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Bioorganic & Medicinal Chemistry Letters 13 (2003) 1385–1389

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

Further Exploration of 1-{2-[Bis-(4-fluorophenyl)methoxy]ethyl}piperazine (GBR 12909): Role of *N*-Aromatic, *N*-Heteroaromatic, and 3-Oxygenated *N*-Phenylpropyl Substituents on Affinity for the Dopamine and Serotonin Transporter

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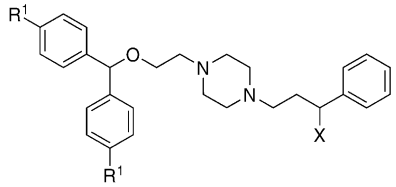
Received 9 October 2002; accepted 21 November 2002

Abstract—A series of *N*-aromatic, *N*-heteroaromatic, and oxygenated *N*-phenylpropyl derivatives of 1-(2-benzhydryloxyethyl)-piperazine and 1-{2-[bis-(4-fluorophenyl)methoxy]ethyl}piperazine, analogues of GBR 12909 (**1a**) and 12935 (**1b**), was synthesized and examined for their dopamine (DAT) and serotonin (SERT) transporter binding properties. One of these compounds, racemic 3-[4-(2-benzhydryloxyethyl)piperazin-1-yl]-1-(3-fluorophenyl)-propan-1-ol (**33**), had DAT affinity as good as, or better than, GBR 12909 and 12935, and was more selective for DAT over SERT than the GBR compounds. Both *trans*- (**43**) and *cis*- (**47**) (±)-2-(4-{2-[bis-(4-fluorophenyl)-methoxy]ethyl}piperazin-1-ylmethyl)-6-methoxy-1,2,3,4-tetrahydronaphthalen-1-ol had relatively good SERT selectivity and, as well, showed high affinity for SERT.

Dopamine reuptake inhibitors[1] have been considered for the treatment of depression and Parkinson's disease, and a prototypic dopamine reuptake inhibitor, GBR 12909 (Fig. 1, 1-{2-[bis-(4-fluorophenyl)methoxy]ethyl}-4-(3-phenylpropyl)piperazine, **1b**), was examined for those purposes.[2] We,[3–7] and others,[8–11] have suggested that a selective high affinity dopamine reuptake inhibitor[12] might be useful as a treatment agent for the abuse of cocaine and other stimulants,[13] and **1b** is currently being evaluated for that purpose and has satisfactorily completed phase 1 clinical trials under the auspices of the National Institute on Drug Abuse, NIH.[11] However, although the bis(4-fluorophenyl compound **1b**, has very high affinity as a dopamine transporter protein (DAT) ligand, it is not very selective over the serotonin transporter (SERT).

The abuse of cocaine and other stimulants is widespread and has unfortunate sequelae for individuals[14–16] and society.[17,18] We have undertaken a program[5–7,19–22] to design and synthesize analogues of GBR 12909 (**1b**) and GBR 12935 (**1a**) in order to study the pharmacological effect of these ligands. In particular, we have examined the effect of structural modifications on their affinity for the DAT and SERT (serotonin transporter), with the



1a: R^1 = H, X = H, H
1b: R^1 = F, X = H, H
2a: R^1 = H, X = O
2b: R^1 = F, X = O
2c: R^1 = H, X = OH, H
2d: R^1 = F, X = OH, H

Figure 1. Structure of GBR 12909 and GBR 12935 analogues.

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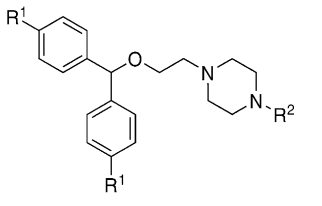
0960-894X/03/$ - see front matter © 2003 Elsevier Science Ltd. All rights reserved.
doi:10.1016/S0960-894X(03)00108-2

hope that new, high affinity, and more selective ligands can be found that have potential as treatment agents capable of reducing the incidence of drug abuse and the concomitant HIV epidemic.

