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N-Alkoxypyrazoles as Biomimetics for the Alkoxyphenyl Group in Tamoxifen

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Abstract—The preparation of a series of novel analogues of the selective antiestrogen tamoxifen is reported. 1*Z*-alkoxyphenyl group in tamoxifen has been replaced by a *N*-alkoxypyrazole, while functionalised phenyl groups or heteroaromatics were introduced at the 2*Z*-position using sequential Suzuki cross coupling of 1,2-(bis)borylpinacol 1-phenylbutene with 4- or 5-iodo-1-*N*,*N*-dimethylaminoethyl or propyl-pyrazoles. Approximately 50 tamoxifen analogues were obtained and tested in an estrogen receptor (ERα) affinity assay. Several compounds exhibited binding affinities 2–5-fold lower than tamoxifen. Dose–response experiments with six selected compounds were carried out using two different human breast cancer cell lines, MCF-7 and the tamoxifen resistant cell line MCF-/TAM^R-1. Both cell lines exhibited growth inhibition upon treatment with the tamoxifen analogues. Co-treatment of the cells, with estradiol and the individual compounds, were also performed. The results indicated that the observed growth inhibitory effect was mediated by the ERα. Analogues of the potent antiestrogen 4-hydroxytamoxifen (4-OHT) were synthesised where the 1*E*-4-hydroxyphenyl was replaced by a 1-hydroxypyrazol-4-yl group. However, modest growth inhibition of MCF-7 cells was observed upon treatment with these analogues. In contrast, 1*Z*-, 2*Z*-ringclosed tamoxifen analogue (**59**) was shown to possess antiproliferative effects on MCF-7 and MCF-/TAM^R-1 cells in lower doses than tamoxifen.

Introduction

Antiestrogens are widely used in the treatment of hormone dependent breast cancer. Tamoxifen[†] is a non-steroidal 1,1,2-triphenylbutene derivative which exhibits antiestrogenic properties in vivo. Up until now tamoxifen has routinely been used as first line endocrine treatment for breast cancer patients with disseminated disease.[1] However, after a period of response tamoxifen resistant tumours eventually develops, creating the need for new potent non-toxic antiestrogens.[2] With this aim various tamoxifen analogues have been synthesised and some of them are now in clinical trial.[3] The search for new analogues with fewer side effects, stronger binding affinity for the estrogen receptor (ERα) and beneficial effect on bone tissue is still ongoing.

Tamoxifen is metabolised in vivo by the CYP3A enzyme giving rise to compounds, which exhibit biological activities ranging from full estrogen antagonism to partial agonism.[4,5] Although tamoxifen and its metabolites have shown promising results as drugs against postmenopausal bone loss,[6] it would be advantageous to have compounds with another metabolic profile, preferably also more resistant to degradation than tamoxifen. With this aim, toremifene and idoxifene were developed and shown to be more metabolically stabile and as potent as tamoxifen (Fig. 1).[4]

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[†]We have named tamoxifen and its derivatives by their IUPAC nomenclature. Namely, the triaryl ethylene is actually a triaryl butene, and will be named according to this chemical nomenclature. According to this, tamoxifen is 1-(*Z*)-4-dimethylaminoethyloxy-1(*E*)-,2(*Z*)-diphenyl-1-butene. We have designated the three aryl groups in tamoxifen 1*Z*, 1*E* and 2*Z* (see Fig. 1).

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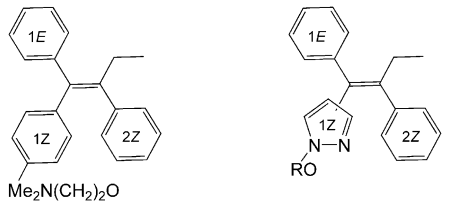


Figure 1. The structure of tamoxifen, (*Z*)-1-(4-[2-*N*,*N*-dimethylaminoethyloxyl]-phenyl)-1,2-diphenyl-1-butene, and analogues *N*-alkoxypyrazole. In order to facilitate the discussion the aryl groups are numbered as *Z*- or *E*-substituents on the butene backbone.

Recently, tamoxifen analogues containing heteroaromatic moieties like thiophene- and selenophene[7] [(*E*/*Z*)-1-aryl-2-phenyl-1-(2-thienyl/selenophen-2-yl)but-1-enes], have been described with emphasis on their synthesis, but to our knowledge, no biological data for these analogues have been published. The 1*E*-phenyl group of tamoxifen has been replaced with a 3- or 4-pyridyl group,[8,9] and the amino side chain in the same analogues, replaced by MeCO, $COCH_2CH_2Hal$ or $COCH{=}CH_2$. Some of the analogues displayed binding to the ERα, and caused a marked tumour growth inhibition on the hormone-dependent MXT mammary carcinoma of the mouse. Other pyridyl analogues[10] of tamoxifen with the 2*Z*-phenyl group replaced by a nitrogen heterocycle have been reported recently but to our knowledge no biological data of these interesting analogues are available. However, different 4-styrylpyridines, derivatives of tamoxifen and 4-hydroxytamoxifen (4-OHT), have shown affinity for the ERα.[11]

Diphenylquinoline- and isoquinoline-derivatives have been synthesised in multistep sequences. They show weak binding to the ERα and cytostatic properties on the cell lines L1210 and MCF-7 in the same concentrations as tamoxifen.[12]

Trisubstituted dihydrobenzo[*a*]carbazoles,[13] have been designed from an estradiol-based pharmacophore for the ERα and show binding affinities for the rabbit uterus ERα in the same range as tamoxifen. In vivo studies show that certain carbazoles effect tumour regression in the same concentration as tamoxifen in rats bearing NMU-induced mammary tumours. (*Z*)-Ferrocifen and (*Z*)-hydroxyferrocifen, where the 2*Z*-phenyl group is replaced with a ferrocenylene, are the first organometallic analogues of tamoxifen and 4-OHT, respectively.[14] η-Complexes between platinum and triphenylethylene have also been synthesised and constitute a new chemotherapeutic agent with an affinity for the ERα comparable to that of tamoxifen.[15] Thioether derivatives of tamoxifen and the sterodial compound ICI 164384 show binding affinity for the ERα identical to the estrogen analogue EM-139 and relatively good antiestrogenic activity in rat uterine cytosol receptor assay.[16] *N*-Substituted (*Z*)-1,1-dichloro-2-[4-(2-aminoethoxy)phenyl]-3-phenylcyclopropanes (derivatives of so-called Analogue II) have been shown lately to act as antiestrogens and antitumour agents in various cell lines.[17,18] Recently, a small library of thiazole, oxazole and pyrazole ligands for the ER has been synthesised on solid support and shown to be ERα-selective agonists.[19,20]

In most of the above mentioned analogues, the phenoxy group has been preserved. To our knowledge, no tamoxifen analogues bearing a potentially bioisosteric group for the 1*Z*-phenoxy group have been reported.

We herein describe the synthesis, ligand-binding properties and the effect on cell growth of several novel tamoxifen analogues where the 1*Z*-hydroxyphenyl group has been replaced with an isosteric 1-hydroxypyrazole. Furthermore, the synthesis of novel analogues of 4-OHT was also achieved, where the 1*E*-phenol was replaced by a 1-hydroxypyrazol-4-yl group. In addition a 1*Z*,2*Z*-ring closed analogue bearing a 1*Z*-1-pyrazolyloxy group was achieved.

Results and Discussion

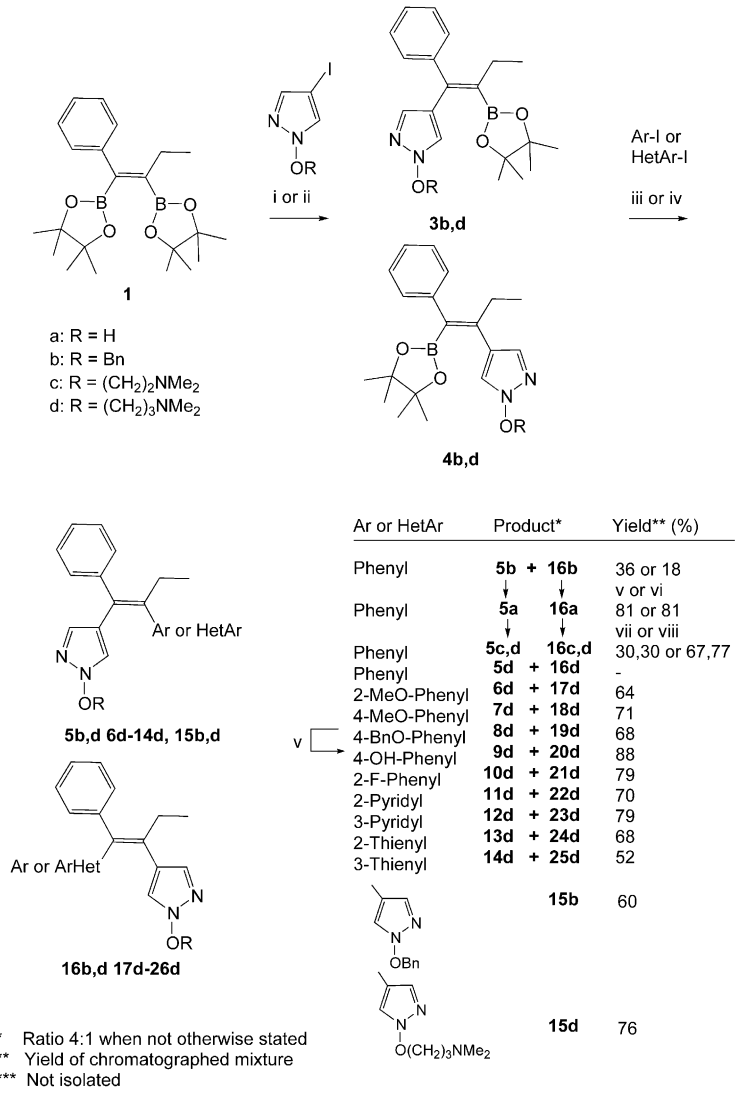
Synthesis of the analogues

Many different chemical approaches for the preparation of tamoxifen and its analogues have been reported. We searched for a route where it would be possible to vary at least two of the aryl groups, preferentially the 1*Z*- and 2*Z*-phenyl group, in the triarylbutene.

Brown and Armstrong[21,22] recently described a two-step, one-pot synthesis of tamoxifen analogues using a resin capture strategy. The key step was a double Suzuki cross-coupling between arylhalides and 1,2-(bis)boryl-pinacol 1-phenylbutene (**1**). Out of four possible compounds formed, only the desired two were captured and subsequently released from the solid support. Unfortunately, in some cases isomerisation around the double bond was observed and so both the *E*- and *Z*-isomers were obtained.

In our approach two independent Suzuki cross-couplings were performed in solution under carefully controlled reaction conditions, which permitted controlled introduction of two different aryl or heteroaryl groups in **1**. At first, 4-iodo-1-benzyloxypyrazole (**2b**) was used in combination with iodobenzene for the two Suzuki cross-couplings (Scheme 1). The C-1/C-2 regioselectivity in the first cross-coupling between **1** and **2b** was 4:1. This preference may be due to the electron withdrawing effect of the phenyl group on C-1 of **1**. The regio isomers could be separated by flash chromatography, yields are presented in Scheme 1. During the two cross-couplings we never observed any isomerisation around the double bond.

Debenzylation of **5b** and **16b** was performed either by hydrogenolysis using H_2 and Pd/C, or by heating in concd HCl. In certain cases debenzylation resulted in poor yields. Subsequent *O*-alkylation using *N*,*N*-dimethylaminoethyl or propyl chloride was performed using Williamsons ether formation to give the final products **5c**, **5d**, **16c** and **16d** in moderate yields (Scheme 1).

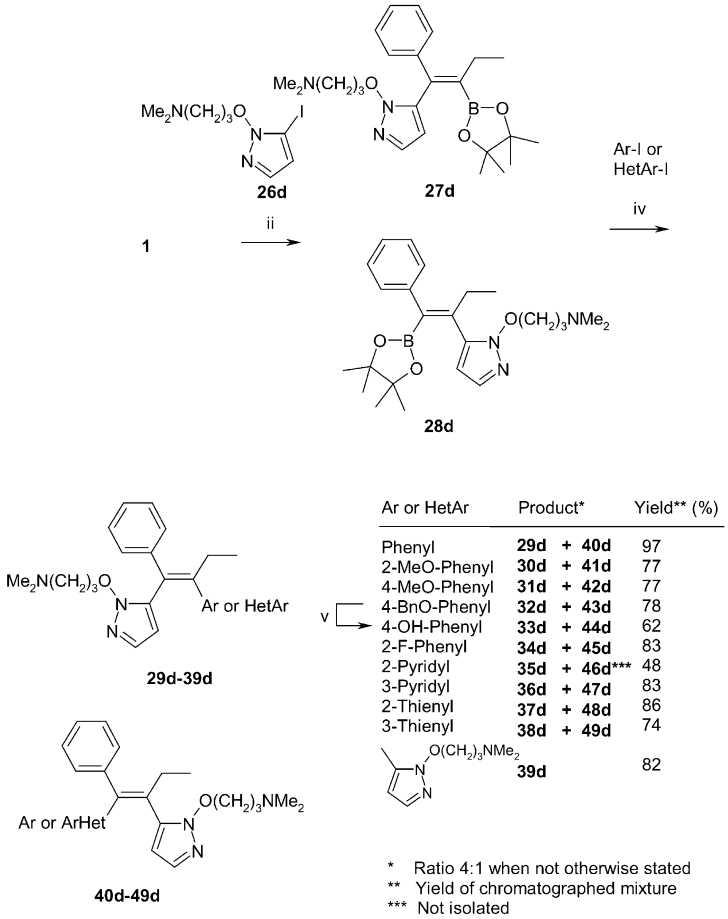


Scheme 1. Step-wise Suzuki cross coupling: (i) 10 equiv 6 M KOH, 5 equiv 3,5-dimethoxyphenol, 5 mol% $Pd(PPh_3)_4$, DME, rt, 24 h; (ii) 3 equiv 2 M K_3PO_4, 5 mol% $Pd(PPh_3)_4$, DME, 80 °C, 24 h; (iii) 1.2 equiv Ar-I, rt, 24 h; (iv) 1.5 equiv Ar-I or HetAr-I, 15 equiv 6 M KOH, 5 equiv 3,5-dimethoxyphenol, 10 mol% $Pd(PPh_3)_4$, dioxane, 80 °C, 24 h; (v) H_2 Pd/C, MeOH, rt 1 h–2 days; (vi) concd HCl 80–90 °C, 1.5 h; (vii) 3 equiv NaH, 1.5 equiv *N*,*N*-dimethylaminoethyl chloride, DMF, 24 h, rt; (viii) 3 equiv NaH, 1.5 equiv *N*,*N*-dimethylaminopropyl chloride, DMF, 24 h, rt.

The tedious workup procedure of the four isomers called for a strategy, where the *N*,*N*-dimethylaminopropyl group was present in the 4- or 5-iodo pyrazole prior to cross-coupling. Therefore, 4- or 5-iodo-1-hydroxypyrazole was *O*-dimethylaminoalkylated as before to give **2d** and **26d** in good yields. Compounds **1**, **2d** and **26d** were used in Suzuki cross coupling varying the base ($KOBu^t$, KOH, K_3PO_4, K_2CO_3, KOAc), solvent (DME, DMF, dioxane, THF) and the temperature (25–80 °C). This resulted in an optimised protocol where only one coupling took place (Schemes 1 and 2; ii) giving rise to **3d**, **4d** and **27d**, **28d** in good yields as a mixture of the two regioisomers in the ratio approximately 4:1. Similarly, an optimised protocol for the second Suzuki cross coupling was developed. A broad variety of halide containing aromatics or heteroaromatics was successfully used for the second cross coupling (Schemes 1 and 2; iv).

The workup of these compounds bearing the basic side chain was much easier than for the benzylated analogues (**5b**, **16b**) chromatography being unnecessary in several cases. Instead they could be isolated as the oxalates, giving the two regioisomers in fair to good yield in a ratio of 4:1 (Schemes 1 and 2). Their absolute configuration was established using NOE and 2-D NMR experiments.

A prerequisite for antiestrogenic effect, seems to be binding of a dimethylaminoalkyl side chain to a specific site on ERα.[23] This site is identified as Asp-351.[24] In order to evaluate the necessity of a certain length of the side chain in Idoxifene, the dimethylaminoethyloxy side chain was extended by several carbon atoms.[25] This did not improve its antagonistic potency in MCF-7 cells compared with tamoxifen. Concordantly Deplassand et al. demonstrated that derivatization at this site did not significantly interfere with recognition by the ERα.[26] Chain elongation has also been explored on the analogue II (1,1-dichloro-2,3-*cis*-diphenylcyclopropane).[27] The optimal length of the basic side chain seems to be



Scheme 2. See legends for Scheme 1.

arbitrary and depends highly on the structure of the molecule.

