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Estrogenic Diazenes: Heterocyclic Non-steroidal Estrogens of Unusual Structure with Selectivity for Estrogen Receptor Subtypes

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Abstract—Estrogens regulate many biological functions, often acting in a tissue-selective manner. Their tissue-selective action is believed to involve differential estrogen action through the two estrogen receptor (ER) subtypes, ERα and ERβ, as well as differential interaction of the ligand–receptor complexes with promoters and coregulator proteins. In the latter case, selectivity is based on the induction of specific conformations of the ligand–ER complex, conformations that are influenced by the structure of the ligand. Estrogen pharmaceuticals having an ideal balance of tissue-selective activity are being sought for menopausal hormone replacement, breast cancer prevention and therapy, and other actions. To expand on the structural diversity of ER ligands that might show such tissue selectivity, we have prepared a series of diazenes (pyrazines, pyrimidines, and pyridazines) substituted with two to four aryl groups and various short-chain aliphatic substituents. All of the pyrazine and pyrimidines bind to ER, some with high affinity and with a considerable degree of preferential binding to either ERα or ERβ. One pyrimidine and one pyrazine have ERα affinity preferences as high as 23 and 9, respectively, and one pyrimidine has an ERβ affinity preference of 8. The pyridazines, by contrast, are quite polar and have only very low binding affinity for the ER. In cell-based transcription assays, several of the pyrimidines and a pyrazine were found to be considerably more agonistic on ERα than on ERβ. Because these triaryl diazenes have the largest volumes among the ER ligands so far investigated, their high affinity demonstrates the flexibility of the ligand binding pocket of the ERs and its tolerance for large substituents. Thus, these novel heterocyclic ligands expand the repertoire of chemical structures that bind to the estrogen receptor, and they could prove to be useful in elucidating the biological behavior of the two ER subtypes and in forming the basis for new estrogen pharmaceuticals having desirable tissue selectivity.

Introduction

The estrogen receptor (ER) is a ligand-regulated transcription factor that mediates the action of estrogens in many tissues. Estrogen action is required for the development and function of the female reproductive system, and it plays supportive roles in cardiovascular health, in cognitive and neuronal function, and in maintaining bone mineral density. On the other hand, estrogenic stimulation is a risk factor for the development and growth of some breast cancers, and estrogen antagonists are used for the prevention and treatment of breast cancer. Therefore, to obtain estrogen pharmaceuticals that will provide optimal health benefit for each intended medical use, it would be best to have compounds that act positively in those tissues where estrogenic stimulation is needed, but that are inactive or block estrogen action in those tissues where stimulation poses a risk. Such agents are being developed, and they have been termed, appropriately, selective estrogen receptor modulators, or SERMs.[1–3]

The mechanistic basis for the tissue-selective action of SERMs is not well understood. Part of the selectivity might arise from different activity that these compounds have on the two estrogen receptors, ERα and ERβ;[4] these receptor subtypes have different tissue distributions and transcriptional activity.[5–7] Another important element of this selectivity is thought to arise from differential interaction that various ligand–receptor complexes have with promoter sites and with coregulator proteins, important mediators of transcriptional activity. Because a large variety of structurally diverse steroidal and non-steroidal compounds can bind to the

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estrogen receptor, and in doing so stabilize different conformations of the ligand–receptor complex,[8,9] it is thought that this spectrum of ligand–receptor conformations is also responsible for the tissue-selective pharmacology of estrogens.[10]

Because of this intriguing link between ligand structure and the selective pharmacology of estrogens, a great effort is being made to discover structurally novel compounds that bind to ER in a manner that induces unusual ligand–receptor conformations that might have optimized pharmacological profiles.[11] A number of heterocyclic systems have been investigated as 'core elements' in the development of novel estrogens, especially ones whose preparation might be expanded through combinatorial synthetic methods.[12–20]

We have investigated amide[15] and heterocyclic motifs[12–14,16,17,19,20] that can be used as core elements in the development of novel estrogens. One of the more promising core systems was the five-membered nitrogen heterocycle, pyrazole, a member of the family of diazole heterocycles (Fig. 1).[11–14,16,17] Although most di- and trisubstituted pyrazoles were feeble ER ligands, we found that tetrasubstituted pyrazoles have high affinity for ER, with some analogues having very high selectivity for ERα in terms of binding affinity and potency as agonists.[11–14,16,17] Other relatively non-polar, tetrasubstituted five-membered heterocycles or carbocycles also proved to be good ligands (e.g., furans, thiophenes, cyclopentadienes), some having very high selectivity for ERα.[19–21] However, certain other azole heterocycles that were inherently more polar (e.g., imidazoles) or afforded sites for only three substituents (e.g., oxazoles, thiazoles, isoxazoles, etc.) were less effective ligands.[12] Thus, it appeared that the heterocyclic core performed not just the role of an inert scaffold to which the required phenol and alkyl substituents could be attached, but also played an integral role in the overall binding of the complete ligand to the ER. The geometry of the heterocycle seemed to be most important in the scaffolding role, and the polarity, most important in the integral role.

In considering a further expansion of this theme of estrogens with novel heterocyclic core systems, we wondered whether the six-membered ring analogues of the diazoles, namely *diazenes*, might also function as suitable core elements for ER ligand development. As illustrated in Figure 1, the three classes of diazenes, namely, pyrazines, pyrimidines, and pyridazines, are all conceptually related to the diazoles through the formal insertion of a ring carbon at either a C–N or an N–N bond, to go from a five-membered to a six-membered heterocycle. In this fashion, pyrazines are analogues of imidazoles, pyridazines are analogues of pyrazoles, and pyrimidines are analogues of both of the diazoles.

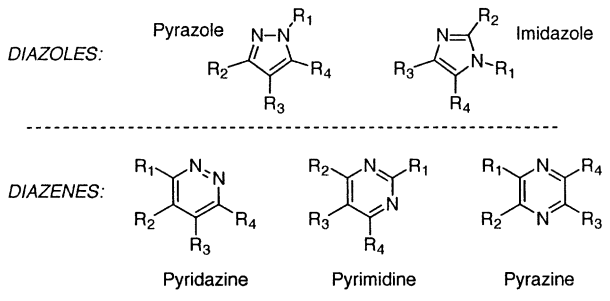


Figure 1. Diazole (above) and diazene (below) heterocyclic cores for estrogen receptor ligands. The diazoles are known core motifs for ER ligands,[11–14,16–17] and the diazenes are proposed core motifs. The substituents R_1–R_4 are either aromatic (phenyl or 4-hydroxyphenyl) or aliphatic (Me, Et, Pr, Bu, etc.).

The diazene core is a common feature of natural products and drugs. Pyridazine fungal metabolites are known,[22] and pyrazines are responsible for the flavor of many foods and are found in insect pheromones and, in dihydro form, in luciferins.[23–25] Pyrimidines, the most widely represented class, are found in nucleic acids and vitamin B_1, and they form the basis of many drugs (antimalarial, antibiotics, herbicides, anti-virals, antihypertensives, etc.).[25]

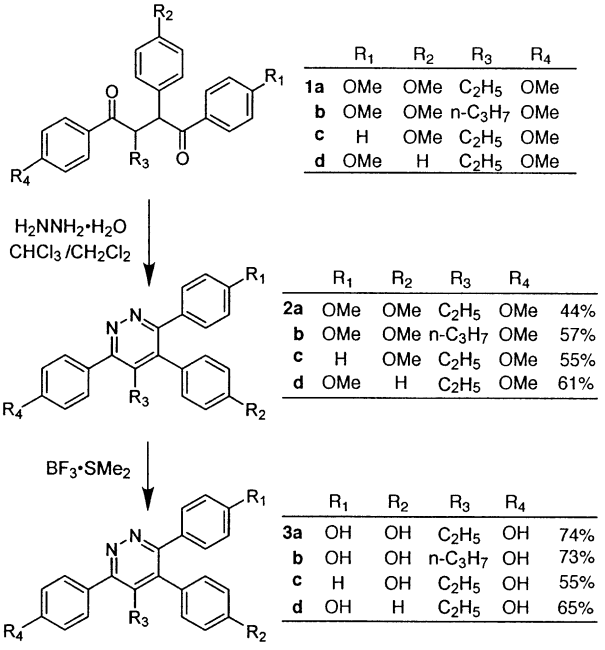
In this report, we describe the synthesis of a series of diazenes bearing aromatic and aliphatic substituents at sites that are patterned after the structures of the high affinity pyrazoles. We have assayed the binding affinity of these compounds for ERα and ERβ and evaluated the transcriptional activity of some of the higher affinity analogues in a cell-based assay. Thus, in this investigation, we have addressed several issues in the development of ER ligands of the heterocycle core design: (a) The role played by the core element—geometric versus integral, (b) the tolerance of ER to ligands of increasing overall size, and (c) the structural basis for ERα versus ERβ selectivity. In the process, we have found diazenes that have high binding affinity for the ERs, and in some cases show preferential affinity for ERα or for ERβ, and exhibit different levels of agonistic activity on the two ER subtypes.

