5a-d. Thus, during the preparation of phosphonic acids, as a result of evaporation procedures, solid, crude products were obtained. Crystallization from a mixture of water and ethanol afforded analytically pure phosphonic acids **4a** and **4b**. In the case of the preparations of phosphinic acids **5a**, **5b**, **5c**, and **5d**, as a result of evaporation procedures, oily materials were obtained. These products were dissolved in water (25 mL), acidified with concentrated hydrochloric acid to pH 1, and concentrated on a rotating evaporator at 80 °C (20 torr). In each case, the residue was mixed with water (10 mL) and concentrated under preceding conditions, repeating this operation three times. Finally, the oily residues were dissolved in anhydrous ethanol (25 mL), and the pH was adjusted with pyridine to the point at which the Congo Red paper no longer changed to blue. The resultant solutions were then set aside for crystallization, which required several days for completion. Filtration and washing of the crystals with anhydrous ethanol and subsequently with ethyl ether afforded analytically pure compounds **5a**, **5b**, and **5d**, as the monohydrochloride salts. Since hydrochloride **5c** did not crystallize from ethanol solution, this solution was concentrated on a rotating evaporator at 50 °C (20 torr) and the oily residue dissolved in water (10 mL) and passed through a column filled with Dowex 50X2-100 ion-exchange resin in hydrogen (H^+) form, eluting with 2 N aqueous ammonia. The fractions with a positive ninhydrin test were combined and concentrated on a rotating evaporator at 80 °C (20 torr) followed by addition of water (10 mL) to the oily residue and repeating the evaporation under the preceding conditions. The remaining oily residue was then dissolved in water (15 mL) and the pH adjusted to 3.8 with 2 N hydrobromic acid. The resultant solution was concentrated to dryness on a rotating evaporator at 80 °C (20 torr) and the solid, crude product recrystallized from anhydrous ethanol to give pure **5c** monohydrobromide. The yields and analytical data for all compounds are shown in Table I.

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Registry No. **1a**, 70-26-8; **1b**, 48047-94-5; **3a**, 3598-60-5; **3b**, 3197-25-9; **4a**, 20820-73-9; **4b**, 96616-24-9; **5a**, 96616-25-0; **5a**·HCl, 96616-26-1; **5b**, 96616-27-2; **5b**·HCl, 96616-28-3; **5c**, 96616-29-4; **5c**·HBr, 96616-30-7; **5d**, 96616-31-8; **5d**·HCl, 96616-32-9; ornithine decarboxylase, 9024-60-6; phosphorus trichloride, 7719-12-2; methyldichlorophosphine, 676-83-5; ethyldichlorophosphine, 1498-40-4; benzyl carbamate, 621-84-1.

Structure-Activity Relationships for Prazosin and WB 4101 Analogues as α_1-Adrenoreceptor Antagonists[1]

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Several α-adrenoreceptor antagonists were prepared by coupling one of the two moieties of WB 4101 (**1**) with one of the two moieties of prazosin (**2**). Their blocking activity and relative selectivity on α_1- and α_2-adrenoreceptors were evaluated in the isolated rat vas deferens. Although retaining a significant selectivity toward α_1-adrenoreceptors, all the drugs were weaker antagonists than the parent compounds **1** and **2**. Opening the piperazine ring of **2** gave **3**, which displayed a very high activity and selectivity toward α_1-adrenoreceptors (α_1/α_2 = 3890). This may have relevance in understanding the mode of action of prazosin. In addition, **3** may represent a valuable tool in the characterization of α-adrenoreceptor subtypes.

Knowledge of receptor structure and function requires not only accessibility to selective ligands (both agonists and antagonists) but at the same time understanding of their mode and site of action. Adrenoreceptors play a fundamental role in human pharmacology for their involvement in many vital functions. Thus knowledge of both the chemical and biochemical nature of these receptors is of paramount importance. A great amount of research has led to a clearer picture for β-adrenoreceptors compared to α-adrenoreceptors. This may be explained by the fact that β-adrenoreceptor ligands can be structurally related to the endogenous catecholamines leading to relevant structure-activity relationships. On the contrary, different classes of α-adrenoreceptor ligands cannot be easily correlated with one another, owing to their different unrelated chemical structures.[2] As a consequence, we know only little about antagonist binding sites at α-adrenoreceptors. Furthermore, the situation is even more complex when one considers that the α-adrenoreceptor is not an homogeneous population.[3-8] In fact, it can be divided into α_1- and α_2-types according to their selectivity toward agonists and antagonists.[9,10] Since many unrelated structures are active at both types of α-adrenoreceptors,[2,11] we have recently undertaken a study aimed at correlating different classes of α-adrenoreceptor antagonists.[12]