In our case, we observe slightly higher affinities for the ERα extending the side chain by one carbon atom going from **5c** to **5d**. The difference in binding affinity for our analogues may be explained by the fact that the *N*-hydroxypyrazole is smaller than the phenoxy group. MM+ calculations[28] of tamoxifen show the distance between the amino group and the butene C-1 to be 8.84 Å. In the *N*,*N*-dimethylaminoethyloxypyrazol-4-yl analogue **5c** the distance was calculated to be only about 8.32 Å. This distance may be too small to fit into the receptor and hence explains why the derivative **5c** with the *N*,*N*-dimethylaminoethyl side chain binds weakly to the ERα. In contrast, the distance for the *N*,*N*-dimethylaminopropyloxypyrazolyl analogue **5d** is 9.58 Å, and hence the dimethylamino group can form salt bridge to the β-carboxylate of Asp-351.[29]

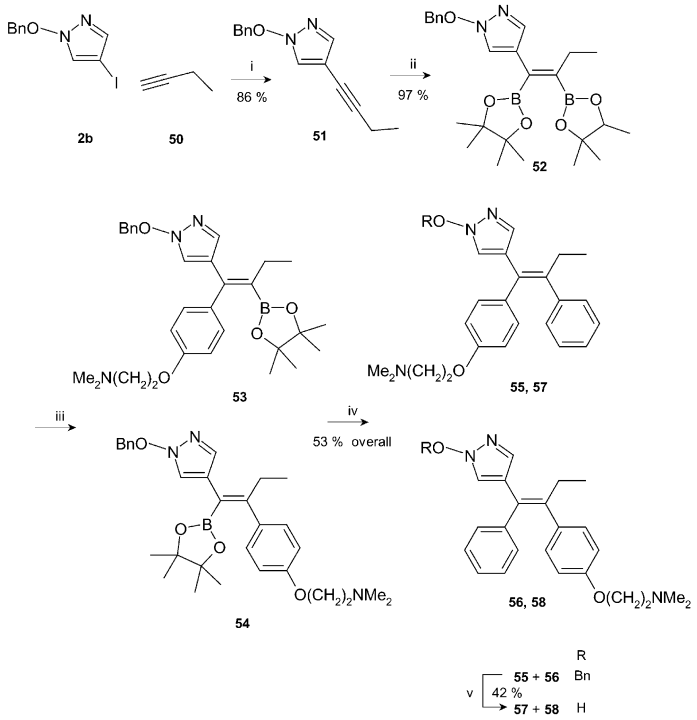
The 4-OHT analogues in which the 1*E*-4-hydroxyphenyl group has been replaced with a 1-hydroxypyrazol-4-yl group was prepared using the same cross-coupling conditions as described above replacing **1** with **52**. The pyrazole **52** was prepared by reaction of 1-butyne[30] and 1-benzyloxy-4-iodopyrazole (**2b**) using slightly modified Sonogashira conditions.[31] Using our optimized protocol for stepwise Suzuki cross-coupling a 2:1 mixture of the two regioisomers **55** and **56** was obtained. The debenzylated regioisomers **57** and **58** could be separated by chromatography (Scheme 3).

A tamoxifen analogue unable to isomerise around the double bond has been made by irradiation of tamoxifen.[32] We prepared a similar analogue **59**. The bond between the 1*Z*-pyrazol group and 2*Z*-phenyl group of was established by treating **10d** with *n*-BuLi affording **59** in 90% yield as one isomer (Scheme 4).

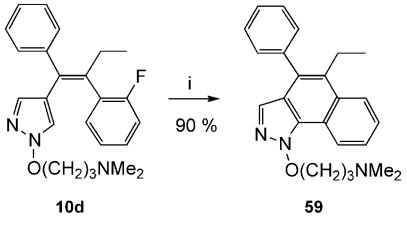
Estrogen receptor binding affinity of the *N*-alkoxypyrazole analogues

The binding affinities (IC_{50}) of the *N*-alkoxypyrazole tamoxifen analogues to the estrogen receptor (ERα) were determined by measuring their ability to compete with [^{3}H]-17β-estradiol for receptor binding in a dextrin coated charcoal assay as described in previous publications.[33,34] The binding affinities of the novel *N*-alkoxypyrazoles are compared with those of tamoxifen in Table 1.

For the 4′-pyrazol series the *N*-hydroxypyrazole analogue **5a** shows some binding to ERα in μM range comparable to that 1*Z*-4-hydroxyphenyl metabolite of



Scheme 3. (i) 4 Equiv K_3PO_4, 2 H_2O, 5 mol% $Pd(PPh_3)_4$, 2.5 mol% CuI, 1.5 equiv 1-butyne (**50**), DMF, 20 °C, 16 h; (ii) 0.99 equiv bisborylpinacolate, 3 mol% $Pt(PPh_3)_4$, DMF 85 °C, 24 h; (iii) 0.98 mol% 4-dimethylaminoethyloxyiodobenzene, 3 equiv K_3PO_4, $2H_2O$, 5 mol% $Pd(PPh_3)_4$, DME 80 °C 24 h, workup; (iv) 1.3 equiv iodobenzene, 15 equiv 6 M KOH, 5 equiv 3,5-dimethoxyphenol, 10 mol% $Pd(PPh_3)_4$, dioxane 85 °C, 24 h; (v) 5 mol% Pd/C, H_2 (1 atm), MeOH 20 °C, 1.5 h.



Scheme 4. (i) 1.3 Equiv *n*-BuLi, THF −78 °C 2 h, then rt.

tamoxifen, which has weak estrogenic effects.[35] This indicates that a phenol at 1*Z*-position can be replaced by *N*-hydroxypyrazole. Whether this effect is now estrogenic rather than anti estrogenic is speculative. Unfortunately The 1*Z*-4-hydroxyphenyl metabolite can isomerise to the very potent estrogen-like compound 1*E*-4-hydroxyphenyl metabolite.[36] In contrast, **5a** can not isomerise by the same mechanism and will therefore not lead to potent estrogen-like metabolites.

The binding affinity of **5c** is in agreement with the MM+ calculations, which predict that the *N*,*N*-dimethylaminoethyl group is too short to reach its binding site in the ERα. This is in agreement with previous reports on the significance of length of *N*,*N*-dimethylaminoalkyl group of tamoxifen.[37,38] The *N*,*N*-dimethylaminopropyl containing compound **5d** is slightly more potent than the corresponding aminoethyl analogue **5c**. However, the corresponding regioisomer **16d** displays a 10-fold reduction in binding affinity. This shows that only one of the isomers binds effectively to the ERα. It has been shown that not only the basic side chain in 4-OHT but also the 2*Z*-phenyl group accounts for the binding affinity to ERα and conformation of the ERα–ligand complex.[39] Therefore, alterations in this position of the novel analogues described herein, might affect the binding affinity to ERα. This is also the observation with the compounds **7d**/**18d**, **10d**/**21d**, **13d**/**24d** and **14d**/**25d** which display better or equal binding affinity to ERα than **5d** (0.38, 0.2, 0.34, 0.6 and 1.1 μM, respectively). The electron attracting 2-fluoro substituent in **10d**/**21d** leads to increased binding. Recently it was shown that 2,6-difluorophenol may serve as a bioisoster for a carboxylic acid in GABA analogues, fluorine acting as a hydrogen bond acceptor.[40] In another approach 1*E*-4-fluorotamoxifen was synthesised and shown to lower the anti estrogenic effect slightly compared with tamoxifen.[41] In our case, the electronic properties of the 2-fluoro atom in the 2*Z*-phenyl group may play a role as hydrogen bond acceptor thereby improving its cytostatic properties compared with tamoxifen.

The analogues **15d** and **39d** bearing two *N*,*N*-dimethyl amino propyl pyrazolyl moieties show no binding for the ERα suggesting that two basic groups are not accepted by the receptor.

For the 5′-pyrazolyl series, only three compounds **29d** and **33d**/**44d** were found to exhibit affinity to the ERα in the concentration range tested (0.001–10 μM). This may be due to the fact that the flexible side chain can reach 'amino acid 351″ in the receptor. For the 2*Z*-4-

Table 1. Binding affinities and cytostatic effects of novel Tamoxifen analogues

Compd	IC_{50} (μM)[a]			Circumvention of the effect on MCF-7 cells[e]
	ERα[b]	MCF-7[c]	Tam^R-1[d]	
Tamoxifen	0.1	2.7	3.3	+
5a	0.5			
16a	0.6			
5c	2.8			
16c	3.8			
5d	1.1	3	2.2	+
16d	10	3		+
6d + 17d	1			
7d + 18d	0.4	2.5		+
7d	0.5	1.3	2.5	+
9d + 20d	4.2			
10d + 21d	0.2	2.5		±
10d	0.8	2.2	3.3	±
11d + 22d	[f]			
12d + 23d	10			
13d + 24d	0.3	3.5		±
13d	0.2	1.9	5	±
14d + 25d	0.6	2.5		+
14d	1.7	1.4	4.2	+
15d	[f]			
29a	10			
29b	10			
29d	1.4			
30d + 41d	[f]			
31d + 42d	[f]			
33d + 44d	1.6			
34d + 45d	[f]			
35d + 46d	[f]			
36d + 47d	[f]			
37d + 48d	[f]			
38d + 49d	[f]			
39d	[f]			
57 + 58		4.8	[f]	−
59		1.0	1.3	−

[a]Tested compounds as pure isomers or a mixture of the two regioisomers 4:1.
[b]Concn of test compound which displace 50% of ^{3}H-estradiol.
[c]Concn of test compound which inhibit 50% growth of MCF-7 cells.
[d]Concn of test compound which inhibit 50% growth of MCF/TAM^R-1 cells.
[e]These were obtained (+), partially (±) or not obtained (−), using estradiol (10 nM).
[f]No binding in the test range 0.001–10 μM.

hydroxyphenyl compound **33d** the IC_{50} value is 1.6 μM. This low binding may originate from contamination with the regio isomer **44d**, which corresponds to the *trans* metabolite E of tamoxifen. Attempts to purify **33d** failed.

Antiproliferative activity

Compounds showing high affinity for ERα were tested for their cytostatic properties on the MCF-7 human mammary carcinoma cell line. The IC_{50} (drug concentration inhibiting cell growth by 50%) data are presented in Table 1.

In the 4′-pyrazolyl series five compounds were tested (**5d**, **7d**/**18d**, **10d**/**21d**, **13d**/**24d**, **14d**/**25d**) both as a mixture of the two isomers and as pure isomers (the major one). All compounds displayed IC_{50} values in the micromolar range (data in Table 1) comparable with tamoxifen (approximately 2.7 μM). No significant difference in growth inhibitory effect was observed between the mix of regioisomers and the major isomer alone. Dose–response experiments showed that all tested tamoxifen analogues exhibited equipotent properties on the growth of the human breast cancer cell line MCF-7, comparable to that of tamoxifen (Fig. 2a).

The 2:1 mixture of the two regioisomers **57** and **58** displayed an IC_{50} value of 4.8 μM cytogenic effect on MCF-7 cells being less potent than tamoxifen (2.7 μM) and 4-OHT (0.03 μM).[19] The tested compounds suppressed the growth of MCF-7 cells in a dose dependent manner. Because of the low cytogenic effect on MCF-7 cells the compounds were not tested on MCF-/TAM^R-1.

Compound **59** strongly inhibited growth of the MCF-7 cell-line (1.0 μM) being the most potent of all synthesised analogues and even more potent than tamoxifen. Compound **59** suppressed the growth of MCF-7 cells in a dose dependent manner.

It was possible to partly circumvent the growth inhibitory effect of all compounds (2.5×10^{-6} M) by simultaneous treatment with 10^{-8} M estradiol (data not shown). This, together with the receptor binding affinity data, indicates that the growth inhibitory effect is mediated via the ERα. At higher concentration (5×10^{-6} M) the effect of the compounds were found to be cytotoxic, and no estradiol circumvention of the growth inhibitory effect was possible (data not shown). However, treatment with estradiol (10 nM) could not circumvent the effect of compound **59** indicating strong binding between **59** and ER or that the antiproliferative effect is not mediated by ER. It can be speculated if this antiprofilerative effect on MCF-7 cells is cytotoxic rather than cytostatic.

Dose–response experiments were also performed on the tamoxifen resistant cell line MCF-/TAM^R-1.[42,43] It was shown that all compounds were able to suppress the cell growth (Fig. 2b). Compound **59** is an efficient growth inhibitor of the MCF/TAM^R-1 cell line, even at low doses ~1 μM. The compound suppresses growth of the resistant cell line in a dose dependent manner. However, in general, slightly higher concentrations of the analogues were required to inhibit growth of the MCF-/TAM^R-1 cells compared to parental MCF-7 cells. A similar reduction of MCF-/TAM^R-1 cells against the very potent steroidal antiestrogens ICI 182780 and ICI 164384 has previously been described.[42] These type II anitestrogens have their action in the cytoplasm where they bind to newly synthesised ER which is then rapidly destroyed.[44] Type II antiestrogens can also inhibit the growth of other tamoxifen-stimulated breast cancer cells[1] and inhibit the growth of endometrial tumours.[45] The observation that MCF-/TAM^R-1 cells displayed sensitivity to other antiestrogens indicates that the novel compounds described in this study may have the potential to inhibit growth of tamoxifen resistant human breast tumours.

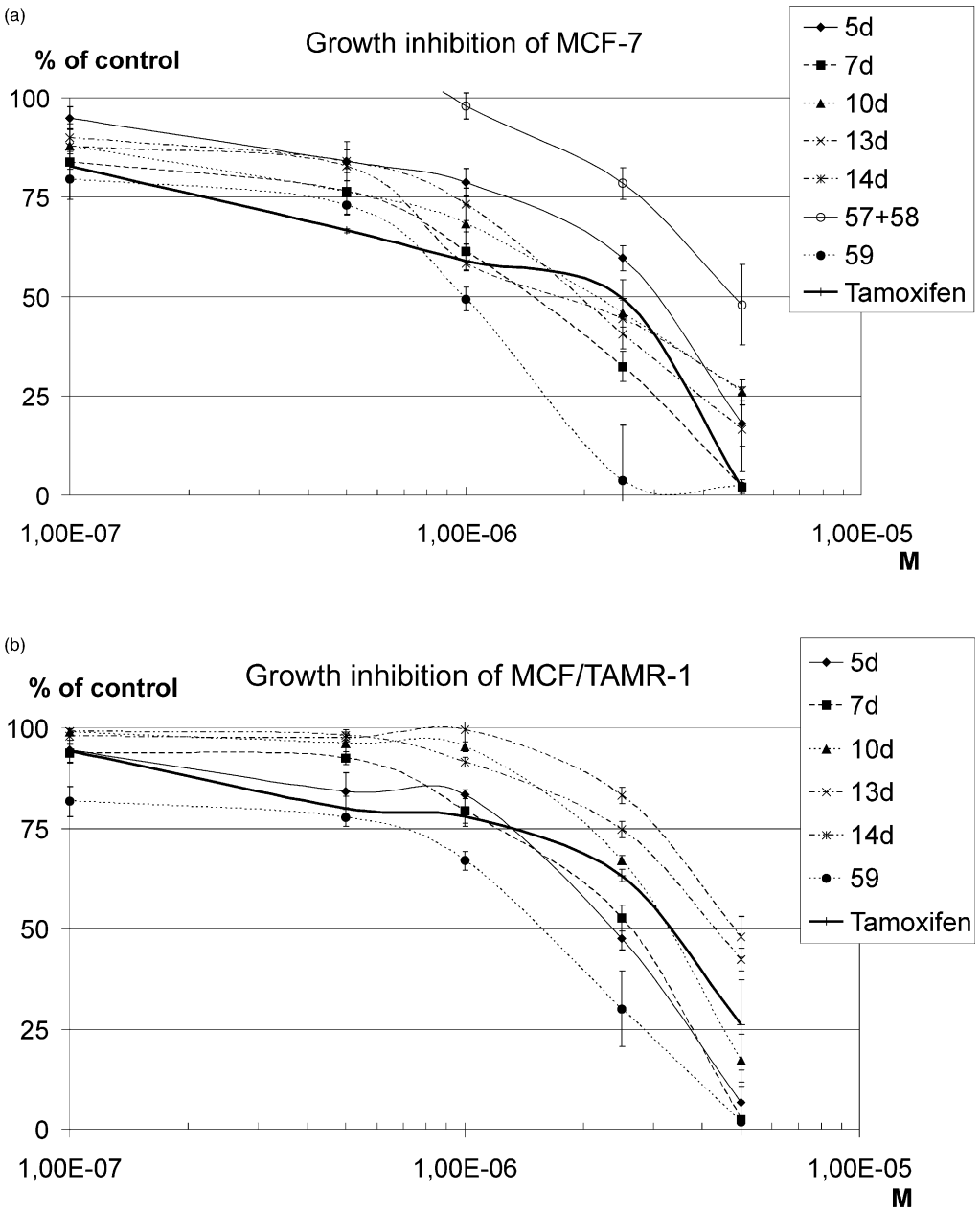


Figure 2. Dose–response curves for the effect of six novel tamoxifen analogues on MCF-7 cells (a) and MCF-/TAM^R-1 cells (b). One week prior to seeding, MCF-/TAM^R-1 cells were withdrawn from tamoxifen containing medium. Cells were seeded in multiwell dishes with 2×10^4 cells per well. Day 2 after seeding experimental medium was added and medium was renewed every 2 or 3 days. After 6 days of treatment the cells were stained with crystal violet. Data are expressed as percent of control, and data points represent mean of quadriplicate samples. SD are indicated and one representative experiment out of a total of three is shown.