Results

Synthesis

In selecting substituents to place on the diazene core motif, we were influenced by our prior work in the azole and furan series.[12–14,16,17,19,20] Thus, we have typically introduced 2–3 aromatic groups (i.e., 4-hydroxylphenyl or, in a few cases, phenyl), and we have filled the remaining positions with short aliphatic substituents, because these types of substituents gave the highest affinity compounds in the pyrazole and furan series.

Pyridazines. The pyridazines were readily synthesized by the reaction of hydrazine with 1,4-diones (**1a–d**, Scheme 1). The intermediate dihydropyridazines underwent spontaneous oxidation to the aromatic heterocycles (**2a–d**) upon exposure to air, and the methyl ether protecting groups were readily removed. All of the 1,4-diones (**1a–d**) that we used to prepare the pyridazines **3a–d** were synthesized by us earlier as precursors for estrogenic furans, by a route involving the cross-coupling of the enolate of a 1,2-diarylethanone with an α-bromoketone.[19,20]

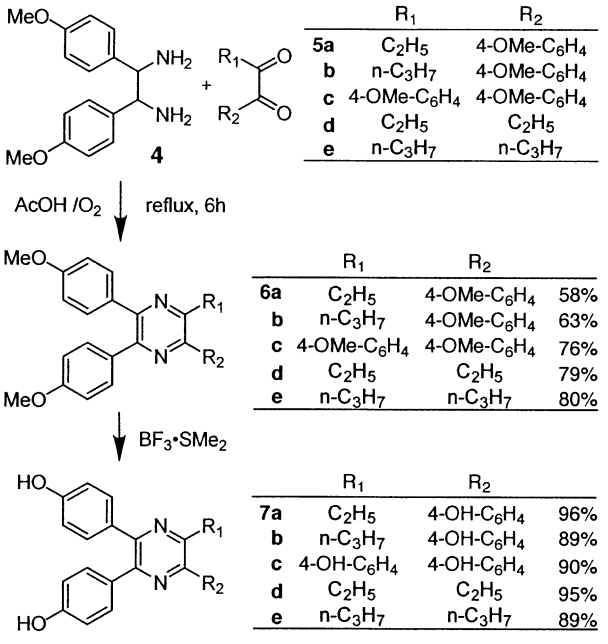


	R_1	R_2	R_3	R_4	
1a	OMe	OMe	C_2H_5	OMe	
b	OMe	OMe	n-C_3H_7	OMe	
c	H	OMe	C_2H_5	OMe	
d	OMe	H	C_2H_5	OMe	
2a	OMe	OMe	C_2H_5	OMe	44%
b	OMe	OMe	n-C_3H_7	OMe	57%
c	H	OMe	C_2H_5	OMe	55%
d	OMe	H	C_2H_5	OMe	61%
3a	OH	OH	C_2H_5	OH	74%
b	OH	OH	n-C_3H_7	OH	73%
c	H	OH	C_2H_5	OH	55%
d	OH	H	C_2H_5	OH	65%

Scheme 1.

Pyrazines. The pyrazines were prepared by two routes, depending on the pattern of aryl and alkyl substituents. Those that bore the same substituents on the C(2) and C(3) positions could be prepared as single regioisomers in reasonable yields by the reaction of a 1,2-dione (**5a–e**) with a 1,2-diamine (**4**), either one of which could be symmetrical, followed by spontaneous oxidation of the intermediate dihydropyrazine.[26] Removal of the methyl ether protecting groups gave the free phenols (**7a–e**, Scheme 2).

If symmetrical, the 1,2-diones (**5c–e**), which are all known compounds, were prepared by acyloin condensation from an ester precursor (in the presence of chlorotrimethylsilane), followed by bromination of the enediol disilyl ether product.[27,28] If they were unsymmetrical (**5a–b**), they were prepared by oxidation of an α-hydroxy-ketone[29] or selenium dioxide oxidation[30] of an appropriate ketone precursor. The 1,2-diamine (**4**) used was symmetrical and commercially available.



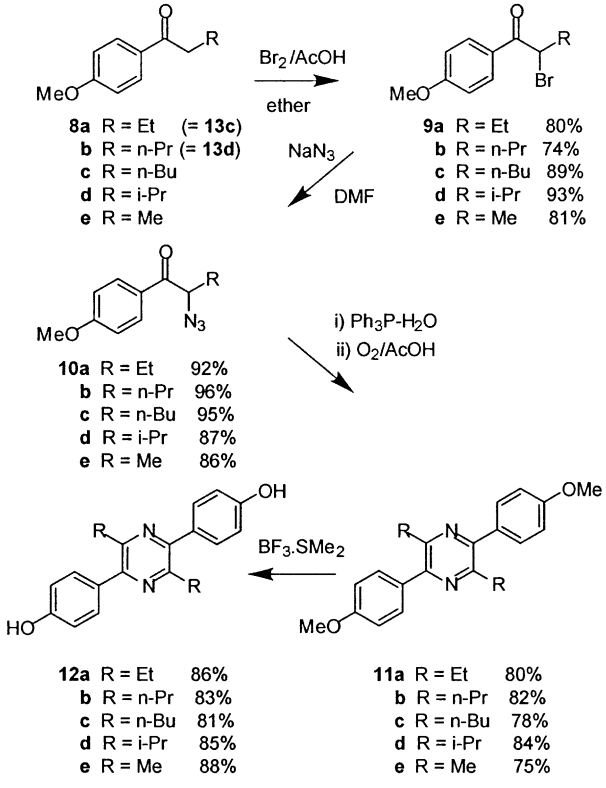
	R_1	R_2	
5a	C_2H_5	4-OMe-C_6H_4	
b	n-C_3H_7	4-OMe-C_6H_4	
c	4-OMe-C_6H_4	4-OMe-C_6H_4	
d	C_2H_5	C_2H_5	
e	n-C_3H_7	n-C_3H_7	
6a	C_2H_5	4-OMe-C_6H_4	58%
b	n-C_3H_7	4-OMe-C_6H_4	63%
c	4-OMe-C_6H_4	4-OMe-C_6H_4	76%
d	C_2H_5	C_2H_5	79%
e	n-C_3H_7	n-C_3H_7	80%
7a	C_2H_5	4-OH-C_6H_4	96%
b	n-C_3H_7	4-OH-C_6H_4	89%
c	4-OH-C_6H_4	4-OH-C_6H_4	90%
d	C_2H_5	C_2H_5	95%
e	n-C_3H_7	n-C_3H_7	89%

Scheme 2.

The pyrazines that had identical substituents at the C(2)/C(5) and C(3)/C(6) position (**12a–e**) were readily prepared in high yield by dimerization of an appropriate α-aminoketone, whose synthesis via the corresponding α-bromo (**9a–e**) and α-azidoketones (**10a–e**) is shown in Scheme 3.[31] Again, oxidation of the dihydropyrazine was spontaneous, and ether deprotection gave the free phenols (**12a–e**) in good yields.

Pyrimidines. The most favorable route to the pyrimidines depended on the pattern of substituents. Those that bore the same groups at the C(2) and C(6) positions were readily prepared by a triple condensation, involving a ketone and two equivalents of a nitrile,[32] as shown in Schemes 4 and 5. Those with other patterns of substituents were prepared from 1,3-diones by the route shown in Scheme 6.