Among α-adrenoreceptor antagonists, WB 4101 (**1**) and prazosin (**2**) have a prominent role in the characterization of α_1-adrenoreceptors owing to their specificity and selectivity.[13] Furthermore, **2** is used in treating patients with hypertension and congestive heart failure.[14] Although many structure-activity relationship studies among derivatives of **1** and **2** are available,[2,13] none, to our knowledge,

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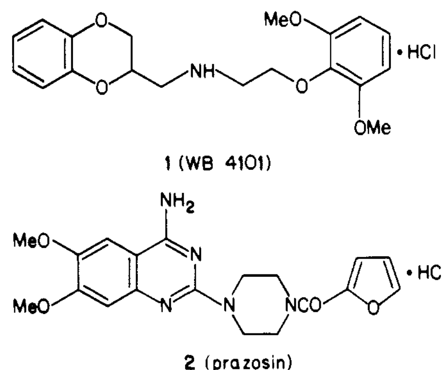

1 (WB 4101)

2 (prazosin)

deals with compounds having one of the two moieties linked to the nitrogen of **1** connected through an amine function to one of the two groups attached to the nitrogen of **2**. In this paper we describe the synthesis and the biological activity of hybrid compounds **5–10** and of **3**[15] and **4**[15] in which the piperazine ring of **2** was replaced by an ethanediamine moiety.

Chemistry. All the compounds were characterized by ^1H NMR, IR, and elemental analysis and were synthesized by standard procedures as shown in Schemes I and II. Thus, condensation of 2-chloro-4-amino-6,7-dimethoxyquinazoline[16,17] (**11**) with **12**,[18] **13**, **14**,[19] **15**, or **16**[20] gave **3**,[15] **4**,[15] **5**, **6**, or **7**, respectively (Scheme I). Compounds **8** and **9** were obtained by condensation of **17**[21] with the amines **18**[17] and **12**[18] (Scheme II). Similarly, **10** was obtained through the alkylation of amine **18** with the chloride **19**[20] (Scheme II).

Pharmacology. The biological profile of the compounds listed in Table I at α_1- and α_2-adrenoreceptors was assessed on isolated rat vas deferens. Since it has been demonstrated that the prostatic and epididymal portions of this tissue have different properties,[22,23] they were employed separately, avoiding the use of the whole vasa.

α_1-Adrenoreceptor blocking activity was assessed by antagonism of (−)-norepinephrine-induced contractions of the epididymal portion of the vas deferens. α_2-Adrenoreceptor blocking activity was determined by antagonism of the clonidine-induced depression of the twitch responses of the field stimulated prostatic portion of vas deferens following the procedure outlined by Michel and Whiting[24] and recently described in detail by Caroon et al.[25] The potency of the drugs was expressed as pA_2 values calculated according to Arunlakshana and Schild[26] or van Rossum.[27]

Table I. α_1- and α_2-Adrenoreceptor pA_2 Values in the Isolated Rat Vas Deferens[a]

antagonist	α_1 pA_2 against norepinephrine	α_2 pA_2 against clonidine	α_1/α_2[b] selectivity ratio
1	8.83 ± 0.02	6.29 ± 0.10	347
2	8.74 ± 0.16	5.81 ± 0.10	851
3	8.81 ± 0.13	5.22 ± 0.05	3890
4	7.18 ± 0.21	5.37 ± 0.07	65
5	7.88 ± 0.06	5.94 ± 0.08	87
6	7.86 ± 0.24	5.91 ± 0.06[c]	89
7	7.22 ± 0.10	6.17 ± 0.08	11
8	6.05 ± 0.08	6.28 ± 0.04[c]	0.59
9	7.19 ± 0.17	5.85 ± 0.04	22
10	6.45 ± 0.24	4.71 ± 0.09[c]	55

[a] pA_2 values plus or minus standard error of estimate were calculated according to Arunlakshana and Schild[26] unless otherwise specified. pA_2 is defined as the negative logarithm to the base 10 of that dose of antagonist that requires a doubling of the agonist dose to compensate for the action of the antagonist. [b] The α_1/α_2 selectivity ratio is the antilog of the difference between pA_2 values at α_1- and α_2-adrenoreceptors. [c] Calculated according to van Rossum[27] since it was not possible to investigate three different concentrations owing to the inhibition of twitch responses of electrically stimulated tissue at concentrations higher than 30 μM.