We previously reported the synthesis and biological activity of a series of analogues of **1a** and **1b**, in which the *N*-phenylpropyl moiety was replaced by a heteroaromatic- or bicyclic aromatic-containing side chain.[21] These analogues were potent and more selective DAT ligands than **1a**, as were a more recently reported series of oxygenated analogues of **1a** and **1b**.[22] Herein, we report the synthesis of a novel series of **1a** and **1b** analogues, which contain both of the structural modifications reported earlier (replacement of the phenylpropyl moiety by a heteroaromatic- or bicyclic aromatic-containing side chain and the addition of an oxygen functionality at the 3-position of the 3-phenylpropyl moiety). A DAT selective, high affinity oxygenated compound could eventually be formulated as an extended-action depot preparation, enabling its examination as a second-generation ultra long-acting agent for the treatment of cocaine abuse.[23,24] One dose of the first-generation drug, the decanoate ester of **2d**, eliminated cocaine self-administration in rhesus monkeys almost completely for nearly a month.[22,25]

The *N*-substituted analogues[26–31] were prepared from the previously described 1-(2-benzhydryloxy-ethyl)piperazine (**3a**) and 1-{2-[bis-(4-fluorophenyl)-methoxy] ethyl}piperazine (**3b**) (Fig. 2). A three step sequence of a modified Mannich reaction, followed by treatment of the corresponding Mannich base with iodomethane, and reaction with either **3a** or **3b** gave ketone analogues, **5–8**, **14–19**, **27–30**, and **36–39** (Schemes 1 and 2).[27] Reduction of the ketone analogues using LAH in THF afforded alcohols, **9–12**, **20–25**, **31–34**, and **40–47**.[28] Alcohols **40–47** were separated into the corresponding *trans* (**40–43**) and *cis* (**44–47**) isomers using preparative thin layer chromatography.[29] Treatment of compounds **44–47** with *p*-toluenesulfonic acid gave alkenes **48–51**, respectively.[30]

Our initial investigations began with varying the *N*-substituent phenyl ring in **2a** and **2b** with either a furan (**5**, **6**) or a thiophene (**7**, **8**). The results from the binding assay showed that neither bioisosteric replacement resulted in a high affinity analogue or a highly selective agent (Table 1). Based on the higher affinity of alcohols, **2c** and **2d** compared to ketones, **2a** and **2b**, we thought that reduction of the ketones in **5–8** might increase affinity. Alcohols **9–12**, did show an increase in affinity compared to ketones **6–8** and desfluoro analogue **9** was found to be almost as DAT-selective as **2c**.



3a: $R^1 = R^2 = H$
3b: $R^1 = F$, $R^2 = H$
3c: $R^1 = F$, $R^2 = trans\text{-}CH_2CH{=}CHPh$

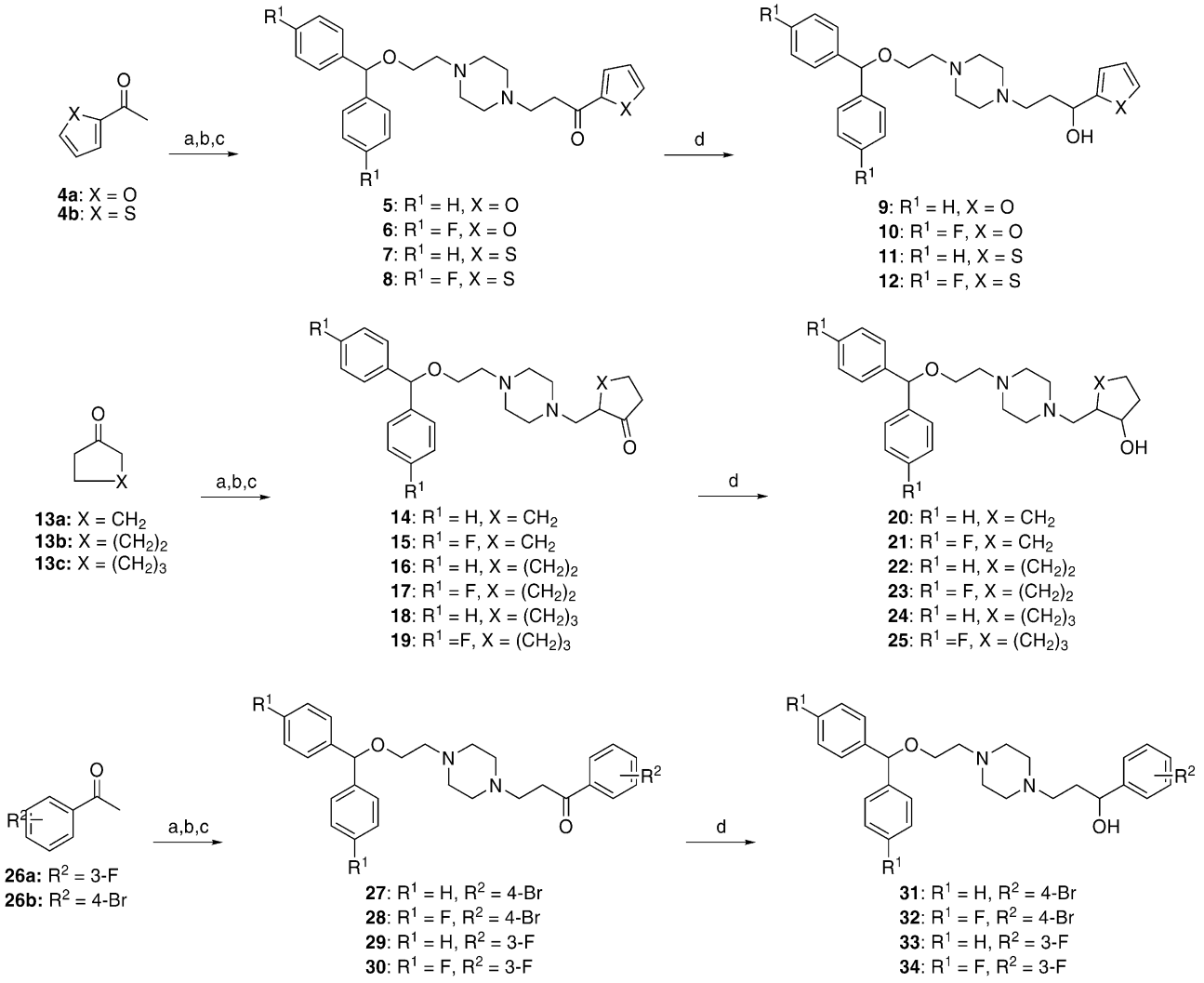
Figure 2. Structures of 1-(2-benzhydryloxy-ethyl)piperazine (**3a**), 1-{2-[bis-(4-fluorophenyl)-methoxy]ethyl}piperazine (**3b**), and GBR 13069 (**3c**).