The triple condensation approach was well suited for the synthesis of 2,4,6-triaryl-pyrimidines (and certain 2,4-diaryl-pyrimidines, that is, those that utilized methyl ketone precursors).[32] With the alkylphenones (**13a–d**), this cyclization proceeded regioselectively and in good yield (Scheme 4), because these ketones can enolize only in one direction. However, with the methyl alkyl ketones (**13e–f**), which can form two different enols, the cyclization yields were considerably lower. Byproducts



8a R = Et (= **13c**)
b R = n-Pr (= **13d**)
c R = n-Bu
d R = i-Pr
e R = Me

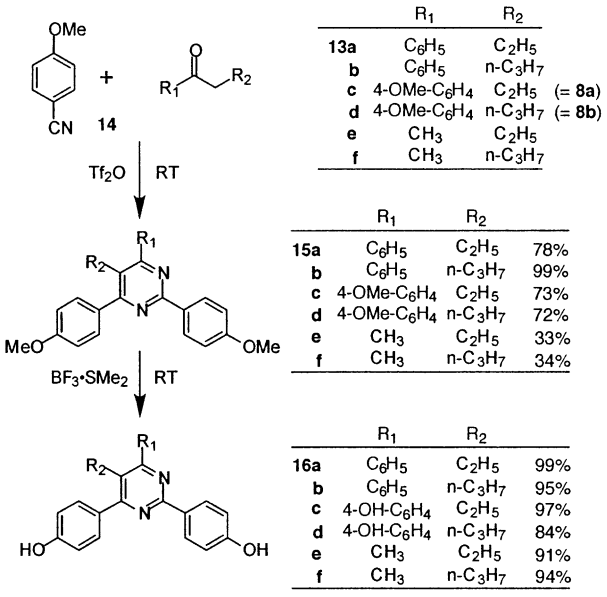
9a R = Et 80%
b R = n-Pr 74%
c R = n-Bu 89%
d R = i-Pr 93%
e R = Me 81%

10a R = Et 92%
b R = n-Pr 96%
c R = n-Bu 95%
d R = i-Pr 87%
e R = Me 86%

12a R = Et 86%
b R = n-Pr 83%
c R = n-Bu 81%
d R = i-Pr 85%
e R = Me 88%

11a R = Et 80%
b R = n-Pr 82%
c R = n-Bu 78%
d R = i-Pr 84%
e R = Me 75%

Scheme 3.

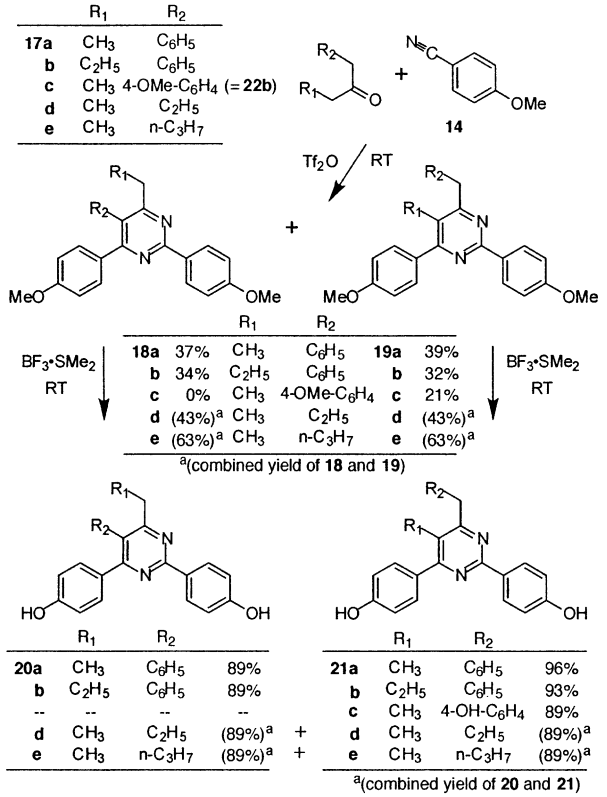


	R_1	R_2	
13a	C_6H_5	C_2H_5	
b	C_6H_5	$n\text{-}C_3H_7$	
c	4-OMe-C_6H_4	C_2H_5	(= **8a**)
d	4-OMe-C_6H_4	$n\text{-}C_3H_7$	(= **8b**)
e	CH_3	C_2H_5	
f	CH_3	$n\text{-}C_3H_7$	

	R_1	R_2	
15a	C_6H_5	C_2H_5	78%
b	C_6H_5	$n\text{-}C_3H_7$	99%
c	4-OMe-C_6H_4	C_2H_5	73%
d	4-OMe-C_6H_4	$n\text{-}C_3H_7$	72%
e	CH_3	C_2H_5	33%
f	CH_3	$n\text{-}C_3H_7$	34%

	R_1	R_2	
16a	C_6H_5	C_2H_5	99%
b	C_6H_5	$n\text{-}C_3H_7$	95%
c	4-OH-C_6H_4	C_2H_5	97%
d	4-OH-C_6H_4	$n\text{-}C_3H_7$	84%
e	CH_3	C_2H_5	91%
f	CH_3	$n\text{-}C_3H_7$	94%

Scheme 4.



	R_1	R_2	
17a	CH_3	C_6H_5	
b	C_2H_5	C_6H_5	
c	CH_3	4-OMe-C_6H_4	(= **22b**)
d	CH_3	C_2H_5	
e	CH_3	$n\text{-}C_3H_7$	

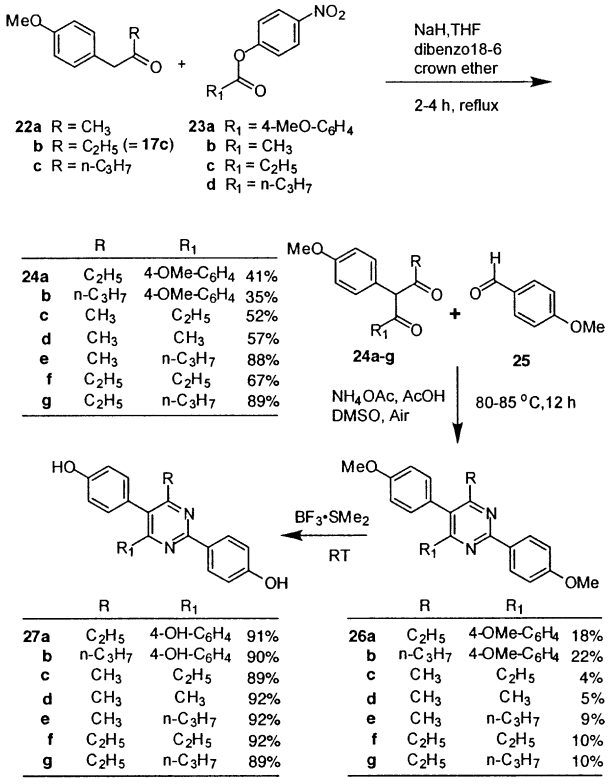
	R_1	R_2			R_1	R_2	
18a	CH_3	C_6H_5	37%	**19a**	CH_3	C_6H_5	39%
b	C_2H_5	C_6H_5	34%	**b**	C_2H_5	C_6H_5	32%
c	CH_3	4-OMe-C_6H_4	0%	**c**	CH_3	4-OMe-C_6H_4	21%
d	CH_3	C_2H_5	(43%)[a]	**d**	CH_3	C_2H_5	(43%)[a]
e	CH_3	$n\text{-}C_3H_7$	(63%)[a]	**e**	CH_3	$n\text{-}C_3H_7$	(63%)[a]

	R_1	R_2			R_1	R_2	
20a	CH_3	C_6H_5	89%	**21a**	CH_3	C_6H_5	96%
b	C_2H_5	C_6H_5	89%	**b**	C_2H_5	C_6H_5	93%
--	--	--	--	**c**	CH_3	4-OH-C_6H_4	89%
d	CH_3	C_2H_5	(89%)[a] +	**d**	CH_3	C_2H_5	(89%)[a]
e	CH_3	$n\text{-}C_3H_7$	(89%)[a] +	**e**	CH_3	$n\text{-}C_3H_7$	(89%)[a]

Scheme 5.

were observed, but they were unstable and were not isolated. All of the free phenols (**16a–f**) were readily obtained after ether deprotection.