Results and Discussion

In the present study, the α_1- and α_2-adrenoreceptor blocking properties of **1** (WB 4101) and **2** (prazosin) were also studied and compared with those of **3–10**. The results obtained are shown in Table I. It can be seen that all the compounds exhibited a marked selectivity toward α_1-adrenoreceptors with the only exception being **8**. Furthermore, it is evident that potency at α_1-adrenoreceptors ranged within 3 orders of magnitude whereas activity at α_2-adrenoreceptors did not vary dramatically among investigated drugs. This allows us to draw the conclusion that structural changes that markedly affect the binding at α_1-sites do not alter the affinity for α_2-sites. Next, the results clearly indicate that all the drugs obtained by coupling alternatively one of the two moieties of **1** with one of the moieties of **2**, that is, **5–10**, are significantly weaker antagonists than the parent compounds. Although this might indicate that **1** and **2** bind at unrelated sites, the possibility that they recognize an identical site cannot be excluded since the decrease in activity observed for hybrid compounds **5–10** may simply reflect a decrease in affinity for such a site.

N-Methylation in **1** caused a 1000-fold decrease in activity,[28] which indicates that optimum activity is associated with a secondary amine function. On the other hand, opening the piperazine ring of **2** to give **3** clearly suggests that the anionic binding site of **2** can accept both secondary and tertiary positively charged amines as also shown by N-methylation of **5** to give **6**. However, one could argue that N-methylation of **3** to give **4** does not follow the same pattern. However, it is our opinion that the significant decrease in activity found for **4** might indicate that the two *N*-methyl groups, owing to steric hindrance, force the molecule to assume a conformation that is different from that probably adopted by **2** and **3**. In this light, it is possible that the piperazine ring as such does not contribute to the binding while being important in stabilizing an optimal conformation for the drug–receptor interaction mechanism. Thus, the high activity and selectivity toward α_1-adrenoreceptors displayed by **3** could be the result of hydrogen-bond formation between amine and amide

