no further significant improvement in bradycardic potency could be achieved. Whereas monosubstitution in ring positions 1 (**19**), 6 (**8**, **43**, **45**, **46**), and 7 (**24**) seems to be widely tolerated, methoxylation in position 4 (**7**, **42**) markedly reduces the bradycardic activity. Substitution in ring position 5 exerts no clear-cut effect: depending on the nature of the substituent, preservation (e.g. **22**) or marked reduction (e.g. **20**) of the bradycardic potency can be observed.

Regarding the selectivity $S$ of these compounds, no correlation with the nature or the position of the substituent could be established. The same is true for the duration of action, and the occurrence of particularly short-acting compounds (**7**, **22**, **48**) seems to be erratic.

Considering sets of homologous heteroaromatic compounds differing only in the heteroatom (**3**, **31**; **4**, **32**; **6**, **17**, **40**; **8**, **43**; **7**, **42**; **23**, **48**), thiophenes are consistently associated with the highest bradycardic potency. Again, no such relationship is evident for the selectivity of these homologues. Regarding the duration of action, furans seem to be longer acting than homologous thiophenes (**3**, **31**; **4**, **32**), whereas the opposite is true for methoxy-substituted benzofurans and benzothiophenes, respectively (**8**, **43**; **7**, **42**). Homologous unsubstituted benzofurans, indoles, and benzothiophens (**6**, **17**, **40**) all have the same duration of action.

## Conclusion

The bradycardic activity, selectivity, and duration of action of heteroaromatic analogues **2** of compound **1** is strongly determined by the nature of the heteroaromatic ring Het and the chain length $n$.

High biological activities can be achieved with quite different types of heteroaromatic rings. These findings underline and extend the considerable variability for structural manipulations of the aryl moiety of **1** found in previous investigations.[12] Regarding the length of the alkyl chain connecting the central nitrogen atom and the heteroaromatic ring, the variability even exceeds the previous findings in the benzenoid aromatic series[12] and promises further potential for structural manipulations. In our investigations relationships between structure and bradycardic activity could be established, which may be helpful in the design of new highly active compounds. Concerning the bradycardic selectivity and duration of action, no clear-cut correlations with structural features could be observed. Some of the new compounds, like the thienyl derivative **33**, combine high bradycardic potency and selectivity with a short duration of action and may thus be useful for the development of short-acting specific bradycardic agents.

## Experimental Section

**(a) Chemistry.** Melting points were detemined in open glass capillaries with a Büchi melting point apparatus and are uncorrected. Infrared (IR) spectra were obtained on a Perkin-Elmer Model 298 spectrophotometer. Proton magnetic resonance spectra were recorded on a Bruker AM-400 instrument with tetramethylsilane as internal standard. Microanalyses were conducted by the Thomae Research Microanalysis Laboratory, Biberach, Germany. Silica gel (Silica Woelm$^R$ 32–63 m) was used for column chromatography.

TLC was performed on 0.25 mm thickness silica gel plates (Merck, silica gel 60, F-254) or 0.2 mm thickness aluminium oxide plates (Macherey-Nagel, Polygram Alox N/UV-254), respectively; the following TLC systems were used: (A) $SiO_2/CH_2Cl_2$–MeOH 9:1 v/v; (B) $Al_2O_3/CH_2Cl_2$–EtOH 19:1 v/v; (C) $Al_2O_3/CH_2Cl_2$–MeOH 10:1 v/v; (D) $Al_2O_3/CH_2Cl_2$–MeOH 20:1 v/v; (E) $SiO_2/CH_2Cl_2$–EtOH 10:1 v/v; (F) $Al_2O_3/CH_2Cl_2$–EtOH 20:1 v/v.