It proved to be a greater challenge to prepare the isomeric 2,5,6-triaryl-pyrimidines (and certain other 2,6-diaryl-pyrimidines) by this trimerization route (Scheme 5), because the dialkyl ketone precursors[33]



	R	R_1	
24a	C_2H_5	4-OMe-C_6H_4	41%
b	$n\text{-}C_3H_7$	4-OMe-C_6H_4	35%
c	CH_3	C_2H_5	52%
d	CH_3	CH_3	57%
e	CH_3	$n\text{-}C_3H_7$	88%
f	C_2H_5	C_2H_5	67%
g	C_2H_5	$n\text{-}C_3H_7$	89%

	R	R_1	
27a	C_2H_5	4-OH-C_6H_4	91%
b	$n\text{-}C_3H_7$	4-OH-C_6H_4	90%
c	CH_3	C_2H_5	89%
d	CH_3	CH_3	92%
e	CH_3	$n\text{-}C_3H_7$	92%
f	C_2H_5	C_2H_5	92%
g	C_2H_5	$n\text{-}C_3H_7$	89%

	R	R_1	
26a	C_2H_5	4-OMe-C_6H_4	18%
b	$n\text{-}C_3H_7$	4-OMe-C_6H_4	22%
c	CH_3	C_2H_5	4%
d	CH_3	CH_3	5%
e	CH_3	$n\text{-}C_3H_7$	9%
f	C_2H_5	C_2H_5	10%
g	C_2H_5	$n\text{-}C_3H_7$	10%

Scheme 6.

show little preference for enolization in the two different directions. As a result, the cyclizations shown in Scheme 5 in most cases give 1:1 mixtures of isomeric pyrimidine products. With the alkyl benzyl ketones (**17a–b**), yields were good, and the free phenols of the triaryl-pyrimidines (**20a–b** and **21a–b**) were readily separable. However, when the benzyl substitutent has a *p*-methoxy substituent (**17c**), the vinyl triflate intermediate is less reactive. When the cyclization reaction is conducted at room temperature, only the undesired isomer (**19c**) was obtained, and in low yields, suggesting that the styryl enol triflate is unreactive. At reflux, both isomeric pyrimidines **18c** and **19c** were produced, but they were inseparable either as methyl ethers or free phenols and thus were not studied further. With the dialkyl ketones (**17d–e**), cyclization yields were lower, and both pyrimidine isomers were produced. We were unable to separate these diaryl-pyrimidines as methyl ethers (**20d–e**) or free phenols (**21d–e**), but the phenols were tested as isomeric mixtures.

Our final approach to the pyrimidines involved the condensation of a 2-aryl-1,3-dione (**24a–g**) with an aromatic aldehyde (**25**, Scheme 6). This is a well precedented reaction, and it is well suited for the synthesis of both 2,5-diaryl and 2,4,5-triaryl pyridimines. However, the yields in the key condensation reaction are reported to be low,[34] and they proved to be low in our hands, as well. Nevertheless, the overall route proceeded well, and gave products (**27a–g**), free from the isomeric contaminants that plagued the alternative approach (Scheme 5).

Binding affinity

The relative binding affinity of the diazenes for estrogen receptors was determined by a competitive radiometric receptor binding assay, using purified, full-length human ERα and ERβ.[35,36] The results of these assays are given as relative binding affinity (RBA) values, where the affinity of estradiol is considered to be 100.

The estrogen receptor binding affinities of the pyrimidines and pyrazines are summarized in Tables 1 and 2, respectively. To assist in the analysis of the binding data, we have classified the pyrimidines and pyrazines according to aryl-substitution isomer class, denoted by combinations of a Roman numeral (denoting the type of heterocycle and number of aryl substituents) and a letter (denoting the pattern of aryl substituents on the heterocycle), as illustrated in Figure 2. Table entry numbers are also provided for convenience.

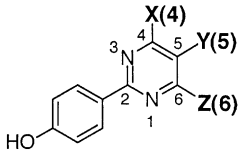
From Fig. 2, it is apparent that we have prepared all of the possible isomers of diarylpyrimidines (classes **II-A** and **II-B**) and triaryl pyrimidines (classes **I-A** and **I-B**) that contain an N(2)-aryl group. (There are two other diarylpyrimidine classes and one triarylpyrimidine class that do not have an N(2)-aryl group, but we have not explored these synthetically, because they require different synthetic methodology than we have used.) We have prepared the only isomeric class of triarylpyrazines (class **III**) and two of the three possible subclasses of diarylpyrazines (classes **IV-A** and **IV-B**).

Pyrimidines (Table 1). The largest number of diazenes we prepared were in the pyrimidine class. Here, we found that affinity for ER and selectivity for ERα versus ERβ depends in a detailed fashion on the number and nature of substituents, and compounds with good binding preferences for both ERα and ERβ were found.

Nearly all of the pyrimidines of the triaryl group (class **I**) have quite good binding affinities for estrogen receptor alpha (ERα); these include two that have high ERα affinity selectivity (entry numbers 3 and 4), which peaks at an ERα/ERβ affinity ratio of 23 for compound **16d** (entry number 4). It is notable that in the **I-A** subclass, the higher ERα/ERβ affinity ratios are found with those pyrimidines that have a propyl rather than an ethyl substituent (i.e., entries 2 vs 1, or 4 vs 3) or are triphenols rather than diphenols (i.e., 3 vs 1, or 4 vs 2). This is the same substitution pattern that was found to give the highest ERα binding selectivity in both the pyrazole and the furan series.[14,18] Trends of this nature are not evident in the **I-B** subclass, however.

Those pyrimidines of the diaryl classes (class **II**) show a wider range of affinities. In general, those from the more symmetrical 2,5-diaryl subclass (**II-B**; entry numbers 16–20) have higher affinity than those from the less symmetrical 2,4-diaryl subclass (**II-A**; entry numbers 9–12). We have included in the **II-A** subclass as an alternate subclass (**II-A^1**), pyrimidines that have a C(6) benzyl rather than alkyl substituents (**21a–c**, entry numbers 13–15). Two of these (**21a–b**, entry numbers 13 and 14) are isomers of the triaryl compounds **20a–b**

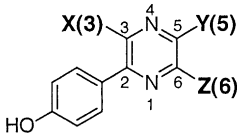
Table 1. Relative binding affinities (RBA) of pyrimidines for estrogen receptors[a]



Entry	Compd	Class	X(4)	Y(5)	Z(6)	ERα[b]	ERβ[b]	α/β[c]	β/α[c]
1	**16a**	**I-A**	*p*-HO-C_6H_4	C_2H_5	C_6H_5	0.99	0.77	1.3	—
2	**16b**	**I-A**	*p*-HO-C_6H_4	*n*-C_3H_7	C_6H_5	3.2	0.56	5.7	—
3	**16c**	**I-A**	*p*-HO-C_6H_4	C_2H_5	*p*-HO–C_6H_4	4.9	0.30	16.3	—
4	**16d**	**I-A**	*p*-HO-C_6H_4	*n*-C_3H_7	*p*-HO–C_6H_4	4.6	0.20	23	—
5	**20a**	**I-B**	*p*-HO-C_6H_4	C_6H_5	C_2H_5	4.5	1.9	2.4	—
6	**20b**	**I-B**	*p*-HO-C_6H_4	C_6H_5	*n*-C_3H_7	4.9	2.8	1.8	—
7	**27a**	**I-B**	*p*-HO-C_6H_4	*p*-HO–C_6H_4	C_2H_5	5.3	1.3	4.1	—
8	**27b**	**I-B**	*p*-HO-C_6H_4	*p*-HO–C_6H_4	*n*-C_3H_7	4.5	1.1	4.1	—
9	**16e**	**II-A**	*p*-HO-C_6H_4	C_2H_5	CH_3	0.21	0.08	2.7	—
10	**16f**	**II-A**	*p*-HO-C_6H_4	*n*-C_3H_7	CH_3	0.19	0.27	—	1.4
11	**20/21d**	**II-A**	*p*-HO-C_6H_4	$C_2H_5 + CH_3$	Et + *n*-Pr	0.57	0.75	—	1.3
12	**20/21e**	**II-A**	*p*-HO-C_6H_4	$C_2H_5 + CH_3$	*n*-Pr + *n*-Bu	0.54	1.0	—	1.9
13	**21a**	**II-A′**	*p*-HO-C_6H_4	CH_3	C_6H_5–CH_2	0.16	0.42	—	2.6
14	**21b**	**II-A′**	*p*-HO-C_6H_4	C_2H_5	C_6H_5–CH_2	1.6	0.56	2.9	—
15	**21c**	**II-A′**	*p*-HO-C_6H_4	CH_3	*p*-OH–C_6H_4–CH_2	0.06	0.03	1.8	—
16	**27c**	**II-B**	C_2H_5	*p*-HO–C_6H_4	CH_3	0.50	1.1	—	2.2
17	**27d**	**II-B**	CH_3	*p*-HO–C_6H_4	CH_3	0.04	0.30	—	7.5
18	**27e**	**II-B**	*n*-C_3H_7	*p*-HO–C_6H_4	CH_3	0.93	2.5	—	2.7
19	**27f**	**II-B**	C_2H_5	*p*-HO–C_6H_4	C_2H_5	5.1	11	—	2.1
20	**27g**	**II-B**	*n*-C_3H_7	*p*-HO–C_6H_4	C_2H_5	8.1	8.2	—	1.0