To further probe the effect of the phenyl ring in compounds **2a** and **2b**, we sought to remove it, and in addition, attempt to limit rotational freedom we constrained the ketone moiety by placing it in several cycloalkane rings, **14–19**. Among the cycloalkanone-containing analogues, **14–19**, the bisfluoro analogues **15**, **17**, and **19** had higher affinity than desfluoro analogues **14**, **16**, and **18** respectively. Reduction of the ketones in **14–19** gave alcohols **20–25**. These modifications slightly increased affinity for both the DAT and SERT compared to ketone analogues **14–19**. The binding data of the cycloalkane

Table 1. Binding affinities and selectivities of GBR 12909 analogues

Compd[a]	R^1	DAT K_i (nM)[b]	SERT K_i (nM)[b]	SERT/DAT
1a	H	3.7 (±0.3)	623 (±13)	168
1b	F	3.7 (±0.4)	126 (±5)	34
2a	H	208 (±4)	1310 (±30)	6
2b	F	48 (±2)	220 (±6)	5
2c	H	6.1 (±0.2)	700 (±50)	115
2d	F	2.1 (±0.1)	120 (±7)	55
3c	F	0.9 (±0.1)	135 (±7)	158
5	H	300 (±9)	3300 (±120)	11
6	F	72 (±3)	350 (±15)	5
7	H	190 (±9)	1240 (±70)	6
8	F	84 (±4)	110 (±12)	1
9	H	19 (±1)	1940 (±110)	104
10	F	10 (±1)	150 (±5)	15
11	H	15 (±1)	690 (±14)	47
12	F	7.2 (±0.2)	59 (±8)	8
14	H	480 (±10)	5700 (±350)	12
15	F	84 (±2)	970 (±30)	12
16	H	250 (±10)	3300 (±180)	13
17	F	62 (±2)	1130 (±50)	18
18	H	270 (±9)	4100 (±160)	15
19	F	49 (±2)	530 (±12)	11
20	H	170 (±6)	2200 (±10)	13
21	F	32 (±2)	920 (±30)	29
22	H	210 (±11)	3300 (±230)	15
23	F	37 (±2)	580 (±20)	16
24	H	210 (±6)	3900 (±170)	19
25	F	22 (±2)	480 (±20)	22
27	H	290 (±9)	2600 (±110)	9
28	F	37 (±1)	480 (±20)	13
29	H	260 (±10)	1360 (±40)	5
30	F	89 (±4)	220 (±9)	2
31	H	7.5 (±0.3)	340 (±8)	45
32	F	2.5 (±0.1)	50 (±2)	20
33	H	4.1 (±0.2)	910 (±50)	221
34	F	3.9 (±0.2)	53 (±2)	14
36	H	390 (±20)	1050 (±50)	3
37	F	57 (±4)	110 (±6)	2
38	H	78 (±2)	70 (±3)	0.9
39	F	22 (±2)	3.0 (±0.3)	0.1
40	H	59 (±2)	440 (±40)	7
41	F	18 (±2)	32 (±1)	2
42	H	40 (±4)	93 (±5)	2
43	F	18 (±1)	3.0 (±0.2)	0.2
44	H	35 (±2)	500 (±30)	14
45	F	1.3 (±0.2)	30 (±2)	23
46	H	32 (±1)	100 (±6)	3
47	F	7.3 (±0.2)	3.0 (±0.3)	0.4
48	H	38 (±2)	1360 (±60)	36
49	F	6.4 (±0.6)	260 (±10)	41
50	H	39 (±1)	530 (±30)	14
51	F	14 (±1)	57 (±3)	4