**7,8-Dimethoxy-3-(3-chloropropyl)-1,3,4,5-tetrahydro-2*H*-3-benzazepin-2-one (2e).** A solution of 7,8-dimethoxy-3-(3-chloropropyl)-1,3-dihydro-2*H*-3-benzazepin-2-one[12] (59.2 g, 0.2 mol) in 50 mL of glacial acetic acid was hydrogenated in the presence of 5 g of 10% palladium/charcoal for 6 h at 50 °C and at 5 bar. The catalyst was suction filtered, the glacial acetic acid was distilled off in vacuo, and after the addition of water, the residue was neutralized with potassium carbonate. The precipitate

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was suction filtered, washed with water until free from salt, and recrystallized from acetone–$H_2O$ to give 53 g (89 %) of **2e**, mp 100–102 °C. Anal. ($C_{15}H_{20}ClNO_3$) C, H, N.

**7,8-Dimethoxy-3-[3-(methylamino)propyl]-1,3,4,5-tetrahydro-2*H*-3-benzazepin-2-one Hydrochloride (2g·HCl).** A mixture of **2e** (5.9 g, 20 mmol) and methylamine (14 g, 0.45 mol) was heated to 130 °C for 1 h in a sealed tube. The cooled reaction product was taken up in 20% NaOH solution and extracted with $CH_2Cl_2$. After the extract had been dried and concentrated, the hydrochloride of **2g** was precipitated from acetone–ether with ethereal hydrochloric acid to give 5.2 g (80%), mp 110 °C. Anal. ($C_{16}H_{24}N_2O_3$·HCl) C, H, N.

A representative example for the synthesis of target compounds **2** by method A (Scheme I) follows.

**7,8-Dimethoxy-3-[3-[(2-benzo[*b*]thien-3-ylethyl)methylamino]propyl]-1,3,4,5-tetrahydro-2*H*-3-benzazepin-2-one Hydrochloride (40).** A mixture of **2e** (0.80 g, 2.7 mmol), 3-[2-(methylamino)ethyl]benzo[*b*]thiophene[16] (0.52 g, 2.7 mmol), and 5 mL of triethylamine was heated to 60 °C for 30 min. The temperature was then increased to reflux temperature and maintained for 3 h. After the triethylamine had been distilled off, the mixture was heated to 100 °C for a further 5 h. The product obtained was purified over a silica gel column with $CH_2Cl_2$–$CH_3OH$ 25:1 as eluant, taken up in $CH_3OH$, and precipitated with ethereal hydrochloric acid to give 0.86 g (65%) of **40**: mp 195 °C; IR (KBr) 1650 $cm^{-1}$ (C=O); $^1H$ NMR (DMSO-$d_6$–$CD_3OD$) 1.99 (quintet, 2 H), 2.91 (s, 3 H), 3.0–3.15 (m, 3 H), 3.15–3.5 (m, 7 H), 3.70 (s, 6 H), 3.75–3.9 (m, 4 H), 6.70 (s, 1 H), 6.71 (s, 1 H), 7.40–7.50 (m, $A_2B_2$-type, 2 H), 7.56 (s, 1 H), 7.94 (d, 1 H), 7.99 (d, 1 H) ppm. Anal. ($C_{26}H_{32}N_2O_3S$.HCl) C, H, N.

A representative example for the synthesis of target compounds **2** by method B (Scheme I) follows.

**7,8-Dimethoxy-3-[3-[[4-(1*H*-imidazol-1-yl)butyl]methylamino]propyl]-1,3,4,5-tetrahydro-2*H*-3-benzazepin-2-one (12).** A mixture of **2g**·HCl (1.65 g, 5.0 mmol), 4-(1*H*-imidazol-1-yl)-1-chlorobutane[17] (0.80 g, 5.0 mmol), and anhydrous $K_2CO_3$ (2.6 g, 20 mmol) in 50 mL of DMF was refluxed for 2 h. The solvent was evaporated in vacuo, and the residue was taken up in 20% NaOH solution and extracted with $CHCl_3$. The extract was washed with NaCl solution, dried with $Na_2SO_4$, concentrated in vacuo, and purified over an alumina column (eluant: $CH_2Cl_2$) to give 0.91 g (44%) of **12**. IR ($CH_2Cl_2$) 1647 $cm^{-1}$ (C=O); $^1H$ NMR ($CDCl_3$–$CD_3OD$) 1.46 (quintet, 2 H), 1.73–1.84 (m, 4 H), 2.23 (s, 3 H), 2.34–2.42 (m, 4 H), 3.09 (t, 2 H), 3.44 (t, 2 H), 3.77 (t, 2 H), 3.81 (s, 2 H), 3.84 (s, 3 H), 3.85 (s, 3 H), 3.98 (t, 2 H), 6.61 (s, 1 H), 6.63 (s, 1 H), 6.98 (br s, 1 H), 7.01 (br s, 1 H), 7.54 (br s, 1 H) ppm. Anal. ($C_{23}H_{34}N_4O_3$) C, H, N.