[a]Relative binding affinity (RBA) values are determined by competitive radiometric binding assays (see Experimental). RBA(estradiol) = 100. Under these conditions, the K_d for estradiol is ca. 0.3 nM on ERα and 0.9 nM on ERβ. Values represent the average of 2–4 determinations (CV < 0.25).
[b]Full length human ER expressed in baculovirus and purified (Pan Vera Corp, Madison, WI, USA).
[c]Selectivity of binding to ER subtypes. Ratios of RBA values, as indicated.

Table 2. Relative binding affinity of pyrazines for estrogen receptors[a]



Entry	Compd	Class	X(3)	Y(5)	Z(6)	ERα[b]	ERβ[b]	α/β[c]	β/α[c]
1	**7a**	**III**	*p*-HO-C_6H_4	C_2H_5	*p*-HO–C_6H_4	1.4	0.25	5.4	—
2	**7b**	**III**	*p*-HO-C_6H_4	*n*-C_3H_7	*p*-HO–C_6H_4	2.9	0.55	5.3	—
3	**7c**	—[d]	*p*-HO-C_6H_4	*p*-HO-C_6H_4	*p*-HO–C_6H_4	0.02	0.01	2.0	—
4	**7d**	**IV-A**	*p*-HO-C_6H_4	C_2H_5	C_2H_5	0.16	0.42	—	2.6
5	**7e**	**IV-A**	*p*-HO-C_6H_4	*n*-C_3H_7	*n*-C_3H_7	1.2	1.9	—	1.6
6	**12a**	**IV-B**	C_2H_5	*p*-HO–C_6H_4	C_2H_5	2.5	1.5	1.6	—
7	**12b**	**IV-B**	*n*-C_3H_7	*p*-HO–C_6H_4	*n*-C_3H_7	30	3.2	9.4	—
8	**12c**	**IV-B**	*n*-C_4H_9	*p*-HO–C_6H_4	*n*-C_4H_9	1.4	1.4	1.0	—
9	**12d**	**IV-B**	*i*-C_3H_7	*p*-HO–C_6H_4	*i*-C_4H_9	10	2.4	4.3	—
10	**12e**	**IV-B**	CH_3	*p*-HO–C_6H_4	CH_3	0.02	0.06	—	3.0

[a]Relative binding affinity (RBA) values are determined by competitive radiometric binding assays (see Experimental). RBA (estradiol) = 100; under these conditions, the K_d for estradiol is ca. 0.3 nM on ERα and 0.9 nM on ERβ. Values represent the average of 2–4 determinations (CV < 0.25).
[b]Full length human ER expressed in baculovirus and purified (PanVera Corp, Madison, WI, USA).
[c]Selectivity of binding to ER subtypes. Ratios of RBA values, as indicated.
[d]Tetraarylpyrazine.

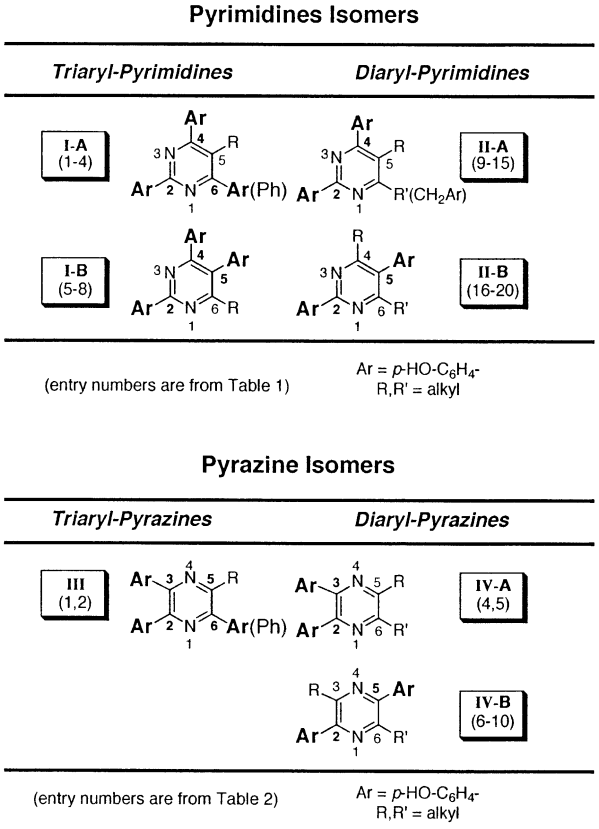


Figure 2. Display of various diaryl- and triaryl-substituted pyrimidine and pyrazine isomers and designation of structural classes and subclasses.

(subclass **I-B**; entry numbers 5 and 6), and they are produced as byproducts during their synthesis (cf., Scheme 5). These two diaryl benzyl pyrimidines have lower affinity than their corresponding isomeric triaryl isomers. It is also of note that the compounds (**20d/21d** and **20e/21e**, entry numbers 11 and 12) were a mixture of two structural isomers, in a roughly 1:1 ratio, obtained as a result of a non-regioselective synthetic route (cf., Scheme 5). Because it proved very difficult to separate these isomers, we tested them as a mixture; their affinities were not sufficiently high to warrant further efforts at isomer separation.

The five representatives of the 2,5-diarylpyrimidine subclass (**II-B**) span a large affinity range. There is a general trend for increased affinity as the number of carbon atoms in the two alkyl substituents increase (i.e., in the entry number series, 17, 16, 18, 19, 20). However, ERβ affinity appears to peak (entry 19) before ERα affinity (entry 20). The dimethyl analogue (**27d**; entry number 17) was the ligand with the greatest preferential affinity for ERβ (ERβ/ERα = 7.5). It is interesting that the highest ERβ/ERα affinity preference is not necessarily associated with the highest ERβ binding affinity.

Pyrazines (Table 2). The affinity of the pyrazines varied considerably with the nature and orientation of the substituents. The two triaryl members (class **III**; compounds **7a** and **7b**; entry numbers 1 and 2) have significant affinities, with good ERα subtype affinity preference. The one *tetraaryl* analogue (compound **7c**; entry number 3) has remarkably low affinity for both receptors. Aside from the pyridazines (see section below), it was the lowest affinity diazine we have investigated, a result which suggests that there is a size limit in the ER ligand binding pocket.

As was the case with the pyrimidines (see above), the affinities of the diarylpyrazines (class **IV**) span a large range and vary in a detailed manner with changes in the alkyl substituents. Overall, the affinities of those in the 2,3-diaryl class (subclass **IV-A**) were rather low and somewhat ERβ selective in comparison with those in the 2,5-diaryl subclass (**IV-B**), whose affinities are, in general, higher and depend in an interesting way on the size of the two alkyl substituents: Both ERα and ERβ affinity increase in the progression methyl to ethyl to propyl (entries 10, 6, and 7), where they peak, and then

decline to isobutyl and *n*-butyl (entries 9 and 8). In fact, the analogues with two additional propyl or iso-propyl substituents (**12b** and **12d**; entry numbers 7 and 9, respectively) had the highest affinity of all of the diazenes we investigated, and the analogue with two propyl substituents (**12b**; entry 7) was the third most selective for ERα (ERα/ERβ = 9.4; for the two most ERα selective diazenes, see **16c** and **16d**; Table 1, entries 3 and 4). It is of note that the high affinity diarylpyrazines of subclass **IV-B** are isomeric with the diarylpyrimidines of subclass **II-B**, yet the pyrimidines are generally ERβ selective, whereas the corresponding pyrazines are ERα selective.