[a]Prepared and tested as dimaleate salt.
[b]Value determined as in ref 22.

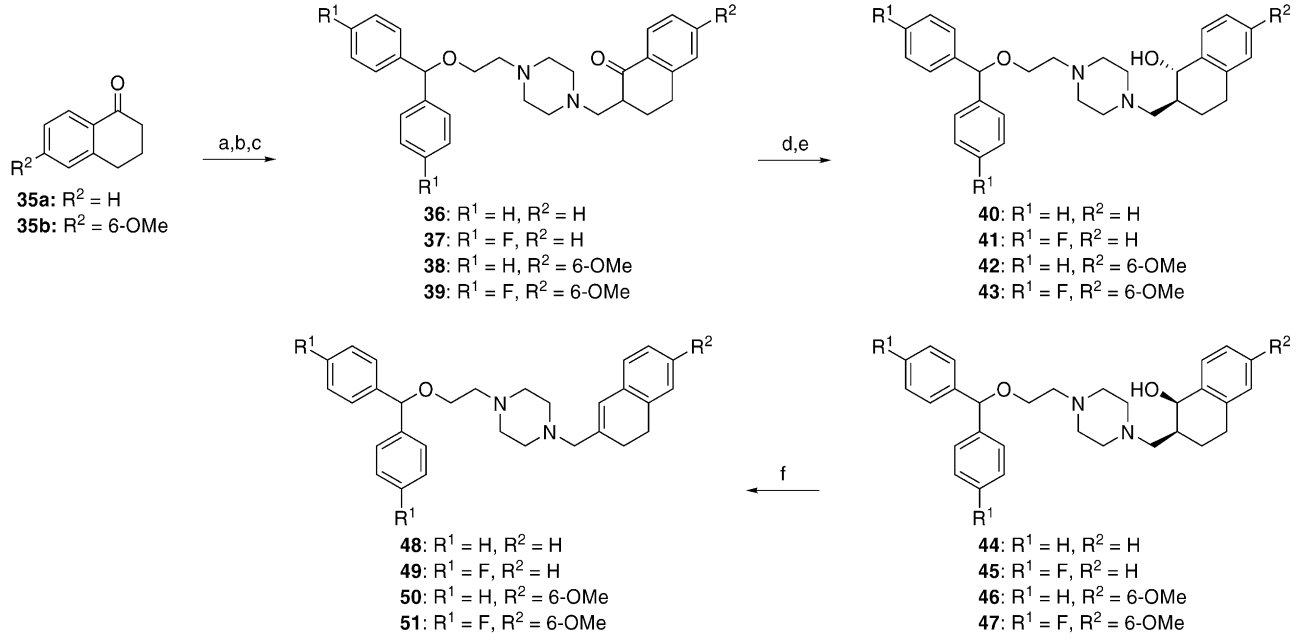


Scheme 1. (a) $(CH_3)_2NH_2{\cdot}HCl$, $(CH_2O)_n$, HCl, EtOH; (b) CH_3I, EtOH; (c) **3a** or **3b**, $NaHCO_3$, $PhCH_3$; (d) LAH, THF.

analogues **14**–**19** and **20**–**25** confirmed our previous finding that an aromatic ring in the side-chain appears to be a requirement for high affinity at the DAT.[32]