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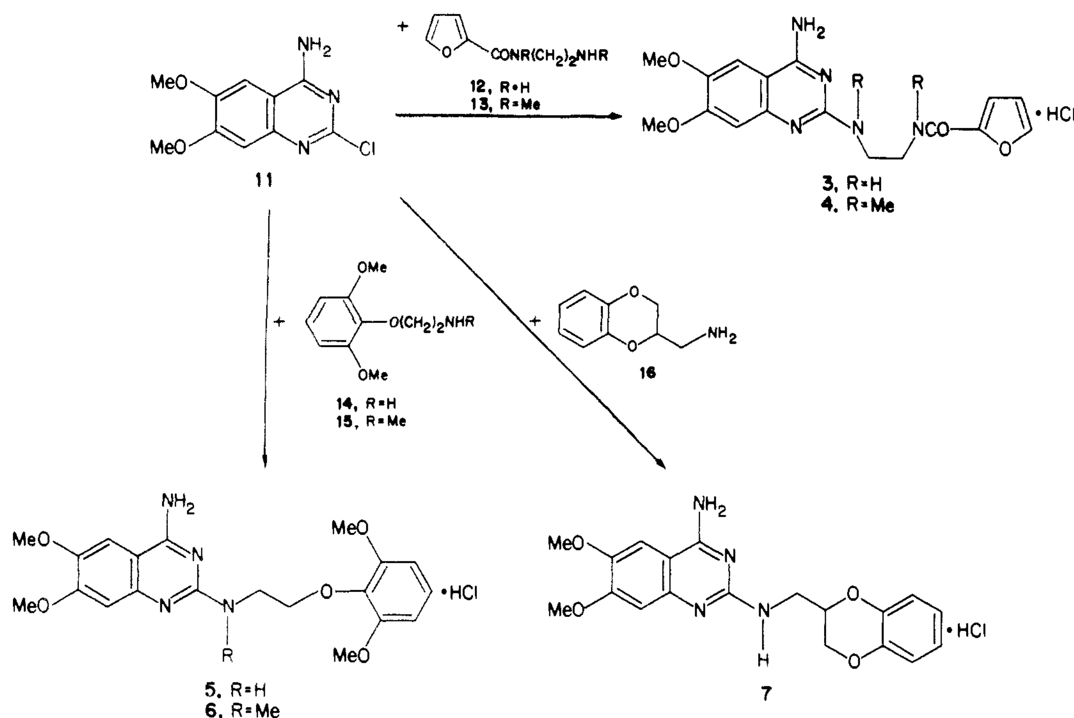
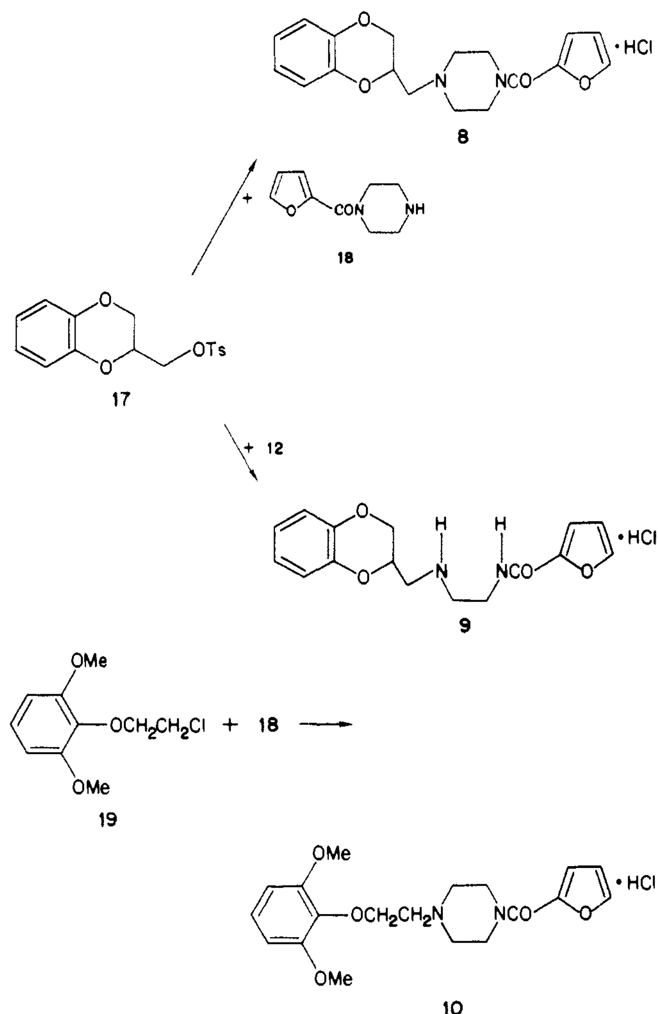
Scheme I



Scheme II



functions that would stabilize a conformation similar to that of **2**. In addition, opening of the piperazine ring to give **3** appears to diminish affinity for α_2-adrenoreceptors. In fact, the selectivity ratio of 3890 displayed by **3**, along with the topographical implications discussed above, represents the most striking result of the present investigation. To our knowledge, **3** represents, until now, the most selective antagonist toward α_1-adrenoreceptors in in vitro experiments and it might be an useful tool in the characterization of α-adrenoreceptor subtypes.

Experimental Section

Chemistry. Melting points were taken in glass capillary tubes on a Büchi SMP-20 apparatus and are uncorrected. IR and NMR spectra were recorded on Perkin-Elmer 297 and Varian EM-390 instruments, respectively. Although the IR and NMR spectra data are not included (because of the lack of unusual features), they were obtained for all compounds reported and were all consistent with the assigned structures. The microanalyses were performed by the Microanalytical Laboratory of the Department of Chemical Sciences of the University of Camerino and the elemental compositions of the compounds agreed to within ±0.4% of the calculated values. Chromatographic separations were performed on silica gel columns (Kieselgel 40, 0.063–0.200 mm, Merck). The term "dried" refers to the use of anhydrous sodium sulfate. Petroleum ether refers to the fraction with a boiling point of bp 40–60 °C.