Pyridazines. The four pyridazines we investigated (**3a–d**) all had exceedingly low ER binding affinity, with RBA values below the detection limit of our assay (i.e., <0.0008, data not shown). These diazines are by far the most polar of the three classes of diazenes we studied. The low affinity of these polar isomers is consistent with the behavior in the diazole series, where we found that the more polar imidazoles had ER binding affinities that were 50–100-fold less than that of their less polar pyrazole isomers (see Discussion).[12]

Transcriptional activity

Based on their ER binding affinity and/or ERα versus ERβ binding selectivity, we selected a set of 19 diazine ligands from several of the structural series to be assayed for their transcriptional activity through both ER subtypes. (Because of their low affinity, no pyridazines were selected for this assay.) These cotransfection assays are conducted in human endometrial carcinoma (HEC-1) cells, using expression plasmids for human ERα or ERβ and an estrogen-responsive luciferase reporter gene system containing estrogen response elements.[37] The transcriptional activity of these 19 compounds was initially screened with ERα and ERβ at two concentrations in the agonist mode (i.e., 10^{-8} and 10^{-6} M of compound alone) and at one concentration in the antagonist mode (i.e., 10^{-6} M compound together with 10^{-9} M estradiol). The results of these screening assays are summarized in Tables 3 and 4 as percent efficacy relative to 10^{-9} M estradiol.

Based on the level of efficacy achieved in the agonist and antagonist modes, the compounds were classified as 'agonists' (full to nearly full efficacy; $>80\%$), 'partial agonists' (50–85% efficacy), 'partial antagonists' (10–50% efficacy) or 'antagonists' (very little efficacy; $<10\%$). In addition, compounds that showed similar efficacy in the agonist mode at 10^{-8} and 10^{-6} M were considered to be 'potent', whereas those that failed to reach a similar level of efficacy at 10^{-6} M in both agonist and antagonist modes were classifed as 'weak'. From this initial screen, as is noted below, four compounds were selected for full dose response assays (see below).

Pyrimidines (Table 3). In general, the 12 pyrimidines studied in these transcription assays were more potent and more efficacious on ERα than on ERβ. This was most striking with the triaryl pyrimidines of subclasses **I-A** and **I-B**, and the diaryl pyrimidines of subclass **II-A**. All of these pyrimidines have minimal efficacy on ERβ and are weak on this subtype, as well (according to our definition above). The efficacy of these compounds on ERα differs, but aside from compounds **16b** and **16d** (entries 1 and 2), efficacies are $\geq 50\%$. From this set, compound **27b** (entry 5), which appears to be quite potent on ERα, was selected for further study (see below and Fig. 3). Its pharmacological character is reminiscent of that of the structurally related propylpyrazole triol (PPT) that we have studied earlier.[14]

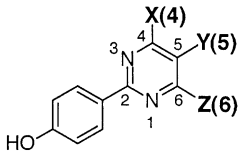
The pyrimidines of subclass **II-B**, which are 2,5-diaryl-4,6-dialkyl isomers, are quite different from the other pyrimidine classes. They are potent on ERα and all but compound **27d** (entry 10) are highly efficacious on this ER subtype; all four of those tested are also more efficacious on ERβ than were those of the other three classes, although the level of efficacy varies from 25 to 50%. These differences could arise from the generally greater ERβ affinity that is characteristic of this class (cf., Table 1), although this is not true in every case. [Note compound **27d**, which has low ERβ affinity (Table 1, entry 17), yet has good potency on ERβ (Table 3, entry 10)]. From this subclass, two were selected for further study, compounds **27c** and **27g** (entries 9 and 12); both are potent on both ERs and highly efficacious on ERα, but the first is somewhat more agonistic on ERβ than is the second (see below and Figs 4 and 5).

Pyrazines (Table 4). Seven pyrazines were assayed for their transcriptional activity. Those of the triaryl class **III** and the 2,3-diaryl subclass **IV-A** (Table 4, entries 1, 2 and 4) were very weak on both ERα and ERβ. Those of class 2,5-diaryl subclass **IV-B** (Table 4, entries 5–7), however, were for the most part potent partial agonists on ERα and rather potent complete or nearly complete antagonists on ERβ. It is interesting that in both the pyrimidine and the pyrazine series, it is the 2,5-diaryl motif that engenders high potency on ERβ. From the four compounds in subclass **IV-B**, we selected compound **12b** (entry 6) for further study, because this compound appeared to be a high potency agonist on ERα and a high potency antagonist on ERβ. In this sense, it is reminiscent of the R,R-diethyl-tetrahydrochrysene compound (R,R-THC) that we have studied earlier.[35,37]

Full dose–response curves for agonist and antagonist activity with ERα and ERβ were run with the four compounds, pyrimidines **27b**, **27c**, and **27g**, and pyrazine **12b**. As stated above, these compounds were selected for further study based on a combination of their high potency as agonists on ERα and differences in ERα versus ERβ potency or efficacy. The results of these assays are given in Figures 3–6.

The triarylpyrimidine **27b** (Fig. 3) is, as expected, weak and very low efficacy on ERβ, as was the case with the propylpyrazole triol compound, PPT.[14] In the full dose response on ERα, the level of efficacy of pyrimidine **27b** is moderate, but its potency (measured as the ratio of

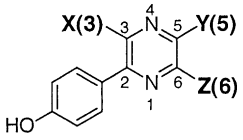
Table 3. Transcriptional efficacy and potency of pyrimidines[a]



Entry	Compd	Class[b]	X(4)	Y(5)	Z(6)	% Efficacy on ERα[c]				% Efficacy on ERβ[c]			
						Agonist (M)[d]		Antg (M)[d] 10^{-6}	Pharm. char.[e]	Agonist (M)[d]		Antg (M)[d] 10^{-6}	Pharm. char.[e]
						10^{-8}	10^{-6}			10^{-8}	10^{-6}		
1	**16b**	**I-A**	Ar[f]	Pr	Ph	12	33	65	Weak part. agonist	5	17	68	Weak part. agonist
2	**16d**	**I-A**	Ar	Pr	Ar	12	10	33	Part. antagonist	3	2	58	Weak part. antagonist
3	**20b**	**I-B**	Ar	Ph	Pr	12	50	70	Part. agonist	2	3	52	Weak part. antagonist
4	**27a**	**I-B**	Ar	Ar	Et	28	57	78	Agonist	2	3	67	Weak part. antagonist
5	**27b**	**I-B**	Ar	Ar	Pr	26	52	60	Part. agonist	3	4	57	Weak part. antagonist
6	**16f**	**II-A**	Ar	Pr	CH_3	5	65	85	Agonist	2	3	55	Weak part. antagonist
7	**20/21d**	**II-A**	Ar	Et + Me	Et + Pr	17	75	80	Agonist	2	3	33	Weak part. antagonist
8	**21b**	**II-A′**	Ar	Et	Bn	4	28	52	Part. agonist	2	3	85	Very weak
9	**27c**	**II-B**	Et	Ar	CH_3	78	87	92	Potent agonist	30	42	45	Potent part. agonist
10	**27d**	**II-B**	CH_3	Ar	CH_3	25	33	37	Part. antagonist	20	48	60	Part. agonist
11	**27e**	**II-B**	Pr	Ar	CH_3	75	72	80	Potent agonist	30	43	70	Weak part. agonist
12	**27g**	**II-B**	Pr	Ar	Et	80	82	87	Potent agonist	16	25	30	Potent part. antagonist

[a]Transcriptional efficacy determined in cotransfection assay in HEC-1 cells using ERα and ERβ expression plasmids and an estrogen regulated reporter gene plasmid (see Experimental for details). Values are percent of the transcriptional response of estradiol at 10^{-9} M.
[b]For a description of compound class, see Figure 2.
[c]Values are percent of the transcriptional response of estradiol at 10^{-9} M, and they represent the average of triplicate determinations (CV < 0.15).
[d]Agonist assays are done with compound alone; antagonist assays are done with compound together with 10^{-9} M estradiol.
[e]For a definition of these terms, see text.
[f]Ar = *p*-HO–C_6H_4–.