Since the phenyl ring appeared to be important, we decided to probe the effects of different substituents in the phenyl ring on the affinity of **2a** and **2b**. We chose to evaluate a 4-bromo substituent, that is, **27** and **28**, and a 3-fluoro substituent, **29** and **30**. The 4-bromo substituent was chosen based on our previous work that showed a 4-methoxy group was tolerated by GBR12909 analogues.[22] We were curious if that was the result of the polar oxygen atom or from a favorable steric interaction. Similarly, the 3-fluoro substituent was chosen because it most resembled the size of the H while having different electronic characteristics. The new ligands, **27**–**30**, had similar affinity and selectivity for the DAT compared to **2a** and **2b**. This seemed to indicate that substitution in the 3- and 4-position was tolerated but did not enhance affinity or selectivity. To further test the role of the 3- and 4-positions of the *N*-substituent, ketones **27**–**30** were reduced to alcohols, **31**–**34**. Once again we saw an increase in affinity for both the DAT and the SERT. In addition, the presence of a 4-bromo group was better tolerated by the DAT than the SERT. The introduction of a 3-fluoro group to **2c**, that is, **33**, resulted in the best selectivity (SERT/DAT = 221) of any of the examined compounds. Curiously, this effect was not observed in the bisfluoro analogue. The addition of a 3-fluoro group to the *N*-substituent in **2d**, that is, **34**, decreased affinity at the DAT ($K_i = 3.9$ nM vs $K_i = 2.1$ nM) and increased affinity at the SERT ($K_i = 53$ nM vs $K_i = 120$ nM).

It occurred to us that to test whether the effect of the ketone moiety is related to its conformational mobility; we locked the ketone group in **2a** and **2b** into a ring, that is, **36** and **37**. This resulted in a slight decrease in the affinity of **36** and **37** for the DAT compared to **2a** and **2b** respectively. In addition, this modification increased affinity for the SERT of **36** and **37** compared to **2a** and **2b**. Based on our finding[22] that addition of a methoxy group into the 4-position of the phenyl ring was tolerated, we added a corresponding methoxy group in the locked conformers



Scheme 2. (a) $(CH_3)_2NH_2{\cdot}HCl$, $(CH_2O)_n$, HCl, EtOH; (b) CH_3I, EtOH; (c) **3a** or **3b**, $NaHCO_3$, $PhCH_3$; (d) LAH, THF; (e) PTLC (SiO_2, $CHCl_3$/MeOH); (f) *p*-TsOH, benzene.

of **2a** and **2b**, giving compounds **38** and **39**. This modification seems to be more favored by the SERT than the DAT. We observed a 10-fold increase in affinity at the SERT when a 6-methoxy group is added to **41**, that is, **43**. Curious if this might be also be paralleled in the case of the corresponding alcohols, ketones **36–39** were reduced to their *trans*- (**40–43**) and *cis*- (**44–47**) isomers. Generally, the *cis*- isomers, **44–47**, had higher DAT affinity and selectivity than the *trans*- isomers, **40–43**. In this series, **45** had higher affinity for the DAT ($K_i = 1.3$ nM) than **2d** but was not as selective over the SERT (SERT/ DAT = 23). It occurred to us that if **47** were dehydrated to form an alkene, that is **49**, it might serve as locked conformer of GBR 13069 (**3c**).[21] It is interesting that **49** has lower affinity ($K_i = 6.4$ nM vs $K_i = 0.9$ nM) and reduced DAT selectivity (41-fold vs 158-fold) compared to **3c**. This would seem to indicate that the greater flexibility in **3c** adds to its high affinity and selectivity. Alkenes **50** and **51**, which are locked conformers of compounds previously described,[22] however, had similar affinity and selectivity to the previous described compounds indicating that this conformation was preferred for DAT affinity and selectivity. This also indicates that the 6-methoxy analogues might not be binding like other GBR 12909 analogues.

Various *N*-substituted GBR 12909 and GBR 12935 analogues have been prepared. Despite their structural similarity not all of these ligands appear to be binding in an identical manner. Compound **33** has been identified as a high affinity DAT ligand with good selectivity over the SERT (SERT/DAT = 221). This compound has a hydroxyl function that might be esterified and could possibly be converted to a long-acting drug. Further pharmacological and SAR studies on this ligand and others with high affinity and selectivity are in progress and will be published in due course.

Acknowledgements

The authors (LMC, NIDDK) thank the National Institute on Drug Abuse, NIH, for partial financial support of our research program. We also thank Noel Whittaker (NIDDK, NIH) for mass spectral data.