Conclusion

4′- and 5′-Pyrazolyl analogues showed a significant difference in binding to the ERα. In the 5′-pyrazolyl series, only **29d** showed weak binding (IC_{50} 1.4 μM).

In the 4′-pyrazolyl series several compounds showed a good binding to the ERα, and growth inhibitory effect on MCF-7 cells. The close tamoxifen analogue **5d** was as efficient as tamoxifen itself, showing IC_{50} values for growth inhibition of 3 and 2.7 μM, respectively. This indicates that the phenoxy group in tamoxifen can be replaced by a 1-pyrazoloxy group while maintaining the antiestrogenic activity. A longer dimethylaminoalkyl side chain seems to compensate for the smaller size of hydroxypyrazol compared with a phenol. Introduction of substituents in the 2*Z*- or 1*Z*-phenyl group or introduction of a thienyl group does not seem to change the potency significantly. However, the difference between the IC_{50} values of the novel compounds might be explained by the hydrogen bonding capability of the 2*Z*-groups. Compound **59**, the bridged analogue of **5d**, which is unable to isomerise around the double bond, appears to be more cytostatic than tamoxifen.

Further activation by 4-hydroxylation of the 1*E*-phenyl group in these new antiestrogens is possible and will probably lead to even more potent compounds, as has

been observed for 4-OHT. The compounds may interconvert between the *Z* and *E* isomers, giving rise to both potent and weak antiestrogens, respectively. For compound **59** this modification, like observed for similar compounds,[36] will lead to an even more active antiestrogen since the product is unable to isomerise. Unfortunately, the compounds **57** and **58** did not show antiproliferative effects as expected, demonstrating that a 1-hydroxypyrazol-4-yl group cannot replace the 4-hydroxyphenol group in 4-OHT.

We are currently investigating the stability of these new analogues and until now, have found no isomerisation around the double bond in either acidic- or basic solution suggesting that these analogues exhibit pharmacokinetic properties better than tamoxifen. If so, they may be promising new candidates for second line treatment of tamoxifen resistant breast cancer. However, further investigations both in vitro and in vivo must be performed before this issue will be elucidated.

Experimental

Estrogen receptor binding assay

The receptor binding assays were carried out on pure subtype ERα as previously described.[33,34] The assays were performed as triplets at least two times, using tamoxifen as a reference. The IC_{50}-value equals the drug concentration at which 50% of the [^{3}H]-17β-estradiol is displaced from ERα.

Cell lines and culture conditions

The MCF-7 cell line was obtained from Breast Cancer Task Force Cell Culture Bank, Mason Research Institute (Worchester, MA, USA), and has been adapted to grow at low serum concentration.[46] The tamoxifen resistant cell line (MCF-/TAM^R-1), used for the present study, was derived from the human breast cancer cell line MCF-7.[38,39] Both cell lines were maintained in control DME/F12 medium supplemented with 1% heat inactivated fetal calf serum (Life Technologies), 6 ng/mL bovine insulin (Novo Nordisk A/S, Bagsværd, Denmark), and 2.5 mM Glutamax (Life Technologies)[19] However, medium used for cultivation of the tamoxifen resistant cell lines was supplemented with 10^{-6} M tamoxifen. Growth medium was changed every second or third day, and the cultures were subcultivated by trypsinization once a week (split ratio about 20). The resistant cell line was withdrawn from tamoxifen one week before cells were seeded for experiments, to avoid reminiscent effects of the antiestrogen.

Dose–response and co-treatment experiments

Cells were seeded in multiwell dishes with 2×10^4 cells per well in the antiestrogen-free medium described above. On day two after seeding, experimental media containing concentrations of tamoxifen (Sigma) and the tamoxifen analogues ranging from 10^{-7} to 5×10^{-6} M, were added either alone (dose–response experiment) or in combination with 10^{-8} M estradiol (co-treatment experiment). Medium was renewed every 2 or 3 days. After six days of treatment cells were stained with crystal violet for 10 min (0.5% w/v crystal violet and 25% v/v methanol), washed twice with water, dried and redissolved in citrate buffer (0.1 M sodiumcitrate, 50% ethanol) before $OD_{570\,nm}$ was measured. Data were expressed as percent of control, data points represents mean of quadruplicate samples and SD are shown.

Chemical synthesis—general. All reagents were used as purchased except for THF, which was distilled from sodium and benzophenone, and $Pd(PPh_3)_4$ which was prepared as previously described.[47] *n*-BuLi was titrated prior to use.[48] Flash chromatography (FC) was performed on silicagel (Merck 60, 70–230 mesh). Melting points (uncorrected) were determined on an Electrothermal IA9100 Digital melting point apparatus. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively. Chemical shifts are given as δ-values (ppm) using TMS as internal standard. Heteroaromatic protons are assigned to the pyrazole (Py), pyridine (Pyri) or the thiophene (Th) nuclei. Microanalyses were carried out at Mikroanalytisches Laboratorium, Waehringer Str. 42 A-1090, Vienna. All values were within ±0.4% of the theoretical values. HPLC was carried out on an YMC-column, 120 Å, 15 µ, 10 mm × 250 mm, eluent: isocratic acetonitrile/H_2O 45/55 1‰ TFA, flow 10 mL/min, detecting at 210 and 225 nm. All reactions using air-sensitive reagents were conducted under a nitrogen atmosphere.

1,2-(Bis)pinacolatoborolanyl-1-phenyl-1-butene (1). The title compound was prepared from 1-phenyl-1-butyne (2.08 g, 16.0 mmol) and bis(pinacolato)diboron (4.02 g, 15.84 mmol) as previously described.[49] The resulting brown oil was ball tube distilled (0.2 mm Hg, 180–210 °C) to give a yellow oil (5.79 g, 95%) identical (^{1}H and ^{13}C NMR) with the material described previously.[21]

1-Hydroxy-5-iodopyrazole (26a). Pyrazole **26b** (5.00 g, 16.6 mmol) and concd HCl (50 mL) were heated to 90 °C for 1 h. The reaction mixture was cooled to rt and evaporated to dryness. Evaporation four times with toluene and drying in vacuo, gave **26a** (3.60 g, 89%) as off-white crystals, mp 135–139 °C. ^{1}H NMR ($CDCl_3$) δ 7.2 (d, 1H, $J=3$ Hz, H-3); 6.32 (d, 1H$J=3$ Hz, H-4); 3.6 (bs, 1H, OH). ^{13}C NMR (CD_3OD) δ 133.17; 111.29; 74.46.

***O*-Alkylation of 1-hydroxypyrazoles—general procedure A.** The *N*-hydroxypyrazole (24 mmol.) was dissolved in dry DMF (75 mL) under N_2 in a flame-dried flask. NaH (60% in mineral oil, 72 mmol, 3 equiv) was added in portions during 5 min. After stirring 1 h at 0 °C *N*,*N*-dimethyl 2-chloroethylammonium chloride or 3-chloropropylammmonium chloride (1.5 equiv) was added in portions during 5 min and stirring was continued at rt or 50 °C for 24 h H_2O (75 mL) was added and the mixture was extracted with Et_2O. The ethereal layer was washed with H_2O (3 × 50 mL), brine (50 mL), dried over anhydrous Na_2SO_4 and evaporated to dryness in vacuo.

1-(2-*N*,*N*-Dimethylaminoethyloxy)-4-iodopyrazole (2c). In this way, 1-hydroxy-4-iodopyrazole (**2a**) (1.00 g) and *N*,*N*-dimethyl 2-chloroethylammonium chloride gave a crude product which by FC eluting with heptane/EtOAc/Et_3N (1:1:0.1) afforded **2c** (0.86 g, 64%, R_f 0.23) as an oil. LC–MS (282 M^+) 0.76 min. HPLC 0.76 min 100% ^1H NMR ($CDCl_3$) δ 7.46 (d, 1H, J = 1 Hz, Py); 7.31 (d, 1H, J = 1 Hz, Py); 4.39 (t, 2H, J = 5.7 Hz, $CH_2\alpha$); 2.63 (t, 2H, J = 5.7 Hz, $CH_2\beta$); 2.32 (s, 6H, $N(CH_3)_2$). ^{13}C NMR ($CDCl_3$) δ 138.55; 126.30; 76.63; 56,42; 53.46; 45.52. Anal. C, H, N.

1-(3-*N*,*N*-Dimethylaminopropyloxy)-4-iodopyrazole (2d). Similarly, **2a** (1.00 g) and *N*,*N*-dimethyl 3-chloropropylammmonium chloride after FC (heptane/EtOAc/Et_3N 1:1:0.01) gave **2d** (1.26 g, 90%, R_f 0.3) as an oil. ^1H NMR ($CDCl_3$) δ 7.40 (d, 1H, J = 1 Hz, Py); 7.30 (d, 1H, J = 1 Hz, Py); 4.36 (t, 2H, J = 7 Hz, $CH_2\alpha$); 2.43 (t, 2H, J = 7 Hz, $CH_2\gamma$); 2.23 (s, 6H, $N(CH_3)_2$); 1.87 (hep, 2H, J = 7 Hz, $CH_2\beta$). ^{13}C NMR ($CDCl_3$) δ 138.41; 126.02; 77.80; 55.54; 53.57; 45.33; 25.76. Anal. C, H, N.

1 - (3 - *N*,*N* - Dimethylaminopropyloxy) - 5 - iodopyrazole (26d). Similarly, **26a** (1.90 g, 9.05 mmol) and *N*,*N*-dimethyl 3-chloropropylammmonium chloride after FC (heptane/EtOAc/Et_3N 1:1:0.1) afforded **26d** (2.48 g, 93%, R_f 0.23) as crystals, mp 72–73 °C. LC–MS (296 M^+) 1.1 min. ^1H NMR ($CDCl_3$) δ 7.31 (d, 1H, J = 3 Hz, Py); 6.33 (d; 1H,J = 3 Hz, Py); 4.36 (t, 2H, J = 6 Hz, $CH_2\alpha$); 2.51 (t, 2H, J = 9 Hz, $CH_2\gamma$); 2.26 (s, 6H, $N(CH_3)_2$); 1.97 (tt, 2H, J = 6 Hz and 9 Hz, $CH_2\beta$). ^{13}C NMR ($CDCl_3$) δ 135.77; 112.75; 77.77; 72.87; 55.86; 45.34; 25.92. Anal. C, H, N.

One-pot sequential double Suzuki coupling. (*Z*)-1-(1-Benzyloxypyrazol-4-yl)-1,2-diphenyl-1-butene (5b), (*Z*)-1,2-di-(1-benzyloxypyrazol-4-yl)-1-phenyl-1-butene (15b) and (*Z*)-2-(1-benzyloxypyrazol-4-yl)-1,1-diphenyl-1-butene (16b). A solution of (bis)pinacolatoborolanyl-1-phenyl-1-butene (**1**) (0.50 g, 1.3 mmol), 1-benzyloxy-4-iodopyrazole[50] (**2b**) (0.39 g, 1.3 mmol) KOH (3.3 mL, 6 M, 20 mmol), 3,5dimethoxyphenol (1.0 g, 6.5 mmol) and $Pd(PPh_3)_4$ (75 mg, 0.05 equiv) in DME (30 mL) was stirred under nitrogen at rt for 24 h. Then iodobenzene (0.4 g, 1.95 mmol) was added and the reaction mixture was stirred at rt for another 24 h. The reaction mixture was poured into H_2O and extracted with CH_2Cl_2. Drying ($MgSO_4$) and removal of the CH_2Cl_2 gave a 4.5:2.5:2:1 mixture of **5b**, **16b**, **15b**, and 1,1,2-triphenyl-1-butene as an oil. FC (heptane/EtOAc 6:1) first gave 1,1,2-triphenyl-1-butene. (40 mg, 10%, R_f 0.6) as an oil. LC/MS: 284. ^1H NMR ($CDCl_3$) δ 7.6–6.9 (m, 15H, Ph); 2.48 (q, 2H, J = 7.2 Hz, CH_2); 0.95 (t, 3H, J = 7.2 Hz, CH_3). The second fraction contained **5b** (0.22 g, 45%, R_f 0.35) as an oil: ^1H NMR ($CDCl_3$) δ 7.4–7.1 (m, 15H); 6.27 (d, 1H, J = 1.1 Hz); 5.94 (d, 1H, J = 1.1 Hz); 5.08 (s, 2H); 2.22 (q, 2H, J = 7.6 Hz); 0.84 (t, 3H, J = 7.6 Hz). ^{13}C NMR ($CDCl_3$) δ 142.74; 141.82; 140.32; 133.71; 133.44; 129.52; 129.36; 129.17; 129.06; 128.81; 128.74; 128.53; 128.26; 128.21; 126.86; 126.81; 122.26; 80.18; 29.35; 13.00. The next fraction contained **16b** (0.12 g, 25%, R_f 0.25) as an oil. ^1H NMR ($CDCl_3$) δ 7.45–7.10 (m, 10H, Ph); 6.82 (d, 1H, J = 1 Hz, Py); 6.43 (d, 1H, J = 1 Hz, Py); 5.32 (s, 2H, CH_2Ph); 2.46 (q, 2H, J = 7,4 Hz, CH_2); 1.1 (t, 3H, J = 7.4 Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ 138.01; 135.03; 134.20; 133.84; 131.08; 130.21; 130.15; 129.69; 129.39; 129.08; 128.93; 128.65; 128.54; 126.90; 126.81; 124.19; 120.49; 80.93; 23.78; 14.16. The eluent was changed to heptane/EtOAc (4:1). This gave a fraction containing **15b** (0.124 g, 20%, R_f 0.36) as an oil. ^1H NMR ($CDCl_3$) δ 7.4–7.15 (m, 13H, Ph); 7.1–7.0 (m, 2H, Ph); 7.07 (d, 1H, J = 1 Hz, Py); 6.74 (d, 1H, J = 1 Hz, Py); 6.65 (d, 1H, J = 1 Hz, Py); 6.35 (d, 1H, J = 1 Hz, Py); 5.28 (s, 2H, CH_2Ph); 5.18 (s, 2H, CH_2Ph); 2.06 (q, 2H, J = 7.5 Hz, CH_2); 0.81 (t, 3H, J = 7.5 Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ 142.68; 134.19; 134.08; 133.78; 133.53; 131.24; 130.17; 130.05; 129.80; 129.7; 129.60; 129.37; 129.11; 129.01; 128.53; 127.14; 122.8; 122.17; 121.4; 119.66; 80.76; 80.64; 29.10; 13.9. MS *m*/*z*: 476 (M^+). Anal. C, H, N.

(*Z*)-2-(1-Hydroxypyrazol-4-yl)-1,1-diphenyl-1-butene (16a). **16b** (0.13 g, 0.34 mmol) was suspended in concd HCl (10 mL) and heated to reflux for 1 h. The reaction mixture was evaporated four times with toluene to give **16a** (80 mg, 81%) as an oil. HPLC 14.0 min 100%. ^1H NMR (CD_3OD) δ 7.35–7.05 (m, 10H, Ph); 6.86 (d, 1H, J = 1.2 Hz, Py); 6.73 (d, 1H, J = 1.2 Hz, Py); 2.40 (q, 2H, J = 7.4 Hz, CH_2); 1.07 (t, 3H, J = 7.4 Hz, CH_3). ^{13}C NMR (CD_3OD) δ 144.31; 143.66; 138.60; 132.22; 131.78; 129.91; 129.03; 128.38; 128.26; 126.65; 126.59; 122.64; 119.83; 27.06; 13.61.

(*Z*)-2-(1-[2-*N*,*N*-Dimethylaminoethyloxy]-pyrazol-4-yl)-1,1-diphenyl-1-butene (16c). **16a** (6 mg, 0.02 mmol) was *O*-alkylated as described in general procedure A using *N*,*N*-dimethyl 2-chloroethylammonium chloride (6 mg, 0.041 mmol). FC (heptane/EtOAc/Et_3N 1:1:0.025) afforded **16c** (5 mg, 67%, R_f 0.26) as an oil. LC/MS (5.45 min) 100% (M +) 362.4. ^1H NMR ($CDCl_3$) δ 7.35–7.05 (m, 10H, Ph); 6.90 (d, 1H, J = 1.0 Hz, Py); 6.70 (d, 1H, J = 1.0 Hz, Py) 4.27 (t, 2H, J = 3.5 Hz, $CH_2\alpha$); 2.54 (t, 2H, J = 3.5 Hz, $CH_2\beta$); 2.40 (q. 2H, J = 7.5 Hz, CH_2); 2.27 (s, 6H, $N(CH_3)_2$); 1.08 (t, 3H, J = 7.5 Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ 143.75; 143.22; 138.28; 133.05; 131.34; 129.85; 129.01; 128.36; 128.19; 126.58; 126.54; 121.92; 119.38; 76.14; 56.51; 45.66; 27.18; 14.29.