Table 4. Transcriptional efficacy and potency of pyrimidines[a]



Entry	Compd	Class[b]	X(3)	Y(5)	Z(6)	% Efficacy on ERα[c]				% Efficacy on ERβ[c]			
						Agonist (M)[d]		Antg (M)[d] 10^{-6}	Pharm. char.[e]	Agonist (M)[d]		Antg (M)[d] 10^{-6}	Pharm. char.[e]
						10^{-8}	10^{-6}			10^{-8}	10^{-6}		
1	**7a**	**III**	Ar[g]	Et	Ar	4	28	78	Weak part. agonist	2	3	100	Very weak
2	**7b**	**III**	Ar	Pr	Ar	11	25	82	Weak	1	2	60	Weak part. antagonist
3	**7c**	—[f]	Ar	Ar	Ar	2	12	82	Weak	2	1	52	Weak part. antagonist
4	**7e**	**IV-A**	Ar	Pr	Pr	4	4	55	Weak part. antgonist	2	2	10	Antagonist
5	**12a**	**IV-B**	Et	Ar	Et	76	80	62	Potent part. agonist	11	22	25	Part. antagonist
6	**12b**	**IV-B**	Pr	Ar	Pr	68	72	70	Potent part. agonist	4	5	7	Antagonist
7	**12c**	**IV-B**	Bu	Ar	Bu	28	51	68	Potent part. agonist	2	3	13	Antagonist

[a]Transcriptional efficacy determined in cotransfection assay in HEC-1 cells using ERα and ERβ expression plasmids and an estrogen regulated reporter gene plasmid (see Experimental for details). Values are percent of the transcriptional response of estradiol at 10^{-9} M.
[b]For a description of compound class, see Figure 2.
[c]Values are percent of the transcriptional response of estradiol at 10^{-9} M, and they represent the average of triplicate determinations (CV < 0.15).
[d]Agonist assays are done with compound alone; antagonist assays are done with compound together with 10^{-9} M estradiol.
[e]For a definition of these terms, see text.
[f]Tetraarylpyrazine.
[g]Ar = *p*-HO–C_6H_4–.

EC_{50} values) is only 0.1% that of estradiol. Thus, this compound is less cleanly an ERα potency selective agonist than is PPT.[14]

The two diaryl pyrimidines, compounds **27c** and **27g**, are both full to nearly full agonists on ERα, with potencies ca. 1% that of estradiol (Figs 4 and 5). On ERβ, they are considerably less agonistic, especially **27g**, and they have potencies ca. 0.1% that of estradiol. Thus, they have modest potency and efficacy selectivity for ERα.

The one diarylpyrazine (**12b**, Fig. 6) is quite efficacious on ERα and is almost a complete antagonist on ERβ.

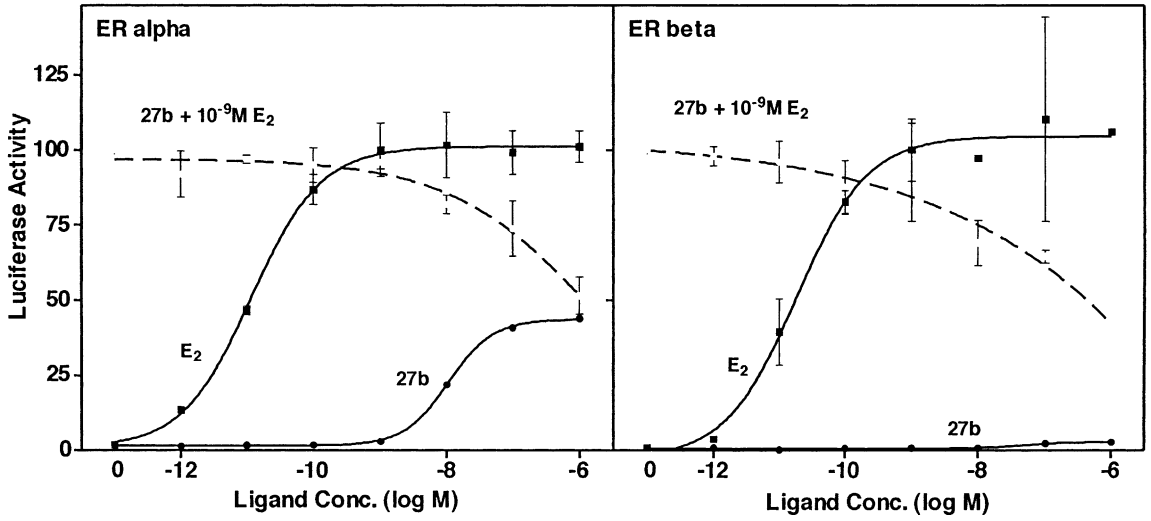


Figure 3. Transcription activation by ERα and ERβ in response to the pyrimidine compound **27b**. Human endometrial cancer (HEC-1) cells were transfected with expression vectors for ERα (left panel) or ERβ (right panel) and an $(ERE)_2$-pS2-luc reporter gene and were treated with the designated concentrations of estradiol (squares), pyrimidine (diamonds, agonist mode), or pyrimidine in the presence of 10^{-9} M estradiol (circles, antagonist mode) for 24 h. Luciferase activity was normalized for β-galactosidase activity from an internal control plasmid. The maximal activity with E_2 was set at 100. Values are the mean ± SD from three separate experiments.

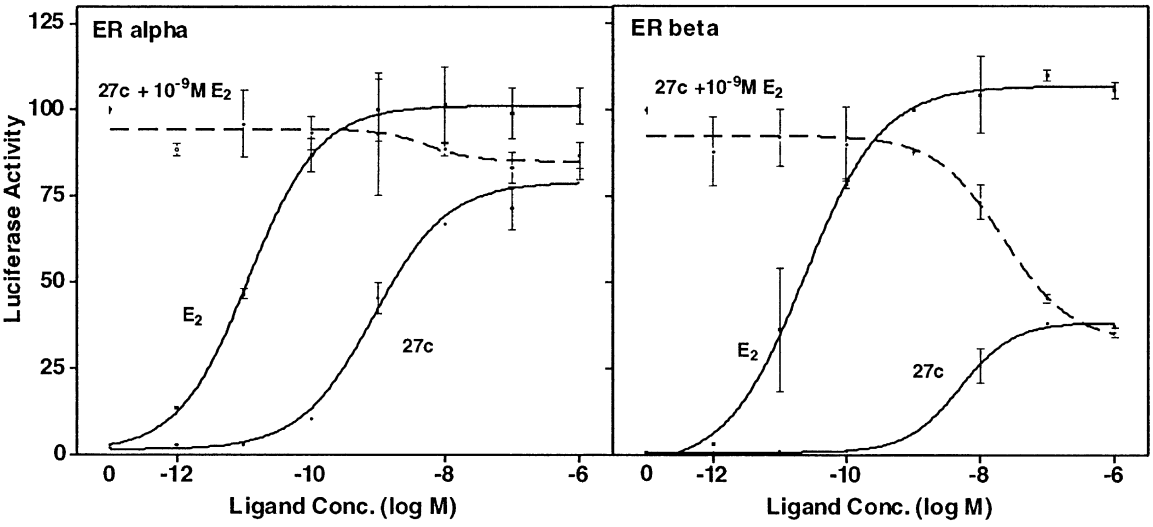


Figure 4. Transcription activation by ERα and ERβ in response to the pyrimidine compound **27c**. For details, see Figure 3 legend.

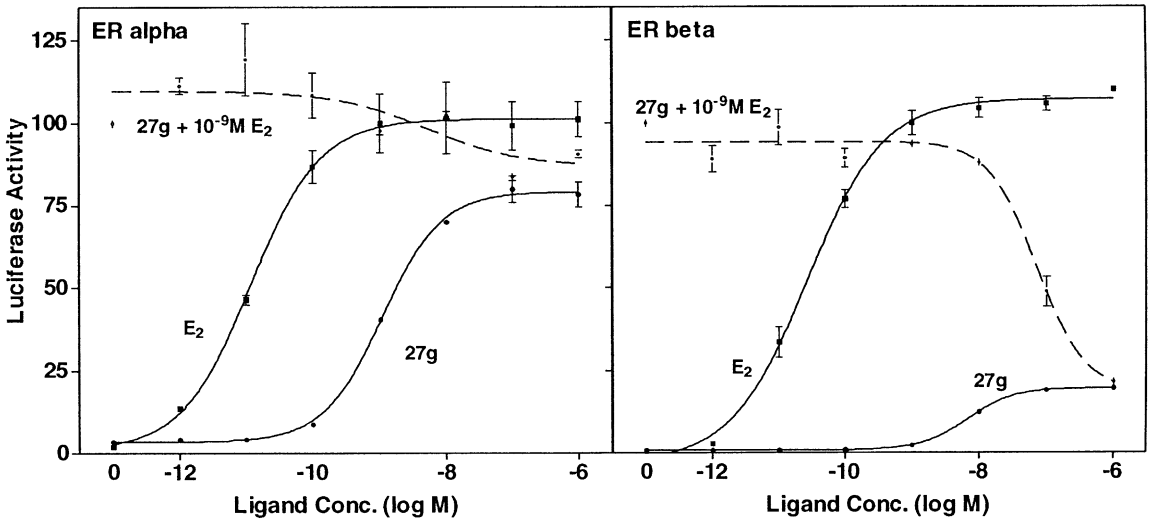


Figure 5. Transcription activation by ERα and ERβ in response to the pyrimidine compound **27g**. For details, see Figure 3 legend.