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26. Satisfactory ^{1}H NMR and mass spectral data were obtained for all final products. Elemental analyses were within $\pm$0.4% for C, H, and N.
27. General procedure: A solution of **4b** (30.2 g, 239.6 mmol) dimethylamine hydrochloride (58.7 g, 712.1 mmol), 95% paraformaldehyde (29.2 g, 971.5 mmol) and concentrated hydrochloric acid (3 mL) in ethanol (200 mL) was heated at reflux overnight. Upon cooling to room temperature, the product crystallized from solution as the hydrochloride salt, and was collected by filtration. The salt was converted to the free base by treatment with aqueous ammonia and extraction with $CHCl_3$ to give 33.5 g of the corresponding Mannich base. A mixture of the Mannich base (33.5 g, 182.7 mmol) and iodomethane (18.0 mL, 289.2 mmol) in ethanol (500 mL) was stirred at room temperature overnight, and the quaternary methiodide mannich base precipitated from solution. The precipitated product was collected by filtration and dried and used directly in the next step without further purification. A mixture of the quaternary methiodide Mannich base (6.4 g, 19.6 mmol), **3a** (3.8 g, 12.8 mmol), and K_2CO_3 (3.3 g, 31.1 mmol) in DMF (50 mL) was heated to reflux for 1 h, cooled to room temperature, and poured into H_2O (200 mL). The aqueous layer was extracted with Et_2O (3$\times$100 mL). The combined Et_2O portion was washed with brine, dried (Na_2SO_4), and concentrated to an oil. The crude ketone were converted to the bis-maleate salt and recrystallized from methanol to afford **7** dimaleate, mp 166–168 °C.
28. General procedure: A 1 M solution of LAH in THF (5 mL, 5 mmol) was added to a solution of **29** (1.3 g, 2.6 mmol) in dry THF (30 mL). The reaction was stirred at room temperature for 15 min and quenched the sequential addition of 1.3 mL of H_2O, 1.3 mL of 15% NaOH, and 1.3 mL of H_2O. The quenched reaction mixture was filtered through a pad of Celite, the cake washed with three portions of THF, and the organic fractions combined and concentrated at reduced pressure. The crude alcohol (racemic) was converted to the bis-maleate salt and recrystallized from methanol to afford **33**• dimaleate, mp 175–176 °C.
29. General procedure: The racemic alcohols were separated using preparative thin layer silica gel chromatography. A Uniplate Silica gel GF 2000 (or 1500) μM plate, with a chromatography system of $CHCl_3$/MeOH, 30:1 to was used separate the *cis*- from the *trans*-isomers. The separated isomers were each converted to their bis-maleate salts. Recrystallization from methanol gave the pure analogues.
30. General procedure: A mixture of **45** (0.4 g, 0.8 mmol), *p*-TsOH (0.3 g, 1.8 mmol) in toluene (30 mL) was heated at reflux for 12 h utilizing a Dean–Stark trap to remove generated water. The reaction mixture was cooled to room temperature, washed with H_2O and brine, dried (Na_2SO_4), and concentrated to an oil. The crude olefin was converted to the bis-maleate salt and recrystallized from methanol to afford **49**• dimaleate, mp 202–204 °C.
31. Uncorrected melting points of dimaleate salts: **5**: 164–167 °C; **6**: 164–166 °C; **9**: 161–162 °C; **10**: 162–164 °C; **11**: 166–167 °C; **12**: 174–176 °C; **14**: 155–160 °C (dec.); **15**: 162–165 °C (dec.); **16**: 164–165 °C; **17**: 152–154 °C; **18**: 165–167 °C; **19**: 150–152 °C; **20**: 185–187 °C; **21**: 186–188 °C; **22**: 174–176 °C; **23**: 178–179 °C; **24**: 169–171 °C; **25**: 162–164 °C; **27**: 177–179 °C; **28**: 176–178 °C; **29**: 164–167 °C; **30**: 159–161 °C; **31**: 167–168 °C; **32**: 172–173 °C; **34**: 171–173 °C; **36**: 160–162 °C; **37**: 162–163 °C; **38**: 154–157 °C; **39**: 166–167 °C; **40**: 186–189 °C; **41**: 183–184 °C; **42**: 181–182 °C; **43**: 176–177 °C; **44**: 180–182 °C; **45**: 176–177 °C; **46**: 181–182 °C; **47**: 178–179 °C; **48**: 197–198 °C; **50**: 199–201 °C; **51**: 179–180 °C.
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