(*Z*)-2-(1-[3-*N*,*N*-Dimethylaminopropyloxy]-pyrazol-4-yl)-1,1-diphenyl-1-butene (16d). Similarly, **16a** (6 mg, 0.02 mmol) and *N*,*N*-dimethyl 3-chloropropylammmonium chloride (5 mg, 0.41 mmol) gave **16d** (6 mg, 77%) as an oil. LS/MS 5.68 min (100%) (M +) 376.6. ^1H NMR ($CDCl_3$) δ 7.31–7.08 (m, 10H, Ph); 6.90 (d, 1H, J = 1.1 Hz, Py); 6.64 (d, 1H, J = 1.1 Hz, Py); 4.21 (t, 2H, J = 6.6 Hz, $CH_2\alpha$); 2.44–2.33 (m, 4H, $CH_2CH_2\gamma$); 2.21 (s, 6H, $N(CH_3)_2$); 1.74 (q, 2H, J = 6.6 Hz, $CH_2\beta$); 1.07 (t, 3H, J = 7.4 Hz, CH_3).

(*Z*)-1-(1-Hydroxypyrazol-4-yl)-1,2-diphenyl-1-butene (5a). Compound **5b** (0.13 g, 0.34 mmol) was suspended in concd HCl (10 mL) and heated to reflux for 1 h. The reaction mixture was evaporated four times with toluene to give **5a** (0.08 g, 81%) as an oil. HPLC 14.5 min 100%. ^1H NMR (CD_3OD) δ 7.45–7.23 (m, 10H); 6.20

(d, 1H, $J=1.5$ Hz); 6.13 (d, 1H, $J=1.5$ Hz); 2.22 (q, 2H, $J=7.0$ Hz, CH_2); 0.9 (t, 3H, $J=7.0$ Hz, CH_3). ^{13}C NMR (CD_3OD) δ 143.27; 142.29; 140.47; 132.16; 129.47; 129.41; 129.07; 128.91; 128.45; 127.08; 122.26; 121.68; 29.29; 12.23.

(*Z*)-1-(1-[2-*N*,*N*-Dimethylaminoethyloxy]-pyrazol-4-yl)-1,2-diphenyl-1-butene (5c). Using general procedure A **5a** (10 mg, 0.03 mmol) was *O*-alkylated with *N*,*N*-dimethyl 2-chloroethylammonium chloride (10 mg, 0.07 mmol) giving after workup **5c** (4.4 mg, 30%) as an oil. LS/MS 5.78 min (100%) (M+) 362.2. ^1H NMR ($CDCl_3$) δ 7.45–7.15 (m, 10H, Ph); 6.27 (s, 2H, Py); 4.18 (t, 2H, $J=5.7$ Hz, $CH_2\alpha$); 2.48 (t, 2H, $J=5.7$ Hz, $CH_2\beta$); 2.25 (t, 2H,$J=7.5$ Hz, CH_2); 2.22 (s, 6H, $N(CH_3)_2$); 0.86 (t, 3H, $J=7.5$ Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ 142.87; 141.83; 140.45; 133.29; 129.40; 128.89; 128.82; 128.30; 127.72; 127.00; 126.88; 121.69; 121.22; 76.07; 56.47; 45.60; 29.43; 13.00.

(*Z*)-1-(1-[3-*N*,*N*-Dimethylaminopropyloxy]-pyrazol-4-yl)-1,2-diphenyl-1-butene (5d). Similarly, **5a** (5 mg, 0.02 mmol) and *N*,*N*-dimethyl 3-chloropropylammmonium chloride (4.2 mg, 0.03 mmol) after FC (heptane/EtOAc/Et_3N, 1:1:0.25) gave **5d** (2 mg, 30%, R_f 0.12) as an oil. HPLC 3.56 min (100%). ^1H NMR ($CDCl_3$) δ 7.44–7.25 (m, 10H, Ph); 6.28 (d, 1H, $J=0.8$ Hz, Py); 6.23 (d, 1H, $J=0.8$ Hz, Py); 4.15 (t, 2H, $J=6.5$ Hz, $CH_2\alpha$); 2.34 (t, 2H, $J=7.2$ Hz, $CH_2\gamma$); 2.25 (t, 2H, $J=7.4$ Hz, CH_2); 2.21 (s, 6H, $N(CH_3)_2$); 1.74 (m, 2H, $CH_2\beta$); 0.89 (t, 3H, $J=7.4$ Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ 143.10; 142.05; 140.62; 133.45; 130.53; 129.62; 129.12; 129.02; 128.52; 127.16; 127.09; 121.66; 121.45; 55.95; 45.55; 31.15; 30.29; 29.91; 13.21.

Stepwise Suzuki couplings. First coupling. (*Z*)-1-(1-[3-*N*,*N*-Dimethylaminopropyloxy]-pyrazol-4-yl)-2-pinacolatoborolanyl-1-phenyl-1-butene (3d) and (*Z*)-2-(1-[3-*N*,*N*-dimethylaminopropyloxy]-pyrazol-4-yl)-1-pinacolatoborolanyl-1-phenyl-1-butene (4d). Compound **1** (5.0 g, 13 mmol), **2d** (3.8 g, 13 mmol), K_3PO_4*$5H_2O$ (3.5 g, 39 mmol), $Pd(PPh_3)_4$ (0.75 g, 0.65 mmol) in dry DME (50 mL) were purged with N_2 for 5 min and stirred under N_2 at 80 °C for 24 h. The mixture was cooled to rt, poured into H_2O (50 mL) and extracted with CH_2Cl_2 (100 + 3 × 50 mL). The combined organic phases were washed with H_2O (30 mL), brine (30 mL), dried (Na_2SO_4) and evaporated to dryness in vacuo. The resulting yellow oil was purified by FC (heptane/EtOAc/Et_3N 1:1:0.05), affording a 4:1 mixture of **3d** and **4d** (5 g, 90%, R_f 0.34) as a light yellow oil. The mixture (**Mixture A**) was used for the second Suzuki-coupling described below. **3d**: ^1H NMR ($CDCl_3$) δ 7.4–7.1 (m, 7H, Ph + Py); 4.30 (t, 2H, $J=6.5$ Hz, $CH_2\alpha$); 2.42 (t, 2H, $J=7.4$ Hz, $CH_2\gamma$); 2.22 (s, 6H, $N(CH_3)_2$); 2.13 (q, 2H, $J=7.5$ Hz, CH_2); 1.86 (tt, 2H, $J=7.4$ and 6.5 Hz, $CH_2\beta$); 1.29 (s, 12H, pinacol); 1.00 (t, 3H, $J=7.5$ Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ 142.20; 133.12; 132.28; 128.87; 128.49; 128.38; 128.05; 126.85; 121.57; 83.57; 77.25; 55.71; 45.08; 25.63; 24.76; 24.49; 14.56. **4d**: ^1H NMR ($CDCl_3$) δ 7.4–7.1 (m, 7H, Ph + Py); 4.38 (t, 2H, $J=6.6$ Hz, $CH_2\alpha$); 2.48 (t, 2H, $J=7.4$ Hz, $CH_2\beta$); 2.26 (s, 6H, $N(CH_3)_2$); 2.25 (q, 2H, $J=7.0$ Hz, CH_2); 1.90 (tt, 2H, $J=7.4$ and 6.6 Hz, $CH_2\beta$); 1.15 (s, 12H, pinacol); 0.93 (t, 3H, $J=7.5$ Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ 140.09; 132.91; 132.02; 128.93; 128.63; 128.47; 128.22; 126.05; 123.18; 83.56; 77.33; 55.75; 45.14; 26.28; 24.72; 24.43; 13.60. Anal. C, H, N.

(*Z*)-1-(1-[3-*N*,*N*-Dimethylaminopropyloxy]-pyrazol-5-yl)-2-pinacolatoborolanyl-1-phenyl-1-butene (27d) and (*Z*)-2-(1-[3-*N*,*N*-dimethylaminopropyloxy]-pyrazol-5-yl)-1-pinacolatoborolanyl-1-phenyl-1-butene (28d). Similarly, **1** (6 g, 15.6 mmol) and **26d** (4.6 g, 15.6 mmol) gave a yellow oil (6 g, 90%) containing **27d** and **28d** (4:1) as the only products. The mixture (**Mixture B**) was used for the second Suzuki-coupling described below. **27d**: ^1H NMR ($CDCl_3$) δ 7.4–7.15 (m, 5H, Ph); 7.14 (d, 1H, $J=2.2$ Hz, Py); 6.07 (d, 1H, $J=2.2$ Hz, Py); 4.03 (t, 2H, $J=6.6$ Hz, $CH_2\alpha$); 2.23 (s, 6H, $N(CH_3)_2$); 2.4–2.2 (m, 4H, $CH_2\gamma + CH_2$); 1.75 (tt, 2H, $J=7.3$ and 6.6 Hz, $CH_2\beta$);1.21 (s, 12H, pinacol); 1.09 (t, 3H, $J=7.5$ Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ 139.67; 136.31; 136.29; 131.82; 128.96; 128.61; 128.17; 128.07; 127.32; 105.27; 83.55; 76.74; 56.04; 45.26; 25.88; 24.74; 14.33. **28d**: ^1H NMR ($CDCl_3$) δ 7.4–7.15 (m, 6H, Ph + Py); 6.18 (d, 1H, $J=2.5$ Hz, Py); 4.35 (t, 2H, $J=6.6$ Hz, $CH_2\alpha$); 2.4–2.2 (m, 4H, $CH_2\gamma + CH_2$); 2.23 (s, 6H, $N(CH_3)_2$); 2.0–1.85 (m, 2H, $CH_2\beta$); 1.11 (s, 12H, pinacol); 0.89 (t, 3H, $J=7.4$ Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ 140.46; 137.26; 136.36; 132.19; 128.74; 128.45; 128.21; 128.07; 126.43; 104.82; 83.55; 77.37; 56.20; 45.38; 26.12; 24.54; 13.36. Anal. C, H, N.

Second coupling—general procedure B. The 4:1 mixture of **3d** and **4d** (Mixture A, 0.30 g, 0.70 mmol) or the 4:1 mixture of **27d** and **28d** (Mixture B, 0.70 mmol) described above, 3,4-dimethoxyphenol (0.54 g, 3.53 mmol 5 equiv), 6 M KOH (1.76 mL, 10.6 mmol 15 equiv), $Pd(PPh_3)_4$ (0.08 g, 0.07 mmol 0.1 equiv), dioxane (5 mL) and the aromatic/heteroaromatic halide (1.5 equiv, 1.1 mmol) were mixed, purged with N_2 for 5 min and heated to 80 °C under N_2 with shaking for 24 h. After cooling to rt the reaction mixture was poured into H_2O (50 mL) and extracted with CH_2Cl_2 (25 mL), the organic solution was washed with 1 M NaOH (3 × 10 mL), H_2O (3 × 20 mL), brine (10 mL), dried ($MgSO_4$) and evaporated to dryness in vacuo. As specified below, the crude product was flash chromatographed or purified by conversion to oxalate by dissolution in a minimum amount of Et_2O and pouring the solution into an excess of a saturated solution of oxalic acid in Et_2O. The suspension was left at 5 °C overnight. Subsequent filtration, washing with Et_2O and drying in vacuo gave the crystalline oxalates. The oxalates were converted to free base by dissolution in CH_2Cl_2 and washing with excess of 0.5 M aqueous NaOH. Drying ($MgSO_4$) and removal of the CH_2Cl_2 afforded the free base.

(*Z*)-1-(1-[3-*N*,*N*-Dimethylaminopropyloxy]-pyrazol-4-yl)-2-(2-methoxyphenyl)-1-phenyl-1-butene (6d) and (*Z*)-2-(1-[3-*N*,*N*-dimethylaminopropyloxy]-pyrazol-4-yl)-1-(2-methoxyphenyl)-1-phenyl-1-butene (17d). Using procedure B, Mixture A and 2-iodoanisole (0.25 g, 1.1 mmol) afforded a light yellow oil which was purified as the oxalates as described above producing **6d** and **17d** (4:1)

(0.22 g, 64%) as white crystals. **6d**: ^{1}H NMR ($CDCl_3$) δ 7.5–6.8 (m, 9H, Ph + C_6H_4); 6.29 (d, 1H, J = 1.1 Hz, Py); 6.26 (d, 1H, J = 1.1 Hz, Py); 4.13 (t, 2H, J = 6.5 Hz, $CH_2\alpha$); 3.78 (s, 3H, OCH_3); 2.15–2.45 (m, 4H, $CH_2\gamma + CH_2$); 2.19 (s, 6H, $N(CH_3)_2$); 1.8–1.6 (m, 2H, $CH_2\beta$); 0.84 (t, 3H, J = 7.5 Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ 157.02; 141.85; 134.48; 132.99; 131.36; 130.92; 129.60; 129.24; 128.25; 127.89; 126.78; 126.70; 121.55; 121.03; 111.37; 76.97; 55.66; 55.65; 45.27; 27.90; 25.66; 12,76. **17d**: ^{1}H NMR ($CDCl_3$) δ 7.5–6.8 (m, 9H, Ph + C_6H_4); 6.90 (d, 1H, J = 1.1 Hz, Py); 6.63 (d, 1H, J = 1.1 Hz, Py); 4.19 (t, 2H, J = 6.5 Hz, $CH_2\alpha$); 3.62 (s, 3H, OCH_3); 2.15–2.45 (m, 4H, $CH_2\gamma + CH_2$); 2.23 (s, 6H, $N(CH_3)_2$); 1.8–1.6 (m, 2H, $CH_2\beta$); 1.09 (t, 3H, J = 7.4 Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ 156.83; 142.94; 137.32; 132.99; 132.55; 132.16; 130.85; 129.24; 128.63; 128.46; 128.42; 126.25; 120.96; 119.65; 111.56; 77.06; 55.51; 55.50; 45.30; 26.16; 25.68; 14.32.

(*Z*)-1-(1-[3-*N*,*N*-Dimethylaminopropyloxy]-pyrazol-4-yl)-2-(4-methoxyphenyl)-1-phenyl-1-butene (7d) and (*Z*)-2-(1-[3-*N*,*N*-dimethylaminopropyloxy]-pyrazol-4-yl)-1-(4-methoxyphenyl)-1-phenyl-1-butene (18d). Using procedure B, Mixture A and 4-iodoanisole (0.25 g, 1.06 mmol) afforded a light yellow oil which was purified as the oxalates as described above producing (0.25 g, 71%) of **7d** and **18d** (4:1) as white crystals. **7d**: ^{1}H NMR ($CDCl_3$) δ 7.45–7.25 (m, 5H, Ph); 7.14 and 6.94 (each a d, 2H, J = 8.5 Hz, C_6H_4); 6.29 (d, 1H, J = 1 Hz, Py); 6.26 (d, 1H, J = 1 Hz, Py); 4.14 (t, 2H, J = 6 Hz, $CH_2\alpha$); 3.85 (s, 3H, OMe); 3.23 (t, 2H, J = 8.4 Hz, $CH_2\gamma$); 2.81 (s, 6H, $N(CH_3)_2$); 2.21 (q, 2H, J = 7.4 Hz, CH_2); 2.15–2.0 (m, 2H, $CH_2\beta$); 0.85 (t, 3H, J = 7.4 Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ 158.67; 142.10; 140.12; 134.99; 133.30; 131.05; 130.00; 129.43; 128.32; 126.84; 121.51; 121.45; 114.21; 77.00; 55.65; 55.14; 45.24; 29.34; 25.65; 12.91. **18d**: δ 7.45–7.25 (m, 5H, Ph); 7.20 (d, 1H, J = 1 Hz, Py); 7.03 and 6.75 (each a d, 2H, J = 8.8 Hz, C_6H_4); 6.87 (d, 1H, J = 1 Hz, Py); 4.24 (t, 2H, J = 5 Hz, $CH_2\alpha$); 3.76 (s, 3H, OMe); 3.30 (t, 2H, J = 8.8 Hz, $CH_2\gamma$); 2.85 (s, 6H, $N(CH_3)_2$); 2.38 (q, 2H, J = 7.6 Hz, CH_2); 2.15–2.0 (m, 2H, $CH_2\beta$); 1.06 (t, 3H, J = 7.6 Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ 158.30; 143.61; 137.80; 136.18; 133.22; 130.93; 129.03; 128.83; 128.19; 126.49; 121.63; 119.59; 113.71; 77.13; 55.68; 55.13; 45.28; 27.40; 27.06; 25.69; 25.67; 14.16.