According to the preparation of **40** and **12**, the target compounds shown in Table I were synthesized by either method A or B.

**(b) Pharmacology.** Male rats of the strain Chbb:THOM, weighing between 200 and 250 g, were anesthetized with pentobarbital sodium, 50 mg/kg ip. The trachea was cannulated and artificial respiration was performed. The heart rate was recorded continuously on an ink-writing polygraph by means of an instantaneous beat to beat recording tachograph triggered by the electrocardiogram (ECG). Blood pressure was measured by means of a cannula introduced into the carotid artery and connected to an electromechanical transducer. Test substances were injected via the jugular vein.

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**Registry No. 2d**, 85175-59-3; **2e**, 85175-65-1; **2g**·HCl, 85175-52-6; **3**, 106891-30-9; **3**·HCl, 106891-48-9; **4**, 106891-26-3; **5**, 108783-46-6; **5**·HCl, 131104-60-4; **6**, 108783-07-9; **7**, 108783-35-3; **8**, 108783-45-5; **8**·HCl, 108802-14-8; **9**, 106891-52-5; **10**, 106891-35-4; **11**, 106891-43-4; **12**, 106891-22-9; **13**, 106891-45-6; **14**, 106891-49-0; **15**, 108783-30-8; **16**, 108783-06-8; **16**·2HCl, 131079-78-2; **17**, 98784-70-4; **18**, 131079-63-5; **19**, 131079-64-6; **20**, 98784-72-6; **21**, 131079-65-7; **22**, 131079-66-8; **23**, 131079-67-9; **24**, 131079-68-0; **25**, 108783-51-3; **25**·2HCl, 106891-54-7; **26**, 131079-69-1; **26**·2HCl, 106891-57-0; **27**, 131079-70-4; **27**·2HCl, 106891-55-8; **28**, 131079-71-5; **28**·2HCl, 106891-60-5; **29**, 131079-72-6; **29**·2HCl, 106891-56-9; **30**, 108783-52-4; **30**·2HCl, 106891-58-1; **31**, 131079-73-7; **31**·2HCl, 106891-31-0; **32**, 106891-62-7; **32**·2HCl, 106891-28-5; **33**, 108783-48-8; **33**·2HCl, 106891-41-2; **34**, 131079-74-8; **34**·HCl, 131079-79-3; **35**, 131079-75-9; **35**·2HCl, 131079-80-6; **36**, 131079-76-0; **36**·HCl, 131079-81-7; **37**, 108783-56-8; **37**·2HCl, 108783-19-3; **38**, 108783-37-5; **38**·HCl, 131079-82-8; **39**, 131079-77-1; **39**·2HCl, 108783-12-6; **40**, 108783-47-7; **40**·HCl, 106891-40-1; **41**, 108783-53-5; **41**·HCl, 108783-10-4; **42**, 108783-55-7; **43**, 108771-78-4; **43**·2HCl, 106891-20-7; **44**, 108783-03-5; **45**, 108783-39-7; **46**, 108783-41-1; **46**·HCl, 131079-83-9; **47**, 108783-54-6; **47**·2HCl, 108783-13-7; **48**, 108783-17-1; 3-[2-(methylamino)ethyl]benzo[*b*]thiophene, 52994-61-3; 4-(1*H*-imidazol-1-yl)-1-chlorobutane, 73828-78-1.

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