***N*-2-Furoyl-*N*,*N'*-dimethyl-1,2-ethanediamine (13).** HBr (48%, 8.73 mL) and 2-furoyl chloride (5.0 g, 38.3 mmol) were added separately to a stirred solution of 1,2-ethanediamine (9.44 g, 107 mmol) in ethanol (71 mL) and water (9 mL), at such a rate that the temperature was kept below 40 °C. The mixture was stirred at 80 °C for 1.5 h and then it was cooled (0 °C) and left to stand overnight. Removal of solvent gave a residue which was taken up in water and washed with chloroform (3 × 50 mL). Aqueous solution was made basic with NaOH pellets and extracted with chloroform (3 × 50 mL). Removal of dried solvents gave a residue which was purified by column chromatography; eluting with chloroform–petroleum ether–methanol–28% ammonia (12.5:7.5:4:0.25) yielded 2.3 g (33%) of an oil, which was used in the next step without further purification.

2-(2,6-Dimethoxyphenoxy)-*N*-methyl-1-ethanamine (15). Chloride **19**[20] (1.0 g, 4.62 mmol) in absolute ethanol (20 mL) and 17% methylamine in ethanol (12.6 mL, 69.3 mmol) were heated in a sealed glass tube at 110 °C for 70 h. After removal of solvent, the residue was taken up in 10% NaOH (25 mL) and extracted with chloroform (3 × 50 mL). Removal of dried solvent gave an oil, which was purified by column chromatography, eluting with

Table II

compd	mp,[a] °C	yield, %	recrystn solvent	formula[b]
3	257–259	32	MeOH/i-PrOH	$C_{17}H_{20}ClN_5O_4$
4	240–242	53	MeOH/i-PrOH	$C_{19}H_{24}ClN_5O_4$
5	230–232	31	MeOH	$C_{20}H_{25}ClN_4O_5$
6	221–223	19	MeOH/i-PrOH	$C_{21}H_{27}ClN_4O_5$
7	254–256	30	MeOH	$C_{19}H_{21}ClN_4O_4$
8	267–270	22	MeOH	$C_{18}H_{21}ClN_2O_4$
9	177–180	31	i-PrOH	$C_{16}H_{19}ClN_2O_4$
10	181–183	32	MeOH/Et_2O	$C_{19}H_{25}ClN_2O_5$

[a] The heating rate was 1 °C/min. [b] Analyses for C, H, N were within ±0.4% of the theoretical value required.

ethyl acetate–petroleum ether–methanol–28% ammonia (7:3:2:0.15), to give 0.58 g (60%) of **15**, which was used in the next step without further purification.

General Procedure for the Synthesis of 3–10. The procedure adopted for the synthesis of **3** is described.

A mixture of chloride **11**[16,17] (0.35 g, 1.5 mmol) and amine **12**[18] (0.25 g, 1.6 mmol) in isoamyl alcohol (15 mL) was heated at reflux with stirring for 6 h. The precipitate was filtered off, washed with isoamyl alcohol (3 × 2 mL), and ether (3 × 5 mL) and purified by column chromatography, eluting with chloroform–petroleum ether–methanol-28% ammonia (8:10:2:0.1), to give **3** as the free base. This was treated with an excess of hydrogen chloride in ethanol to give the hydrochloride salt, which then was recrystallized.

Similarly **4** and **6** were obtained from suitable starting materials (Scheme I).

Compounds **8–10** (Scheme II) were synthesized with use of 2-methoxyethanol instead of isoamyl alcohol as solvent. After refluxing, this solvent was removed in vacuo to give a residue, which was purified by column chromatography as described for **3**.

Compounds **5** and **7** (Scheme I) were prepared with the following modification. The precipitate obtained after refluxing was filtered and then purified by recrystallization to give the expected hydrochlorides directly.

The physical characteristics of **3–10** are reported in Table II.

Pharmacology. Male albino rats (175–200 g) were killed by a sharp blow on the head and both vasa deferentia were isolated, free from adhering connective tissue, and transversely bisected. Prostatic portions, 12 mm in length, and epididymal portions, 14 mm in length, were prepared and mounted individually in baths of 20 mL working volume containing Krebs solution of the following composition: 118.4 mM NaCl, 4.7 mM KCl, 2.52 mM $CaCl_2$, 1.2 mM $MgSO_4{\cdot}7H_2O$, 1.2 mM KH_2PO_4, 25.0 mM $NaHCO_3$, 11.1 mM glucose. The $MgSO_4{\cdot}7H_2O$ concentration was reduced to 0.6 mM when twitch response to field stimulation was studied. The medium was maintained at 37 °C and gassed with 95% O_2–5% CO_2. The loading tension used to assess α_1- or α_2-blocking activities was 0.4 g or 0.5–0.8 g, respectively, and the contractions were recorded by means of force transducers connected to a two-channel Gemini 7070 polygraph.