(*Z*)-1-(1-[3-*N*,*N*-Dimethylaminopropyloxy]-pyrazol-4-yl)-2-(4-benzyloxyphenyl)-1-phenyl-1-butene (8d) and (*Z*)-2-(1-[3-*N*,*N*-dimethylaminopropyloxy]-pyrazol-4-yl)-1-(4-benzyloxyphenyl)-1-phenyl-1-butene (19d). Using procedure B, Mixture A and 4-benzyloxybromobenzene (0.28 g, 1.1 mmol) after workup afforded a light yellow oil which was purified as the oxalates as described above to give **8d** and **19d** (4:1) (0.23 g, 68%) as white crystals. **8d**: ^{1}H NMR ($CDCl_3$) δ 7.5–7.25 (m, 10H, 2Ph); 7.20 and 7.0 (each a d, 2H, J = 8.8 Hz, C_6H_4); 6.31 (d, 1H, J = 1.1 Hz, Py); 6.29 (d, 1H, J = 1.1 Hz, Py); 5.09 (s, 2H, CH_2Ph); 4.16 (t, 2H, J = 6.6 Hz, $CH_2\alpha$); 2.5–2.3 (m, 2H, $CH_2\gamma$); 2.20 (s, 6H, $N(CH_3)_2$); 2.3–2.1 (m, 2H, CH_2); 1.86–1.69 (m, 2H, $CH_2\beta$); 0.86 (t, 3H, J = 7.4 Hz, CH_3). ^{13}C NMR (CD_3OD) δ 157.71; 135.99; 134.98; 131.33; 131.30; 128.95; 126.86; 124.87; 123.88; 123.01; 122.22; 121.61; 121.31; 120.82; 120.40; 116.14; 115.68; 108.95; 69.80; 63.61; 48.39; 36.01; 22.78; 16.68. **19d**: ^{1}H NMR ($CDCl_3$) δ 7.5–7.25 (m, 10H, 2Ph); 6.91 (d, 1H, J = 1.1 Hz, Py); 6.83 (d, 2H, J = 8.8 Hz); 6.75 (d, 1H, J = 1.1 Hz, Py); 5.01 (s, 2H, CH_2Ph); 4.25 (t, 2H, J = 6.5 Hz, $CH_2\alpha$); 2.5–2.3 (m, 2H, $CH_2\gamma$); 2.23 (s, 6H, $N(CH_3)_2$); 2.3–2.1 (m, 2H, CH_2); 1.86–1.69 (m, 2H, $CH_2\beta$); 1.06 (t, 3H, J = 7.3 Hz, CH_3). ^{13}C NMR (CD_3OD) δ 152.16; 151.54; 137.36; 132.70; 130.32; 127.12; 124.73; 122.68; 122.64; 122.18; 121.93; 121.57; 121.26; 116.12; 115.95; 113.36; 108.35; 69.93; 63.53; 48.44; 36.05; 22.72; 16.72. Anal. C H N.

(*Z*)-1-(1-[3-*N*,*N*-Dimethylaminopropyloxy]-pyrazol-4-yl)-2-(4-hydroxyphenyl)-1-phenyl-1-butene (9d) and (*Z*)-2-(1-[3-*N*,*N*-dimethylaminopropyloxy]-pyrazol-4-yl)-1-(4-hydroxyphenyl)-1-phenyl-1-butene (20d). A 4:1 mixture of **8d** and **19d** (50 mg, 0.1 mmol) was dissolved in methanol (20 mL). Hydrogenolysis was performed at rt under H_2 with 5% Pd/C (5 mol%) for 2 days. The reaction mixture was purged with N_2 and filtered through a pad of Celite. Removal of the solvent gave **9d** and **20d** (4:1) (36 mg, 88%) as an oil. **9d**: ^{1}H NMR ($CDCl_3$) δ 7.45–7.20 (m, 5H, Ph); 7.05 and 6.87 (each a d, 2H, J = 8.5 Hz, C_6H_4); 6.43 (d, 1H, J = 0.8 Hz, Py); 6.1 (d, 1H, J = 0.8 Hz, Py); 4.12 (t, 2H, J = 6.3 Hz, $CH_2\alpha$); 2.5 (t, 2H, J = 7.6 Hz, $CH_2\gamma$); 2.40 (s, 6H, $N(CH_3)_2$); 2.27 (t, 2H, J = 7.7 Hz, CH_2); 1.85–1.7 (m, 2H, $CH_2\beta$); 0.93 (t, 3H, J = 7.7 Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ 156.00; 141.74; 141.29; 134.67; 130.23; 129.48; 128.98; 128.31; 128.18; 127.49; 126.93; 122.10; 121.77; 76.62; 55.53; 44.65; 28.78; 24.97; 12.96. **20d**: ^{1}H NMR ($CDCl_3$) δ 7.45–7.20 (m, 5H, Ph); 7.1 (d, 1H, J = 1 Hz, Py); 6.92 and 6.71 (each a d, 2H, J = 8.5 Hz, C_6H_4); 6.4 (d, 1H, J = 1 Hz, Py); 4.18 (t, 2H, J = 6.8 Hz, CHα); 2.5 (t, 2H, J = 7.6 Hz, CHγ); 2.41 (s, 6H, $N(CH_3)_2$); 2.33 (t, 2H, J = 7.3 Hz, CH_2); 1.85–1.7 (m, 2H, $CH_2\beta$); 1.14 (t, 3H, J = 7.3 Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ 155.68; 142.95; 138.62; 132.75; 131.25; 129.59; 129.04; 128.18; 127.49; 126.61; 125.86; 120.17; 117.20; 77.20; 55.50; 44.73; 28.77; 26.62; 14.11. Anal. C, H, N.

(*Z*)-1-(1-[3-*N*,*N*-Dimethylaminopropyloxy]-pyrazol-4-yl)-2-(2-fluorophenyl)-1-phenyl-1-butene (10d) and (*Z*)-2-(1-[3-*N*,*N*-dimethylaminopropyloxy]-pyrazol-4-yl)-1-(2-fluorophenyl)-1-phenyl-1-butene (21d). Using procedure B, Mixture A and 2-fluoroiodobenzene (0.23 g 1.1 mmol) after workup and purification by FC (heptane/ethylacetate/Et_3N 1:1:0.1) gave a colourless oil which was purified as the oxalates as described above to give **10d** and **21d** (4:1) (0.22 g, 79%, R_f 0.2). **10d**: ^{1}H NMR ($CDCl_3$) δ 7.5–7.0 (m, 9H, Ph + C_6H_4); 6.35 (d, 1H, J = 1.1 Hz, Py); 6.32 (d, 1H, J = 1.1 Hz, Py); 4.15 (t, 2H, J = 6.5 Hz, $CH_2\alpha$); 2.40–2.20 (m, 4H, $CH_2\gamma + CH_2$); 2.18 (s, 6H, $N(CH_3)_2$); 1.70–1.65 (m, 2H, $CH_2\beta$); 0.87 (t, 3H, J = 7.5 Hz, CH_3).^{13}C NMR ($CDCl_3$) δ 159.93 (d, J = 245.6 Hz); 141.45; 133.84 (d, J = 0.8 Hz); 132.80; 131.52 (d, J = 0.8 Hz); 132.80; 131.31 (d, J = 4.1 Hz); 129.36; 129.01 (d, J = 7.9 Hz); 128.36; 127.06; 124.50 (d, J = 3.6 Hz); 121.18; 121.11; 116.05 (d, J = 22.5 Hz); 77.06; 55.62; 45.26; 28.48 (d, J = 1 Hz); 25.65; 12.61. **21d**: ^{1}H NMR ($CDCl_3$) δ 7.5–7.0 (m, 9H, Ph + C_6H_4); 6.91

(d, 1H, $J=1.1$ Hz, Py); 6.75 (d, 1H, $J=1.1$ Hz, Py); 4.23 (t, 2H, $J=6.5$ Hz, $CH_2\alpha$); 2.40–2.20 (m, 4H, $CH_2\gamma+CH_2$); 2.20 (s, 6H, $N(CH_3)_2$); 1.70–1.65 (m, 2H, $CH_2\beta$); 1.10 (t, 3H, $J=7.5$ Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ 159.71 (d, $J=247.1$ Hz); 142.15 (d, $J=0.5$ Hz); 134.07 (d, $J=0.8$ Hz); 132.67; 131.52 (d, $J=0.4$ Hz); 132.67; 131.78 (d, $J=3.8$ Hz); 128.24; 128.82 (d, $J=7.9$ Hz) 128.80 (d, $J=0.75$ Hz); 126.75; 124.30 (d, $J=3.5$ Hz); 121.09; 119.20; 115.93 (d, $J=22.3$ Hz); 77.14; 55.64; 45.30; 26.61; 25.66; 14.16. Anal. C, H, N.

(*Z*)-1-(1-[3-*N*,*N*-Dimethylaminopropyloxy]-pyrazol-4-yl)-2-(2-pyridyl)-1-phenyl-1-butene (11d) and (*Z*)-2-(1-[3-*N*,*N*-dimethylaminopropyloxy]-pyrazol-4-yl)-1-(2-pyridyl)-1-phenyl-1-butene (22d). Using procedure B, Mixture A and 2-iodopyridine (0.40 g, 1.97 mmol) after FC (heptane/EtOAc/Et_3N 1:1:0.1) gave two fractions. The first fraction contained pure **11d** (0.23 g 47%, R_f 0.2) as an oil. ^1H NMR ($CDCl_3$) δ 8.68 (dd, 1H, $J=3.8$ and 1.5 Hz, Pyri); 7.61 (dt, 1H, $J=6$ and 1.5 Hz, Pyri); 7.42–7.15 (m, 7H, Ph + Pyri); 6.37 (d, 1H, $J=1.1$ Hz, Py); 6.28 (d, 1H, $J=1.1$ Hz, Py); 4.14 (t, 2H, $J=6.6$ Hz, $CH_2\alpha$); 2.41 (t, 2H, $J=7.4$ Hz, $CH_2\gamma$); 2.30 (t, 2H, $J=7.1$ Hz, CH_2); 2.16 (s, 6H, $N(CH_3)_2$); 1.71 (tt, 2H, $J=6.6$ and 7.1 Hz, $CH_2\beta$); 0.86 (t, 3H, $J=7.1$ Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ 162.55; 151.06; 142.84; 141.43; 137.68; 134.43; 131.57; 130.46; 129.53; 128.35; 126.30; 123.13; 122.91; 122.16; 78.38; 69.24; 56.83; 46.47; 29.08; 26.88; 14.10. The second fraction contained **11d** and **22d** (1:2) (0.12 g, 23%, R_f 0.15) as an oil. **22d**: ^1H NMR ($CDCl_3$) δ 8.55 (dd, 1H, $J=3.9$ and 1.5 Hz, Pyri); 7.51 (dt, 1H, $J=6$ and 1.5 Hz, Pyri); 7.43–7.15 (m, 7H, Ph + Pyri); 7.12 (dt, 1H, $J=8$ and 1.5 Hz, Pyri); 6.79 (d, 1H, $J=1.1$ Hz, Py); 6.74 (d, 1H, $J=1.1$ Hz, Py); 4.25 (t, 2H, $J=6.5$ Hz, $CH_2\alpha$); 2.40 (q, 2H, $J=7.4$ Hz, CH_2); 2.35 (t, 2H, $J=7$ Hz, $CH_2\gamma$); 2.21 (s, 6H, $N(CH_3)_2$); 1.75 (tt, 2H, $J=6.4$ and 6.5 Hz, $CH_2\beta$); 1.12 (t, 3H, $J=7.4$ Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ 161.94; 161.33; 149.67; 141.54; 137.95; 136.32; 133.21; 129.69; 129.09; 128.33; 126.89; 125.16; 121.69; 121.45; 119.07; 77.19; 55.63; 45.27; 27.87; 26.98; 25.68; 13.92.

(*Z*)-1-(1-[3-*N*,*N*-Dimethylaminopropyloxy]-pyrazol-4-yl)-2-(3-pyridyl)-1-phenyl-1-butene (12d) and (*Z*)-2-(1-[3-*N*,*N*-dimethylaminopropyloxy]-pyrazol-4-yl)-1-(3-pyridyl)-1-phenyl-1-butene (23d). Using procedure B, Mixture A and 3-iodopyridine (0.22 g, 1.1 mmol) after FC (heptane/EtOAc/Et_3N 1:1:0.1) gave a first fraction containing pure **12d** (0.1 g 38%, R_f 0.2) as an oil. LS/MS 3.77 min (95%) (M +) 377.4. ^1H NMR ($CDCl_3$) δ 8.57 (dd, 2H, $J=4.9$ and 1.7 Hz, Pyri); 7.59 (dt, 1H, $J=7.8$ and 2.1 Hz, Pyri); 7.45–7.25 (m, 7H, Ph + Pyri); 6.35 (d, 1H, $J=1.1$ Hz, Py); 6.32 (d, 1H, $J=1.1$ Hz, Py); 4.16 (t, 2H, $J=6.5$ Hz, $CH_2\alpha$); 2.35–2.25 (m, 4H, $CH_2\gamma+CH_2$); 2.19 (s, 6H, $N(CH_3)_2$); 1.73 (hep, 2H, $J=7.5$ Hz, $CH_2\beta$); 0.87 (t, 3H, $J=7.4$ Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ 150.20; 148.17; 141.44; 138.41; 137.44; 136.75; 133.36; 130.90; 129.18; 128.41; 127.22; 123.60; 121.69; 120.83; 77.13; 55.54; 45.18; 29.00; 25.57; 12.81. The second fraction contained **12d** and **23d** (0.11 g, 41%, R_f 0.07) as an oil. **23d**: ^1H NMR ($CDCl_3$) δ 8.40 (dd, 1H, $J=4.9$ and 1.7 Hz, Pyri); 8.34 (d, 1H, $J=1.4$ Hz, Pyri); 7.50–7.10 (m, 7H, Ph + Pyri); 6.91 (d, 1H, $J=1.1$ Hz, Py); 6.79 (d, 1H, $J=1.1$ Hz, Py); 4.25 (t, 2H, $J=6.6$ Hz, $CH_2\alpha$); 2.50–2.25 (m, 4H, $CH_2\gamma+CH_2$); 2.23 (s, 6H, $N(CH_3)_2$); 1.73 (hep, 2H, $J=7.4$ and 6.6 Hz, $CH_2\beta$); 1.07 (t, 3H, $J=7.5$ Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ 150.97; 147.49; 142.19; 139.34; 136.67; 134.76; 133.76; 133.18; 129.13; 128.44; 127.01; 123.13; 121.64; 118.96; 77.25; 55.57; 45.21; 27.52; 25.61; 13.94.

(*Z*)-1-(1-[3-*N*,*N*-Dimethylaminopropyloxy]-pyrazol-4-yl)-2-(thien-2-yl)-1-phenyl-1-butene (13d) and (*Z*)-2-(1-[3-*N*,*N*-dimethylaminopropyloxy]-pyrazol-4-yl)-1-(thien-2-yl)-1-phenyl-1-butene (24d). Using procedure B, Mixture A and 2-iodothiophene (0.23 g, 1.1 mmol) by FC (heptane/EtOAc/Et_3N 1:1:0.1) gave a first fraction containing the excess of 2-iodothiophene. The second fraction contained an oil which was converted to the oxalates as described above producing **13d** (oxalate) and **24d** (oxalate) (4:1) (0.23 g, 68%, R_f 0.2). **13d** (oxalate): ^1H NMR ($CDCl_3$) δ 7.45–7.20 (m, 6H, Ph + Th); 7.04 (dd, 1H, $J=5.5$ and 3.5 Hz, Th); 6.90 (dd, 1H, $J=3.5$ and 1.5 Hz, Th); 6.48 (d, 1H, $J=1.2$ Hz, Py); 6.45 (d, 1H, $J=1.2$ Hz, Py); 4.20 (t, 1H, $J=5.6$ Hz, $CH_2\alpha$); 3.26 (t, 2H, $J=8.1$ Hz, $CH_2\gamma$); 2.83 (s, 6H, $N(CH_3)_2$); 2.30–2.20 (q, 2H, $J=7.4$ Hz, CH_2); 2.20–2.0 (m, 2H, $CH_2\beta$); 0.95 (t, 3H, $J=7.4$ Hz, CH_3). **13d** (free base): ^{13}C NMR ($CDCl_3$) δ 144.11; 141.64; 133.17; 132.81; 132.01; 129.11; 128.30; 127.19; 127.06; 126.02; 125.23; 121.60; 120.94; 77.12; 55.60; 45.24; 30.03; 25.64; 13.13. **24d** (oxalate): ^1H NMR ($CDCl_3$) δ 7.45–7.20 (m, 6H, Ph + Py); 7.15 (dd, 1H, $J=5.2$ and 1.5 Hz, Th); 7.08 (d, 1H, $J=1.5$ Hz, Py); 6.82 (dd, 1H, $J=5.2$ and 3.5 Hz, Th); 6.55 (dd, 1H, $J=3.5$ and 1.5 Hz, Th); 4.30 (t, 2H, $J=5.6$ Hz, $CH_2\alpha$); 3.36 (t, 2H, $J=8.4$ Hz, $CH_2\gamma$); 2.88 (s, 6H, $N(CH_3)_2$); 2.25 (q, $J=7.5$ Hz, CH_2); 2.12 (m, 2H, $CH_2\beta$); 0.98 (t, 3H, $J=7.5$ Hz, CH_3). (free base): ^{13}C NMR ($CDCl_3$) δ 145.32; 142.57; 133.35; 133.03; 132.04; 129.06; 128.96; 128.18; 127.69; 126.94; 126.33; 118.86; 125.56; 77.10; 55.68; 45.28; 28.39; 25.73; 13.53. Anal. C, H, N.

(*Z*)-1-(1-[3-*N*,*N*-Dimethylaminopropyloxy]-pyrazol-4-yl)-2-(thien-3-yl)-1-phenyl-1-butene (14d) and (*Z*)-2-(1-[3-*N*,*N*-dimethylaminopropyloxy]-pyrazol-4-yl)-1-(thien-3-yl)-1-phenyl-1-butene (25d). Using procedure B, Mixture A and 3-iodothiophene (0.23 g, 1.1 mmol) by FC (heptane/EtOAc/Et_3N 1:1:0.1) gave a first fraction containing unchanged 3-iodothiophene. The second fraction contained an oil which was converted to oxalates as described above affording **14d** and **25d** (4:1) (0.14 g, 52%, R_f 0.1) as white crystals. By addition of HCl in Et_2O an oil precipitated which contained **14d** and **25d** slightly contaminated with triphenylphosphine oxide as apparent from the ^1H NMR signals at 7.8–7.4 ppm. **14d**: ^1H NMR ($CDCl_3$) δ 7.45–7.20 (m, 6H, Ph + Th); 7.09 (dd, 1H, $J=5$ and 3 Hz, Th); 6.94 (d, 1H, $J=5$ Hz, Th); 6.39 (d, 1H, $J=1.1$ Hz, Py); 6.37 (d, 1H, $J=1.1$ Hz, Py); 4.19 (d, 2H, $J=6.5$ Hz, $CH_2\alpha$); 2.3 (t, 2H, $J=7.1$ Hz, $CH_2\gamma$); 2.26–2.10 (m, 2H, CH_2); 2.20 (s, 6H, $N(CH_3)_2$); 1.76 (m, 2H, $CH_2\beta$); 0.90 (t, 3H, $J=7.4$ Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ 142.93; 141.87; 135.22; 133.24; 129.35; 128.34; 128.25; 126.97; 125.66; 122.03; 121.48; 121.28; 119.52; 77.13; 55.68; 45.32; 29.22; 25.73; 13.18. **25d**: ^1H NMR ($CDCl_3$) δ 7.45–7.20 (m, 5H, Ph); 7.14 (dd, 1H,

$J=3$ and 5 Hz, Th); 7.01 (d, 1H, $J=1.1$ Hz, Py); 6.85 (d, 1H, $J=1.1$ Hz, Py); 6.8 (d, 1H, $J=3$ Hz, Th); 6.76 (d, 1H, $J=5$ Hz, Th); 4.29 (t, 2H, $J=6.5$ Hz, $CH_2\alpha$); 2.41–2.30 (m, 4H, $CH_2\gamma + CH_2$); 2.24 (s, 6H, $N(CH_3)_2$), 1.83 (m, 2H, $CH_2\beta$); 1.03 (t, 3H, $J=7.4$ Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ 143.94; 143.08; 132.99; 131.91; 129.85; 129.09; 128.76; 128.40; 126.69; 124.72; 123.71; 121.43; 121.27; 77.29; 55.72; 45.35; 27.36; 25.79; 14.00. Anal. C, H, N.

(*Z*)-1,2-Di-(1-[3-*N*,*N*-Dimethylaminopropyloxy]-pyrazol-4-yl)-1-phenyl-1-butene (15d). Using procedure B, Mixture A and **2d** (0.208 g, 0.70 mmol), after workup and FC (heptane/ethylacetate/Et_3N 1:1:0.1) gave **15d** (0.25 g, 76%, R_f 0.1) as a colourless oil. ^1H NMR (CD_3OD) δ 7.35–7.20 (m, 5H, Ph); 7.18 (d, 1H, $J=1.1$ Hz, Py); 7.14 (d, 1H, $J=1.1$ Hz, Py); 6.74 (d, 1H, $J=1.1$ Hz, Py); 6.69 (d, 1H, $J=1.1$ Hz, Py); 4.35 (t, 2H, $J=6.5$ Hz, $CH_2\alpha$); 4.25 (t, 2H, $J=6.5$ Hz, $CH_2\alpha$); 2.43 (t, 2H, $J=7$ Hz, $CH_2\gamma$); 2.35 (t, 2H, $J=7$ Hz, $CH_2\gamma$); 2.18 (t, 2H, $J=7.4$ Hz, CH_2); 2.25 (s, 6H, $N(CH_3)_2$); 2.20 (s, 6H, $N(CH_3)_2$); 1.87 (q, 2H, $J=7.4$ Hz, $CH_2\beta$); 1.81 (q, 2H, $J=7.4$ Hz, $CH_2\beta$); 0.93 (t, 3H, $J=7.4$ Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ 142.34; 133.16; 123.85; 130.98; 129.71; 129.07; 128.31; 126.90; 121.52; 121.45; 120.98; 119.71; 77.54; 77.32; 55.75; 55.70; 45.33; 45.29; 28.61; 25.85; 25.76; 13.43. Anal. C, H, N.

(*Z*)-1-(1-[3-*N*,*N*-Dimethylaminopropyloxy]-pyrazol-5-yl)-2-(2-methoxyphenyl)-1-phenyl-1-butene (30d) and (*Z*)-2-(1-[3-*N*,*N*-dimethylaminopropyloxy]-pyrazol-5-yl)-1-(2-methoxyphenyl)-1-phenyl-1-butene (41d). Using procedure B, Mixture B and 2-iodoanisole (0.23 g, 1.1 mmol), after FC (heptane/EtOAc/Et_3N 1:1:0.1) afforded (0.22 g, 77%, R_f 0.3) of **30d** and **41d** (4:1) as an oil which was purified as the oxalates to give **30d** and **41d** (4:1) in quantitative yield. **30d**: ^1H NMR ($CDCl_3$) δ 7.40–7.00 (m, 10H, Ph + C_6H_4 + Py); 5.60 (d, 1H, $J=2.3$ Hz, Py); 4.35–4.20 (m, 2H, $CH_2\alpha$); 3.73 (s, 3H, OCH_3); 2.6–2.3 (m, 2H, $CH_2\gamma$); 2.25–2.1 (m, 2H, CH_2); 2.18 (s, 6H, $N(CH_3)_2$); 1.58 (m, 2H, $CH_2\beta$); 0.97 (t, 3H, $J=7.5$ H, CH_3). ^{13}C NMR (CD_3OD) δ 165.25; 156.84; 145.98; 139.70; 136.75; 130.02; 129.09; 128.46; 128.19; 127.69; 127.28; 126.36; 119.91; 110.50; 105.08; 74.37; 60.07; 56.86; 42.01; 26.79; 22.70; 16.94; 13.01. **41d**: ^1H NMR ($CDCl_3$) δ 7.40–7.00 (m, 10H, Ph + C_6H_4 + Py); 5.77 (d, 1H, $J=2.3$ Hz, Py); 4.35–4.20 (m, 2H, $CH_2\alpha$); 3.57 (s, 3H, OCH_3); 2.6–2.3 (m, 2H, $CH_2\gamma$); 2.25–2.1 (m, 2H, CH_2); 2.25 (s, 6H, $N(CH_3)_2$); 1.92 (m, 2H, $CH_2\beta$); 1.12 (t, 3H, $J=7.7$ Hz, CH_3). ^{13}C NMR (CD_3OD) δ 165.24; 156.89; 142.10; 141.63; 135.44; 131.59; 130.30; 129.75; 129.07; 128.51; 126.76; 119.87; 111.30; 105.18; 75.57; 56.83; 54.42; 42.09; 25.79; 22.96; 12.63. Anal. C, H, N.

(*Z*)-1-(1-[3-*N*,*N*-Dimethylaminopropyloxy]-pyrazol-5-yl)-2-(4-methoxyphenyl)-1-phenyl-1-butene (31d) and (*Z*)-2-(1-[3-*N*,*N*-dimethylaminopropyloxy]-pyrazol-5-yl)-1-(4-methoxyphenyl)-1-phenyl-1-butene (42d). Using procedure B, Mixture B and 4-iodoanisole (0.25 g, 1.07 mmol) after workup and FC (heptane/EtOAc/Et_3N 1:1:0.1) afforded (0.22 g, 77%, R_f 0.25) of **31d** and **42d** (4:1) as an oil which was converted to oxalates as described above to give (0.24 g) as white crystals. **31d**: ^1H NMR ($CDCl_3$) δ 7.50–7.20 (m, 5H, Ph); 7.03 (d, 2H, $J=8.2$ Hz, PhOMe); 6.9 (d, 1H, $J=2.3$ Hz, Py); 6.77 (d, 2H, $J=8.2$ Hz, PhOMe); 5.56 (d, 1H, $J=2.3$ Hz, Py); 3.78, (s, 3H, OCH_3); 3.57 (t, 2H, $J=5$ Hz, $CH_2\alpha$); 3.10 (t, 2H, $J=6$ Hz, $CH_2\gamma$); 2.81 (s, 6H, $N(CH_3)2$); 2.53 (q, 2H, $J=7.4$ Hz, CH_2); 1.92 (m, 2H, $CH_2\beta$); 0.99 (t, 3H, $J=7.4$ Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ 158.70; 147.76; 140.71; 136.69; 133.64; 129.54; 129.18; 128.25; 127.14; 125.48; 113.37; 105.21; 75.62; 55.93; 54.98; 45.27; 27.86; 25.83; 22.55; 13.40. **42d**: ^1H NMR ($CDCl_3$) δ 7.50–7.20 (m, 5H, Ph); 6.81 (d, 2H, $J=8.2$ Hz, PhOMe); 6.65 (d, 2H, $J=8.4$ Hz, PhOMe); 6.10 (d, 1H, $J=2.2$ Hz, Py); 4.0 (t, 2H, $J=6.2$ Hz, $CH_2\alpha$); 3.73 (s, 3H, OCH_3); 3.20 (t, 2H, $J=6$ Hz, $CH_2\gamma$); 2.83 (s, 6H, $N(CH_3)_2$); 2.35 (q, $J=7$ Hz, CH_2); 2.10 (m, 2H, $CH_2\beta$); 1.20 (t, 3H, $J=7$ Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ 158.38; 143.46; 142.53; 135.31; 132.44; 132.06; 129.32; 128.62; 128.46; 127.32; 127.18; 113.01; 104. 54.92; 45.34; 51; 76.14; 56.12; 28.12; 22.60; 13.98.

(*Z*)-1-(1-[3-*N*,*N*-Dimethylaminopropyloxy]-pyrazol-5-yl)-2-(4-benzyloxyphenyl)-1-phenyl-1-butene (32d) and (*Z*)-2-(1-[3-*N*,*N*-dimethylaminopropyloxy]-pyrazol-5-yl)-1-(4-benzyloxyphenyl)-1-phenyl-1-butene (43d). Using procedure B, Mixture B and 4-benzyloxybromobenzene (0.28 g, 1.1 mmol) after workup and purification as the oxalates as described above gave **32d** and **43d** (0.26 g, 77%) (4:1) as white crystals. **32d**: ^1H NMR ($CDCl_3$) δ 7.50–7.2 (m, 10H, 2Ph); 7.06 and 6.83 (each a d, 2H, $J=8.6$ Hz, C_6H_4); 6.96 (d, 1H, $J=2.3$ Hz, Py); 5.57 (d, 1H, $J=2.3$ Hz, Py); 4.99 (s, 2H, CH_2Ph); 3.63 (t, 2H, $J=6.5$ Hz, $CH_2\alpha$); 2.52 (q, 2H, $J=7.4$ Hz, $CH_2\gamma$); 2.17 (s, 6H, $N(CH_3)_2$); 2.25–2.15 (m, 2H, CH_2); 1.65–1.5 (m, 2H, $CH_2\beta$); 0.98 (t, 3H, $J=7.1$ Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ 158.91; 152.63; 142.97; 131.60; 131.56; 128.05; 126.37; 123.75; 123.26; 122.66; 122.55; 121.69; 108.56; 100.00; 68.54; 63.86; 48.85; 36.37; 21.82; 17.06 (one signal hidden). **43d**: ^1H NMR ($CDCl_3$) δ 7.50–7.2 (m, 10H, 2Ph); 7.6 (d, 1H, $J=2.1$ Hz, Py); 6.85 and 6.71 (each a d, 2H, $J=9.0$ Hz, Phe); 5.99 (d, 1H, $J=2.3$ Hz, Py); 4.94 (s, 2H, CH_2Ph); 4.05 (t, 2H, $J=6.3$ Hz, $CH_2\alpha$); 2.38 (q, 2H, $J=7.7$ Hz, CH_2); 2.21 (s, 6H, $N(CH_3)_2$); 2.25–2.15 (m, 2H, CH_2); 1.9–1.7 (m, 2H, $CH_2\beta$); 0.97 (t, 3H, $J=7.7$ Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ 158.89; 152.26; 134.78; 134.75; 128.26; 126.85; 124.93; 123.34; 122.86; 122.55; 121.96; 121.65; 119.38; 108.18; 99.98; 64.15; 63.74; 48.98; 36.33; 21.87; 16.80. Anal. C, H, N.

(*Z*)-1-(1-[3-*N*,*N*-Dimethylaminopropyloxy]-pyrazol-5-yl)-2-(4-hydroxyphenyl)-1-phenyl-1-butene (33d) and (*Z*)-2-(1-[3-*N*,*N*-dimethylaminopropyloxy]-pyrazol-5-yl)-1-(4-hydroxyphenyl)-1-phenyl-1-butene (44d). Using the procedure for hydrogenolysis of **8d** and **19d**, a 4:1 mixture of **32d** and **43d** (42 mg, 0.09 mmol) gave **33d** and **44d** (4:1) (21 mg, 62%) as an oil. **33d**: ^1H NMR ($CDCl_3$) δ 7.50–6.9 (m, 5H, Ph); 7.01 (d, 1H, $J=2.4$ Hz, Py); 6.29 and 6.65 (each a d, 2H, $J=8.1$ Hz, C_6H_4); 3.71 (t, 2H, $J=5.8$ Hz, $CH_2\alpha$); 3.25–3.05 (m, 2H, $CH_2\gamma$); 2.85 (s, 6H, $N(CH_3)_2$); 2.53 (q, 2H, $J=7.5$ Hz, CH_2); 1.95–1.80 (m, 2H, $CH_2\beta$); 0.98 (t, 3H, $J=7.3$ Hz, CH_3). **44d**: δ 7.50–6.9 (m, 5H, Ph); 6.74 and 6.65 (each a d, 2H, $J=8.7$ Hz, C_6H_4); 4.04 (t, 2H, $J=5.8$ Hz, $CH_2\alpha$); 3.25–3.05 (m, 2H, $CH_2\gamma$); 2.87 (s, 6H, $N(CH_3)_2$); 2.40

(q, 2H, $J=7.4$ Hz, CH_2); 2.13–2.00 (m, 2H, $CH_2\beta$); 1.3 (t, 3H, $J=7.3$ Hz, CH_3).

(*Z*)-1-(1-[3-*N*,*N*-Dimethylaminopropyloxy]-pyrazol-5-yl)-2-(2-fluorophenyl)-1-phenyl-1-butene (34d) and (*Z*)-2-(1-[3-*N*,*N*-dimethylaminopropyloxy]-pyrazol-5-yl)-1-(2-fluorophenyl)-1-phenyl-1-butene (45d). Using procedure B, Mixture B and 2-fluoroiodobenzene (0.23 g, 1.1 mmol), after FC (heptane/EtOAc/Et_3N 1:1:0.1) gave **34d** and **45d** (4:1) (0.23 g, 83%, R_f 0.30) which was purified as the oxalates as described above to give 0.27 g of **34d** and **45d** (4:1) as white crystals. **34d**: ^{1}H NMR ($CDCl_3$) δ 7.40–6.95 (m, 9H, Ph); 6.92 (d, 1H, $J=2.3$ Hz, Py); 5.65 (d, 1H, $J=2.3$ Hz, Py); 3.74 (t, 2H, $J=6.8$ Hz, $CH_2\alpha$); 2.54 (t, 2H, $J=7.6$ Hz, $CH_2\gamma$); 2.18 (s, 6H, $N(CH_3)_2$); 2.18 (t, 2H, $J=7.4$ Hz, CH_2); 2.00–1.85 (m, 2H, $CH_2\beta$); 0.99 (t, 2H, $J=7.4$ Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ 159.80 ($J=246.23$ Hz); 142.14 ($J=1.1$ Hz); 139.48; 135.54; 130.73 ($J=4.1$ Hz); 129.18; 128.88 ($J=8.2$ Hz); 128.78 ($J=9.8$ Hz); 128.55 ($J=26.9$ Hz); 128.21; 127.40; 123.73 ($J=3.5$ Hz); 115.35 ($J=22.5$ Hz); 104.90; 76.85; 75.99; 55.89; 45.23; 27.36 ($J=1.8$ Hz); 25.75; 12.91. **45d**: ^{1}H NMR ($CDCl_3$) δ 7.40–6.80 (m, 10H, Ph + Py); 5.87 (d, 1H, $J=2.3$ Hz, Py); 4.25 (t, 2H, $J=6.2$ Hz, $CH_2\alpha$); 2.43 (t, 2H, $J=7.7$ Hz, $CH_2\gamma$); 2.24 (s, 6H, $N(CH_3)_2$); 2.22 (t, 2H, $J=7.4$ Hz, CH_2); 1.70–1.55 (m, 2H, $CH_2\beta$); 1.00 (t, 3H, $J=7.4$ Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ 159.75 ($J=247.6$ Hz); 140.97 ($J=0.8$ Hz); 138.07; 134.31; 131.18 ($J=3.7$ Hz); 129.20; 128.91 ($J=8.2$ Hz); 128.48; 127.60 ($J=9$ Hz); 127.28; 123.49 ($J=3.5$ Hz); 121.80 ($J=26.9$ Hz); 115.46 ($J=22.3$ Hz); 104.80 ($J=0.5$ Hz); 77.20; 76.88; 56.03; 45.31; 26.34; 26.05; 13.60. Anal. C, H, N.