Field stimulation of the tissue was carried out by means of two platinum electrodes, placed near the top and bottom of the vas deferens, at 0.1 Hz using square pulses of 3-ms duration at a voltage of 10–35 V. The stimulation voltage was fixed throughout the experiments.

Propranolol hydrochloride (1 μM), cocaine hydrochloride (10 μM), and deoxycorticosterone acetate (40 μM) were present in the Krebs solution throughout the experiments outlined below to block β-adrenoreceptors and neuronal and extraneuronal uptake mechanisms, respectively.

α_1-Adrenoreceptor Blocking Activity. Postsynaptic α_1-adrenoreceptor blocking activity was determined on the epididymal portion of the vas deferens. The tissues were allowed to equilibrate for at least 1 h before the addition of any drug. Norepinephrine dose–response curves were obtained cumulatively, the first one being discarded and the second one taken as a control. After incubation with the antagonist for 30 min, a third dose–response curve was obtained. Responses were expressed as a percentage of the maximal response obtained in the control curve. Parallel experiments, in which tissues did not receive any antagonists, were run in order to correct for time-dependent changes in agonist sensitivity.[29] It was generally verified that the third dose–response curve was identical with the second because the change in dose ratio is less than 2, which usually represents a minimal correction.

The antagonist potency of compounds **1–10** at α_1-adrenoreceptors was expressed in terms of their pA_2 value according to Arunlakshana and Schild.[26] These values were calculated from the ratio of the doses (DR) of agonist causing 50% of the maximal response in the presence and in the absence of the test compound. The log (DR-1) was calculated at three antagonist concentrations and each concentration was tested at least five times.

α_2-Adrenoreceptor Blocking Activity. This was assessed on the prostatic portion of the vas deferens by antagonism to an α_2-adrenoreceptor agonist, clonidine. Clonidine inhibits twitch responses of the field-stimulated vas deferens by acting on the presynaptic α-adrenoreceptor.[30,31]

Since a full recovery from maximal effective concentrations of clonidine could not be obtained by washing,[30] it was not possible to study the effect of clonidine and the α-antagonists on the same preparation. The procedure outlined by Michel and Whiting was followed.[24] Thus, after a 1-h equilibration period, one tissue was incubated for 30 min with the test antagonist whereas the contralateral prostatic portion was used as control. After the incubation period, dose–response curves to clonidine were obtained on both preparations and dose ratio (DR) values were determined from the concentration causing 50% inhibition of the twitch response in the absence and in the presence of antagonist. Each antagonist was tested at three different concentrations and each concentration was investigated at least five times. Compounds **6**, **8**, and **10**, however, were tested at only two concentrations because at concentrations higher than 30 μM there was inhibition of twitch responses of electrically stimulated tissue.

The results are expressed as pA_2 values calculated according to Arunlakshana and Schild[26] for **1–5**, **7**, and **9** whereas for **6**, **8**, and **10** the method of van Rossum[27] was followed. The Student's t test was used to assess the significance of the experimental results.

Acknowledgment. This work was supported by the National Research Council of Italy. A generous gift of prazosin from Pfizer (Rome) is gratefully acknowledged.

Registry No. **1**, 613-67-2; **1**·HCl, 2170-58-3; **2**, 19216-56-9; **2**·HCl, 19237-84-4; **3**, 96649-54-6; **3**·HCl, 96649-37-5; **4**, 96649-38-6; **4**·HCl, 96649-39-7; **5**, 96649-40-0; **5**·HCl, 96649-41-1; **6**, 96649-42-2; **6**·HCl, 96649-43-3; **7**, 96649-44-4; **7**·HCl, 96649-45-5; **8**, 96649-46-6; **8**·HCl, 96649-47-7; **9**, 96649-48-8; **9**·HCl, 96649-49-9; **10**, 96649-50-2; **10**·HCl, 96649-51-3; **11**, 23680-84-4; **12**, 58827-18-2; **13**, 96649-52-4; **14**, 40515-98-8; **15**, 96649-53-5; **16**, 4442-59-5; **17**, 1094-91-3; **18**, 40172-95-0; **19**, 24251-50-1; 2-furoyl chloride, 527-69-5.

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