(*Z*)-1-(1-[3-*N*,*N*-Dimethylaminopropyloxy]-pyrazol-5-yl)-2-(2-pyridyl)-1-phenyl-1-butene (35d). Using procedure B, Mixture B and 2-iodopyridine (150 mg, 1.5 equiv) after FC (heptane/EtOAc/Et_3N 1:1:0.1) gave a first fraction containing 36 mg of **46d** with some impurities. The second fraction contained **35d** (0.09 g, 48%, R_f 0.25) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 8.55 (dd, 1H, $J=3.9$ and 1.5 Hz, Pyri); 7.51 (dt, 1H, $J=6$ and 1.5 Hz, Pyri); 7.43–7.15 (m, 7H, Ph + Pyri); 7.12 (dt, 1H, $J=8$ and 1.5 Hz, Pyri); 6.79 (d, 1H, $J=2.1$ Hz, Py); 5.60 (d, 1H, $J=2.1$ Hz, Py); 3.65 (t, 2H, $J=6.5$ Hz, $CH_2\alpha$); 2.70 (q, 2H, $J=7.4$ Hz, CH_2); 2.25 (t, 2H, $J=6.5$ Hz, $CH_2\gamma$); 2.21 (s, 6H, $N(CH_3)_2$); 1.59 (hep, 2H, $J=6.5$ Hz, $CH_2\beta$); 0.99 (t, 3H, $J=7.4$ Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ 159.87; 149.05; 147.87; 139.97; 136.04; 135.80; 132.20; 129.11; 128.31; 127.57; 127.54; 124.72; 121.90; 105.44; 55.88; 53.34; 45.25; 26.63; 25.76; 13.24.

(*Z*)-1-(1-[3-*N*,*N*-Dimethylaminopropyloxy]-pyrazol-5-yl)-2-(3-pyridyl)-1-phenyl-1-butene (36d) and (*Z*)-2-(1-[3-*N*,*N*-dimethylaminopropyloxy]-pyrazol-5-yl)-1-(3-pyridyl)-1-phenyl-1-butene (47d). Using procedure B, Mixture B and 3-iodopyridine (0.22 g, 1.1 mmol) after FC (heptane/EtOAc/Et_3N 1:1:0.1) gave **36d** and **47d** (4:1) (0.22 g, 83%, R_f 0.2) as an oil. **36d**: ^{1}H NMR ($CDCl_3$) δ 8.43 (m, 2H, Pyri); 7.5–7.1 (m, 8H, Pyri + Ph); 6.95 (d, 1H, $J=2.3$ Hz, Py); 5.57 (d, 1H, $J=2.3$ Hz, Py); 3.7 (t, 2H, $J=6.7$ Hz, $CH_2\alpha$); 2.57 (q, 2H, $J=7.5$ Hz, CH_2); 2.35–2.10 (m, 2H, $CH_2\gamma$); 2.18 (s, 6H, $N(CH_3)_2$); 1.7–1.5 (m, 2H, $CH_2\beta$); 1.0 (t, 3H, $J=7.5$ Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ 149.25; 148.28; 144.44; 139.74; 137.21; 135.97; 135.60; 132.03; 129.03; 128.44; 128.38; 127.63; 122.97; 105.52; 75.87; 55.82; 45.23; 27.83; 25.76; 13.17. **47d**: ^{1}H NMR ($CDCl_3$) δ 8.32 (dd, 1H, $J=4.8$ and 1.7 Hz, Pyri); 8.20 (d, 1H, $J=1.7$ Hz, Pyri); 7.5–7.1 (m, 7H, Py + Pyri + Ph); 7.03 (dd, 1H, $J=4.8$ and 0.8 Hz, Pyri); 6.0 (d, 1H, $J=2.3$ Hz, Py); 4.16 (t, 2H, $J=6.4$ Hz, $CH_2\alpha$); 2.49 (q, 2H, $J=7.5$ Hz, CH_2); 2.39 (t, 2H, $J=7.1$ Hz, $CH_2\gamma$); 2.22 (s, 6H, $N(CH_3)_2$); 1.9–1.8 (m, 2H, $CH_2\beta$); 1.01 (t, 3H, $J=7.5$ Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ 150.40; 147.74; 141.08; 138.23; 136.43; 134.29; 133.19; 132.23; 129.24; 128.60; 128.55; 127.69; 122.52; 104.77; 76.58; 55.97; 45.30; 27.88; 26.06; 13.57.

(*Z*)-1-(1-[3-*N*,*N*-Dimethylaminopropyloxy]-pyrazol-5-yl)-2-(2-thienyl)-1-phenyl-1-butene (37d) and (*Z*)-2-(1-[3-*N*,*N*-dimethylaminopropyloxy]-pyrazol-5-yl)-1-(2-thienyl)-1-phenyl-1-butene (48d). Using procedure B, Mixture B and 2-iodothiophene (0.23 g, 1.1 mmol) after FC (heptane/EtOAc/Et_3N 1:1:0.1) afforded **37d** and **48d** (4:1) (0.23 g, 86%, R_f 0.35). **37d**: ^{1}H NMR ($CDCl_3$) δ 7.45–7.18 (m, 5H, Ph); 7.23 (d, 1H, $J=5.1$ Hz, Th), 7.07 (d, 1H, $J=2.3$ Hz, Py); 6.90 (dd, 1H, $J=5.1$ and 3.6 Hz, Th); 6.85 (dd, 1H, $J=5.1$ and 1.2 Hz, Th); 5.87 (d, 1H, $J=2.3$ Hz, Py); 3.80 (t, 2H, $J=6.6$ Hz, $CH_2\alpha$); 2.57 (q, 2H, $J=7.3$ Hz, CH_2); 2.3–2.1 (m, 2H, $CH_2\gamma$); 2.18 (s, 6H, $N(CH_3)_2$); 1.7–1.6 (m, 2H, $CH_2\beta$); 1.11 (t, 3H, $J=7.3$ Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ 140.65; 138.52; 137.74; 134.13; 130.30; 126.40; 126.35; 126.14; 125.31; 124.52; 124.48; 123.33; 103.09; 71.67; 52.97; 40.83; 26.39; 20.78; 11.54. **48d**: ^{1}H NMR ($CDCl_3$) δ 7.45–7.18 (m, 7H, Ph + Th + Py); 6.77 (dd, 1H, $J=5.1$ and 3.6 Hz, Th); 6.37 (dd, 1H, $J=3.5$ and 1.7 Hz, Th); 6.22 (d, 1H, $J=2.3$ Hz, Py); 4.17 (t, 2H, $J=6.3$ Hz, $CH_2\alpha$); 2.37 (q, 2H, $J=7.5$ Hz, CH_2); 2.3–2.2 (m, 2H, $CH_2\gamma$); 1.9–1.8 (m, 2H, $CH_2\beta$); 0.91 (t, 3H, $J=7.5$ Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ 144.26; 141.41; 137.82; 137.34; 134.21; 132.69; 129.25; 128.70; 128.65; 128.64; 127.45; 127.25; 126.38; 76.38; 56.09; 45.28; 28.51; 26.19; 13.04.

(*Z*)-1-(1-[3-*N*,*N*-Dimethylaminopropyloxy]-pyrazol-5-yl)-2-(3-thienyl)-1-phenyl-1-butene (38d) and (*Z*)-2-(1-[3-*N*,*N*-dimethylaminopropyloxy]-pyrazol-5-yl)-1-(3-thienyl)-1-phenyl-1-butene (49d). Using procedure B, Mixture B and 3-iodothiophene (0.23 g, 1.1 mmol) after FC (heptane/EtOAc/Et_3N 1:1:0.1) gave 38d and **49d** (4:1) (0.20 g, 74%, R_f 0.35) which was purified as the oxalates as described above to give 0.24 g. **38d** (oxalate): ^{1}H NMR ($CDCl_3$) δ 7.50–7.00 (m, 6H, Ph + Th); 7.17 (dd, 1H, $J=5$ and 3 Hz, Th), 7.01 (d, 1H, $J=2.3$ Hz, Py); 6.7 (dd, 1H, $J=5$ and 1.3 Hz, Th); 5.70 (d, 1H, $J=2.3$ Hz, Py); 3.62 (t, 2H, $J=5.6$ Hz, $CH_2\alpha$); 3.11 (t, 2H, $J=7.5$ Hz, $CH_2\gamma$); 2.82–2.81 (s, 6H, $N(CH_3)_2$); 2.54 (t, 2H, $J=7.5$ Hz, CH_2); 1.94 (m, 2H, $CH_2\beta$); 1.04 (t, 3H, $J=7.5$ Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ 142.39; 141.47; 140.39; 136.46; 132.23; 128.99; 128.23; 127.50; 127.19; 125,72; 124.63; 122,90; 104.74; 75.69; 55.85; 45.22; 27.84; 25.81; 13.64. **49d** (oxalate): ^{1}H NMR ($CDCl_3$) δ 7.50–7.00 (m, 7H, Ph + Th + Py); 6.61 (dd, 1H, $J=3$ and 1.3 Hz, Th); 6.42 (dd, 1H, $J=5$ and 1.3 Hz, Th); 6.19 (d,

1H, $J=2.3$ Hz, Py); 3.99 (t, 2H, $J=5.6$ Hz, $CH_2\alpha$); 3.20 (t, 2H, $J=8.2$ Hz, $CH_2\gamma$); (s, 6H, $N(CH_3)_2$); 2.30 (t, 2H, $J=7.5$ Hz, CH_2); 2.1 (m, 2H, $J=5.3$ Hz, $CH_2\beta$); 0.94 (t, 3H, $J=7.5$ Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ 142.61; 142.38; 141.92; 136.45; 140.38; 138.46; 135.15; 132.55; 129.04; 127.27; 124.91; 124.18; 103.98; 76.08; 56.05; 45.28; 28.28; 26.12; 13.30.

(*Z*)-1,2-Di-(1-[3-*N*,*N*-dimethylaminopropyloxy]-pyrazol-5-yl)-1-phenyl-1-butene (39d). Using procedure B, Mixture B and **26d** (0.21 g, 0.71 mmol) after FC (heptane/EtOAc/Et_3N 1:1:0.1) afforded **39d** (0.27 g, 82% R_f 0.1) as a colourless oil. ^1H NMR ($CDCl_3$) δ 7.45–7.25 (m, 5H, Ph); 7.14 (d, 1H, $J=2.3$ Hz, Py); 7.02 (d, 1H, $J=2.3$ Hz, Py); 5.98 (d, 1H, $J=2.3$ Hz, Py); 5.68 (d, 1H, $J=2.3$ Hz, Py); 4.15 (t, 2H, $J=6.6$ Hz, $CH_2\alpha$); 3.58 (t, 2H, $J=6.8$ Hz, $CH_2\alpha$); 2.48 (q, 2H, $J=7.5$ Hz, $CH_2\gamma$); 2.39 (t, 2H, $J=7.2$ Hz, $CH_2\gamma$); 2.20 (s, 6H, $N(CH_3)_2$); 2.13 (s, 6H, $N(CH_3)_2$); 2.13 (t, 2H, $J=7.5$ Hz, CH_2); 1.87 (tt, 2H, $J=7.5$ and 6.6 Hz, $CH_2\beta$); 1.49 (tt, 2H, $J=7.2$ and 6.8 Hz, $CH_2\beta$); 1.01 (t, 3H, $J=7.5$ Hz, CH_3). ^{13}C NMR (CD_3OD) δ 139.24; 135.50; 134.12; 134.05; 132.40; 132.29; 130.98; 129.08; 128.38; 127.83; 104.41; 104.36; 76.71; 75.64; 55.92; 55.88; 45.32; 45.24; 26.90; 25.94; 25.72; 13.49.

1-Butyne (50). 5.5 g (239 mmol, 1 equiv) of sodium was dissolved in liquid ammonia (300–500 mL) at −78 °C and treated as previously described,[30,51] affording 7 g (129 mmol, 54%) of a colourless liquid containing the title compound. ^1H NMR ($CDCl_3$) δ 2.21 (dq, 2H, $J=7.5$ and 2.4 Hz, CH_2); 1.94 (t, 1H, $J=2.4$ Hz, CH); 1.17 (t, 3H, $J=7.5$ Hz, CH_3,). ^{13}C NMR ($CDCl_3$) δ 86.06; 67.35; 13.56; 11.96.

1-Benzyloxy-4-(1-butynyl)-pyrazole (51). Was prepared using slightly modified Sonogashira conditions.[52] 1-Benzyloxy-4-iodopyrazole (4 g, 13.3 mmol), $K_3PO_4\times 2H_2O$ (14.2 g, 53.3 mmol, 4 equiv), $Pd(PPh_3)_4$ (0.77 g 0.67 mmol, 0.05 equiv) and CuI (63 mg, 0.33 mmol, 0.025 equiv) were dissolved in DMF (30 mL). The solution was purged with N_2 for 5 min and cooled to −40 °C before 1-butyne (ca. 2 mL, 1.5 equiv) was bubbled through the reaction mixture. The flask was sealed and allowed to warm to rt and stirred over night. The dark reaction mixture was poured into H_2O (200 mL) and extracted with Et_2O (4×50 mL). The combined Et_2O phases were washed with H_2O (50 mL), brine (50 mL) and evaporated in vacuo affording a dark oil. FC [petrolether–EtOAc (6:1)] afforded 2.6 g (86%) of **51** as a yellow oil, which solidified upon standing. R_f 0.25, mp 34 °C. ^1H NMR ($CDCl_3$) δ 7.40–7.26 (m, 5H, Ph); 7.32 (d, 1H, $J=0.8$ Hz, Py); 7.06 (d, 1H, $J=0.8$ Hz, Py); 5.26 (s, 2H, CH_2Ph); 2.33 (q, 2H, $J=7.4$ Hz, CH_2); 1.17 (t, 3H, $J=7.4$ Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ 136.17; 133.51; 129.64; 129.38; 128.74; 124.85; 101.38; 91.84; 80.43; 70.10; 13.64; 12.83. Anal. C, H, N.

(*E*)-1-(1-Benzyloxypyrazol-4-yl)-1,2-(bis)pinacolatoborolanyl-1-butene (52). Pyrazole **51** (1.00 g, 4.42 mmol) was treated with (bis)borylpinacolester (1.11 g, 4.38 mmol, 0.99 equiv) as described for **1**. Work up as for **1** afforded 2.05 g (97%) of **52** as a slightly yellow oil. ^1H NMR ($CDCl_3$) δ 7.40–7.25 (m, 5H, Ph); 7.2 (d, 1H, $J=1.1$ Hz, Py); 6.87 (d, 1H, $J=1.1$ Hz, Py); 5.27 (s, 2H, CH_2Ph); 2.14 (d, 2H, $J=7.7$ Hz, CH_2); 1.29 (s, 12H, pinacol); 1.26 (s, 12H, pinacol); 0.93 (t, 3H, $J=7.7$ Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ 133.97; 133.30; 129.75; 129.22; 128.65; 121.76; 117.74; 83.70; 83.61; 80.20; 77.19; 25.23; 24.75; 14.09.

(*E*)-1-(1-Benzyloxypyrazol-4-yl)-1-(4-[2-*N*,*N*-dimethylaminoethyloxy]-phenyl)-2-pinacolatoborolanyl-1-butene (53) and (*E*)-1-(1-benzyloxypyrazol-4-yl)-1-pinacolatoborolanyl-2-(4-[2-*N*,*N*-dimethylaminoethyloxy]-phenyl)-1-butene (54). Using the method described for **3d**, **52** (0.37 g, 0.77 mmol, 1 equiv), 4-*N*,*N*-dimethylethyloxyiodobenzene (0.22 g, 0.76 mmol, 0.98 equiv), 2 M K_3PO_4, (1.2 mL, 2.4 mmol, 3 equiv) and $Pd(PPh_3)_4$, (45 mg 0.4 mmol, 0.05 equiv) were dissolved in DME (5 mL). The solution was purged with N_2 for 5 min and heated to 80 °C over night. Workup as for **3d** afforded a yellow oil 0.23 g (0.44 mmol, 58%) which contained a mixture of borylesters (**53**) and (**54**) and the corresponding boronic acids. Attempts to purify the product as the oxalates gave low yield, presumably because of the hydrophilicity of the boronic acids Therefore, the crude product was used with no further purification.

(*E*)-1-(1-Benzyloxypyrazol-4-yl)-1-(4-[2-*N*,*N*-dimethylaminoethyloxy]-phenyl)-2-phenyl-1-butene (55) and (*E*)-1-(1-benzyloxypyrazol-4-yl)-1-phenyl-2-(4-[2-*N*,*N*-dimethylaminoethyloxy]-phenyl)-1-butene (56). Using General procedure B a 2:1 mixture of **53** and **54** (0.16 g, 0.31 mmol, 1 equiv), iodobenzene (82 mg, 0.4 mmol, 1.3 equiv), 6 M KOH (0.77 mL, 4.64 mmol, 15 equiv), 3,5-dimethoxyphenol (0.24 g, 1.55 mmol, 5 equiv) and $Pd(PPh_3)_4$ (36 mg, 0.03 mmol, 0.1 equiv) were dissolved in dioxane (5 mL). The solution was purged with N_2 for 5 min and heated to 85 °C overnight. Workup according to procedure B afforded 0.132 g (91%) of a 2:1 mixture of **55** and **56** as a yellow oil. Major isomer (**55**): ^1H NMR ($CDCl_3$) δ 7.40–6.9 (m, 5H, Ph); 7.15 (d, 1H, $J=1.1$ Hz, Py); 6.79 (d, 1H, $J=1.1$ Hz, Py); 6.71 (d, 2H, $J=8.8$ Hz, C_6H_4); 6.54 (d, 2H, $J=8.8$ Hz, C_6H_4); 5.30 (s, 2H, CH_2Ph); 3.94 (t, 2H, $J=5.8$ Hz, $CH_2\alpha$); 2.66 (t, 2H, $J=5.8$ Hz, $CH_2\beta$); 2.50 (q, 2H, $J=7.7$ Hz, CH_2); 2.30 (s, 6H, $N(CH_3)_2$); 0.89 (t, 3H, $J=7.7$ Hz, CH_3). Minor isomer (**56**): ^1H NMR ($CDCl_3$) δ 7.40–6.9 (m, 5H, Ph); 7.13 (d, 1H, $J=1.1$ Hz, Py); 6.88 (d, 2H, $J=8.8$ Hz, C_6H_4); 6.77 (d, 1H, $J=1.1$ Hz, Py); 6.65 (d, 2H, $J=8.8$ Hz, C_6H_4); 5.29 (s, 2H, CH_2Ph); 3.97 (t, 2H, $J=5.8$ Hz, $CH_2\alpha$); 2.67 (t, 2H, $J=5.8$ Hz, $CH_2\beta$); 2.49 (q, 2H, $J=7.7$ Hz, CH_2); 2.31 (s, 6H, $N(CH_3)_2$); 0.90 (t, 3H, $J=7.7$ Hz, CH_3). Anal. C, H, N.

Debenzylation

(*E*)-1-(1-Hydroxypyrazol-4-yl)-1-(4-[2-*N*,*N*-dimethylaminoethyloxy]-phenyl)-2-phenyl-1-butene (57) and (*E*)-1-(1-hydroxypyrazol-4-yl)-1-phenyl-2-(4-[2-*N*,*N*-dimethylaminoethyloxy]-phenyl)-1-butene (58). 150 mg (0.32 mmol, 1 equiv) of a 2:1 mixture of **55** and **56** was dissolved in MeOH (10 mL) The mixture was purged with N_2, then 5% Pd/C (10 mg) was added and the mixture stirred for 1.5 h in an atmosphere of H_2. Filtration through Celite,

removal of the solvent, addition of CH_2Cl_2 (10 mL), filtration, removal of the CH_2Cl_2 and FC (CH_2Cl_2–MeOH 5:1) first gave 11 mg (7%) of starting material. The next fraction contained 27 mg (24%) of **57**, R_f 0.32. ^{1}H NMR ($CDCl_3$) δ 7.10–6.9 (m, 5H, Ph); 7.10 (d, 1H, J = 1.1 Hz, Py); 6.93 (d, 2H, J = 8.8 Hz, C_6H_4); 6.83 (d, 1H, J = 1.1 Hz, Py); 6.58 (d, 2H, J = 8.8 Hz, C_6H_4); 3.90 (t, 2H, J = 5.7 Hz, $CH_2\alpha$); 2.86 (t, 2H, J = 5.7 Hz, $CH_2\beta$); 2.67 (q, 2H, J = 7.4 Hz, CH_2); 2.44 (s, 6H, $N(CH_3)_2$); 1.01 (t, 3H, J = 7.4 Hz, CH_3). ^{13}C NMR (CD_3OD) δ 156.32; 143.30; 140.49; 135.52; 131.78; 130.96; 130.85; 129.15; 127.43; 125.80; 121.83; 121.08; 113.68; 77.19; 64.45; 57.30; 44.95; 29.05; 13.17. The next fraction to leave the column contained 20 mg (18%) of **58**, R_f 0.11. Which could be purified as the oxalate. ^{1}H NMR ($CDCl_3$) δ 7.20–6.80 (m, 7H, Ph + Py); 6.80 (d, 2H, J = 8.6 Hz, C_6H_4); 6.45 (d, 2H, J = 8.6 Hz, C_6H_4); 3.85 (t, 2H, J = 5.4 Hz, $CH_2\alpha$); 2.83 (t, 2H, J = 5.4 Hz, $CH_2\beta$); 2.69 (q, 2H, J = 7.4 Hz, CH_2); 2.43 (s, 6H, $N(CH_3)_2$); 1.00 (t, 3H, J = 7.4 Hz, CH_3). ^{13}C NMR (CD_3OD) δ 156.30; 143.14; 140.73; 136.14; 132.07; 131.63: 129.73; 128.87; 127.78; 125.74; 121.76; 120.98; 113.20; 77.22; 64.55; 57.38; 44.92; 29.24; 13.21. Anal. C, H, N.

When the hydrogenolysis was performed for longer time the double bond was reduced, providing a complicated mixture as seen in the ^{1}H NMR spectra.

1-(3-*N*,*N*-dimethylaminopropyloxy)-5-ethyl-4-phenylpyrazolo[4,3-*a*]naphthalene (59). Under N_2 a solution of **10d** (0.188 g, 0.48 mmol, 1 equiv) in dry THF (10 mL) was cooled to −78 °C. *n*-BuLi (1.64 M in hexanes, 0.4 mL, 0.66 mmol, 1.3 equiv) was added during 5 min. After stirring at −78 °C for 2 h, the mixture was allowed to heat to rt during 1 h. 1 M NH_4Cl (5 mL) was added, the mixture poured into H_2O (10 mL) and extracted with 3×10 mL CH_2Cl_2. The organic phases were washed with H_2O (3×5 mL) and brine (10 mL). Drying (Na_2SO_4), filtration and removal of the CH_2Cl_2 gave an oil which was dissolved in Et_2O and treated with oxalic acid as described above affording 0.2 g (90%) of the oxalate of **59** as white crystals. The oxalate was converted to the free base as described in procedure B. ^{1}H NMR ($CDCl_3$) δ 8.8–8.7 (m, 1H); 8.25–8.18 (m, 1H); 7.73–7.66 (m, 2H); 7.56–7.39 (m, 5H, Ph); 7.31 (s, 1H, Py); 4.55 (t, 2H, J = 5.8 Hz, $CH_2\alpha$); 3.0 (t, 2H, J = 7.8 Hz, $CH_2\gamma$); 2.75 (t, 2H, J = 7.5 Hz, CH_2); 2.39 (s, 6H, $N(CH_3)_2$); 2.25–2.15 (m, 2H, $CH_2\beta$); 0.75 (t, 3H, J = 7.5 Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ 139.14; 132.37; 131.75; 129.92; 128.76; 128.49; 127.97; 127.81; 127.28; 126.36; 126.10; 123.41; 120.45; 119.93; 76.88; 56.36; 45.70; 45.47; 26.28; 22.69; 16.23. Anal. C, H, N.

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References and Notes

1. Osborne, C. K.; Coronado-Heinsohn, E. B.; Hilsenbeck, S. G.; McCue, B. L.; Wakeling, A. E.; McClelland, R. A.; Manning, D. L.; Nicholson, R. I. *J. Natl. Cancer Inst.* **1995**, *87*, 746.
2. For a recent review, see: Tonetti, D. A.; Jordan, V. C. *J. Steroid Biochem. Mol. Biol.* **1997**, *62*, 119.
3. For a recent review, see: Gradishar, W. J.; Jordan, V. G. *J. Clin. Oncol.* **1997**, *15*, 840.
4. Favoni, R. E.; Cupis, A. *TiPS* **1998**, *19*, 406.
5. Dehal, S. S.; Kupfer, D. *Cancer Res.* **1997**, *57*, 3402.
6. Ruenitz, P. C.; Shen, Y.; Li, M.; Liang, H.; Whitehead, R. D.; Pun, S.; Wronski, T. J. *Bone* **1998**, *23*, 537.
7. Srikanth, N.; Tan, C.-H.; Ng, S.-C.; Loh, T.-P.; Koh, L.-L.; Sim, K.-Y. *J. Chem. Res. (M)* **1997**, 1828.
8. Schwartz, W.; Hartmann, R. W.; Schönenberger, H. *Arch. Pharm.* **1991**, *324*, 223.
9. Schwartz, W.; Hartmann, R. W.; Schönenberger, H. *Arch. Pharm.* **1991**, *324*, 231.
10. Olier-Reuchet, C.; Aitken, D. J.; Husson, H.-P. *Heterocyc. Commun.* **1998**, *1*, 4.
11. Haroutounian, S. A.; Scribner, A. W.; Katzenellenbogen, J. A. *Steroids* **1995**, *60*, 636.
12. Croisy-Delcey, M.; Croisby, A.; Carrez, D.; Huel, C.; Chiaronic, A.; Ducrout, P.; Bisagni, E.; Jin, L.; Leclercq, G. *Bioorg. Med. Chem.* **2000**, *8*, 2629.
13. Segall, A.; Pappa, H.; Casaubon, R.; Martin, G.; Bergoc, R.; Pizzorono, M. T. *Eur. J. Med. Chem.* **1995**, 165.
14. Top, S.; Dauer, B.; Vaissermann, J.; Jaouen, G. *J. Organometallic Chem.* **1997**, *541*, 335.
15. Bérubé, G.; He, Y.; Groleau, S.; Séné, A.; Thérien, H.-M.; Caron, M. *Inorg. Chim. Acta* **1997**, *262*, 139.
16. Auger, S.; Mérand, Y.; Pelletier, J. D.; Poirier, D.; Labrie, F. *J. Steroid. Biochem. Mol. Biol.* **1995**, *52*, 547.
17. Magarian, R. A.; Avor, K. S.; Overacre, L. B.; Kunchandy, J.; Paxton, T. R. *Anti-Cancer Drug Des.* **1995**, *10*, 311.
18. Overacre, S. B.; Magarian, R. A. *Bioorg. Chem.* **1998**, *26*, 15.
19. Fink, B. E.; Mortensen, D. S.; Stauffer, S. R.; Aron, Z. D.; Katzenellenbogen, J. A. *Chem. Biol.* **1999**, *6*, 205.
20. Stauffer, S. R.; Coletta, C. J.; Tedesco, R.; Nishiguchi, G.; Carlson, K.; Sun, J.; Katzenellenbogen, B. S.; Katzenellenbogen, J. A. *J. Med. Chem.* **2000**, 4934.
21. Brown, S. D.; Armstrong, R. W. *J. Am. Chem. Soc.* **1996**, *118*, 6331.
22. Brown, S. D.; Armstrong, R. W. *J. Org. Chem.* **1997**, *62*, 7076.
23. Liberman, M. E.; Gorski, J.; Jordan, V. C. *J. Biol. Chem.* **1983**, *258*, 4741.
24. Brzozowski, A. M.; Pike, A. C. W.; Dauter, Z.; Hubbard, R. E.; Bonn, T.; Engström, O.; Ohman, L.; Greene, G. L.; Gustafsson, J.-A.; Carlquist, M. *Nature* **1997**, *389*, 753.
25. Jin, L.; Legros, N.; Leclercq, G.; Hardcastle, I. R.; Jarman, M. *Cancer Chemo. Pharm.* **1998**, *41*, 339.
26. Deplassand, E. S.; Yang, D. J.; Wallace, S.; Cherif, A.; Quadri, S. M.; Price, J.; Joubert, A.; Inoue, T.; Podoloff, D. A. *J. Pharm. Sci.* **1996**, *85*, 553.
27. Magarian, R. A.; Avor, K. S.; Overacre, L. B.; Kunchandy, J.; Pazton, T. R. *Anti-Cancer Drug Des.* **1995**, *10*, 311.
28. The calculations were performed using Hyper Chem™ Release 4 for Windows, Molecular Modeling System.
29. Shiau, A. K.; Barstad, D.; Loria, P. M.; Cheng, L.; Kushner, P. J.; Agard, D. A.; Greene, G. L. *Cell* **1998**, *95*, 927.
30. Morehouse, F. R.; Maass, O. *Can. J. Res.* **1933**, 306.
31. Yamanaka, H.; Shiraiwa, M.; Yamamoto, E.; Sakamoto, T. *Chem. Pharm. Bull.* **1981**, *29*, 3543. Ezquerra, J.; Pedregal, C.; Lamas, C. *J. Org. Chem.* **1996**, *61*, 5804.
32. Sharma, M. *Biochem. Biophys. Res. Commun.* **2000**, *273*, 40.

33. Andersen, H. R.; Andersson, A.; Arnold, S. F.; Autrup, H.; Barfoed, M.; Beresford, N. A.; Bjerregaard, P.; Christiansen, L. B.; Gissel, B.; Hummel, R.; Bonefeld-Jorgensen, E.; Korsgaard, B.; Le-Guevel, R.; Leffers, H.; McLachlan, V.; Moller, V.; Bo-Nielsen, J.; Olea, N.; Oles-Karasko, A.; Pakdel, F.; Pedersen, K. L.; Perez, P.; Skakkebæk, N. E.; Sonnenschein, C.; Soto, A. M.; Sumpter, J. P.; Thorpe, S. M.; Grandjean, P. *Environ. Health Perspect.* **1999**, *107*, 89.
34. Thorpe, S. M. *Breast Cancer Res. Treat.* **1987**, *9*, 175.
35. Jordan, V. C.; Gosden, B. *Mol. Cel. Endocrinol.* **1982**, *27*, 291.
36. Murphy, C. S.; Langan-Fahey, S. M.; McCague, R.; Jordan, V. C. *Mol. Pharmacol.* **1990**, *38*, 737.
37. Lednicher, D.; Lyster, S. C.; Aspergren, B. D.; Duncan, G. W. *J. Med. Chem.* **1966**, *9*, 172.
38. Lednicher, D.; Lyster, S. C.; Duncan, G. W. *J. Med. Chem.* **1967**, *10*, 78.
39. Shiau, A. K.; Barstad, D.; Loria, P. M.; Cheng, L.; Kushner, P. J.; Agard, D. A.; Greene, G. L. *Cell* **1998**, *95*, 927.
40. Qiu, J.; Stevenson, S. H.; O'Beirne, M. J.; Silverman, R. B. *J. Med. Chem.* **1999**, *42*, 329.
41. Shani, J.; Gazit, A.; Livshitz, T.; Biran, S. *J. Med. Chem.* **1985**, *28*, 1504.
42. Lykkesfeldt, A. E.; Larsen, S. S.; Briand, P. *Int. J. Cancer* **1995**, *64*, 529.
43. Lykkesfeldt, A. E.; Madsen, M. W.; Briand, P. *Cancer Res.* **1994**, *54*, 1587. Larsen, S. S.; Madsen, M. W.; Lensen, B. L.; Lykkesfeldt, A. E. *Int. J. Cancer* **1997**, *72*, 1129.
44. Davois, S.; White, R.; Parker, M. M. G. *J. Cell Sci.* **1993**, *106*, 1377.
45. Gottardis, M. M.; Ricchio, M. D.; Satyaswaroop, P. G.; Jordan, V. C. *Cancer Res.* **1990**, *50*, 3189.
46. Briand, P.; Lykkesfeldt, A. E. *Cancer Res.* **1984**, *44*, 1114.
47. Hegedeus, L. S. In *Organometallics in Synthesis*; Schlosser, M., Ed., Wiley: New York, 1995; p 448.
48. Suffert, J. *J. Org. Chem.* **1989**, *54*, 509.
49. Ishiyama, T.; Matsuda, N.; Miyaura, N.; Suzuki, A. *J. Am. Chem. Soc.* **1993**, *15*, 11018.
50. Felding, J.; Kristensen, J.; Bjerregaard, T.; Sander, L.; Vedsø, P.; Begtrup, M. *J. Org. Chem.* **1999**, *64*, 4196.
51. Picon, M.; Haller, A. *Acad. Sci.* **1914**, 1184.
52. Sonogashira, K. In *Metal-catalyzed Cross-coupling Reactions*; Diederich, F.; Stang, P. J. E., Eds.; Wiley-VCH: 1998.