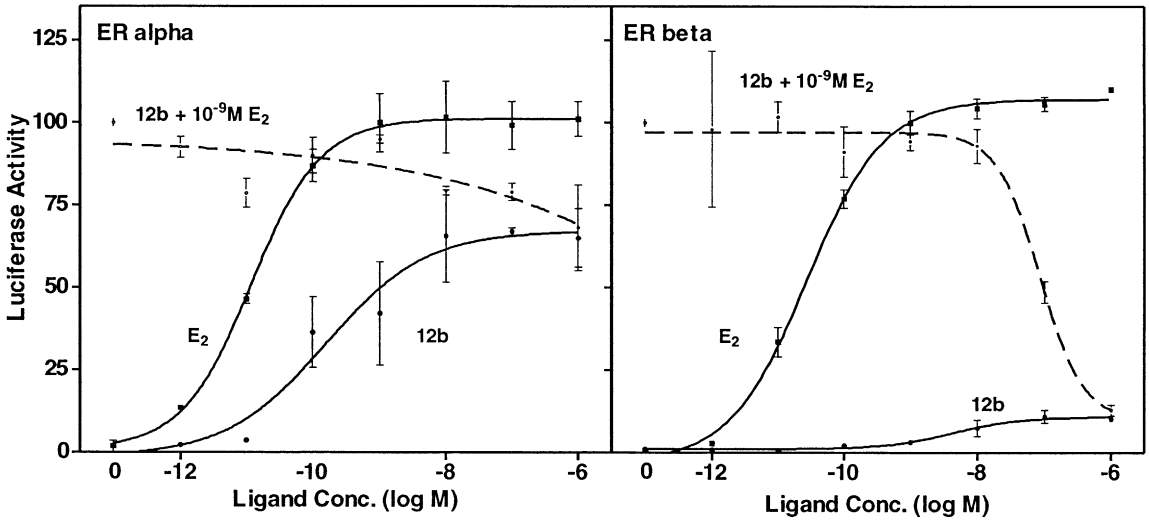


Figure 6. Transcription activation by ERα and ERβ in response to the pyrimidine compound **12b**. For details, see Figure 3 legend.

Again, relative to estradiol, its potency on ERα is 1% and on ERβ is 0.1%. Its pharmacological character is related to that of R,R-THC. However, R,R-THC was a very effective ERβ-selective antagonist, being more potent as an ERβ antagonist than as an ERα agonist.[35,37]

Discussion

We have investigated a novel series of heterocycle ligands for the estrogen receptor based on a diazene core motif. We conceived of these ligands by structural analogy with various pyrazoles and imidazoles that we have investigated extensively in the past (Scheme 1)[12] and from which we have developed both high affinity and highly ERα-selective agonists[14,16] and antagonists.[17,38,39] We have developed efficient synthetic routes to the three classes of diazenes to prepare analogues having the types of substituents (i.e., a balance of aryl and alkyl groups) that we found to be effective in engendering high affinity binding to ERα and high ERα/ERβ affinity selectivity in the other heterocyclic series (pyrazoles and furans).[12,14,16,19] These synthetic routes are generally efficient and convenient, but in certain cases we could not avoid producing regioisomeric diazenes (cf. Scheme 5).

Members of the pyrazine and pyrimidine classes of diazenes were found to have high affinity for the ERs, in some cases with preferences either for ERα or for ERβ being as high as 23- and 7.5-fold, respectively. In this regard, the diazenes were different from the pyrazoles[14,17,39] and furans[19,20] we studied, where, as far as we evaluated, only ERα affinity preference was seen, although others have described ERβ selective compounds in the pyrazole series.[11]

With the pyrimidines, the substituents that gave the highest binding affinities for ERα, namely three aryl groups and an ethyl or propyl substituent (i.e., subclasses **I-A** and **I-B**, Table 1), were very similar to those that gave the highest ERα binding affinities in both the pyrazole and the furan series of ligands.[14,19] The degree of ERα affinity and potency selectivity of the former ligands was much greater than the pyrimidines, however. One of the diaryl-dialkyl pyrimidine classes, the 2,5-diaryl isomers subclass **II-B**, also proved to have high affinity members, provided that they had alkyl groups of appropriate size, but the 2,4-diaryl isomeric subclass (**II-A**) did not. We have recently investigated two classes of dialkyl-diaryl pyrazoles classes and found that some of the 1,4-dialkyl-3,5-diaryl pyrazoles have very high affinity but little ERα/ERβ selectivity, whereas some 4,5-dialkyl-1,3-diaryl pyrazoles have low affinity.[40] Thus, in a general sense, there is an apparent correlation between the preferred disposition of aryl and alkyl substituents on the pyrazole and the pyrimidine rings.

With respect to the relationship between the polarity of the heterocyclic ligand core and binding affinity, however, there is a good parallel between the diazoles and the diazenes. The polarity and basicity of the members of each heterocycle class is given in Table 5.[41] In both the diazoles and diazenes, those members having basic or polar heterocyclic cores had poor affinity, whereas the less basic and less polar ones gave high affinity ligands. Thus, many of the pyrazoles had high affinity, as did the pyrazines, whereas imidazoles and pyridazines were poor binders.[12] The pyrimidines, being of intermediate polarity, produced a number of analogues having good affinities.

This experience reaffirms the thought that the core structure of ER ligands of this design plays two roles,

Table 5. Dipole moment and pK_a of diazenes[41]

Diazene class	Basicity (pK_a)	Dipole moment (μ)[a]
Pyridazines	2.3	3.95
Pyrimidines	1.3	2.10
Pyrazines	0.65	0.00
Imidazoles	7.0	3.70
Pyrazoles	2.52	1.92

[a]In Debye units.

(a) a 'geometric role', through which it provides a two-dimensional scaffold for the attachment of substituents that fill the subpockets of the ligand binding zone of ER, and (b) an 'integral role', through which it has an overall effect on binding affinity. It is the second of these roles that seems to be directly related to core polarity. This is not surprising, because one would expect that more desolvation energy would be required to transfer a ligand with a polar-core from water to the non-polar interior of the ER ligand binding pocket than a ligand having a less polar core.

Although we have not found in the diazene series ligands having ERα binding affinities quite as high as in the pyrazole and furan series,[14,19] some of the ligands have affinities that are at least within a factor of 3–10 equivalent to that of estradiol. This would correspond to K_d values of ca. 1–3 nM.[42] Because these substituted di- and triaryl diazenes have among the largest volumes of ER ligands so far investigated, their high affinity demonstrates again the flexibility of the ligand binding pocket of the ERs and its tolerance for large substituents. This has been documented by various analyses of the eclectic structure–affinity relationships and bulk tolerance of the ER for substituted steroidal and non-steroidal ligands,[42,43] as well as by the varying shape of the internal pocket of these receptors as revealed by X-ray crystallography of various ligand–receptor complexes.[44–46]

In two series of ER ligands based on five-membered heterocycles, namely pyrazoles and furans, we found that even an analogue with four aryl substituents retained very high ERα binding affinity (Katzenellenbogen and Huang, unpublished).[19] By contrast, in the one diazene case where we investigated this, we found that a tetraaryl-pyrazine (**7c**, Table 2) was a very poor ligand. Perhaps, with tetraaryl substitution in this more extended six-membered ring heterocyclic core system, we have finally exceeded the allowable flexible volume of the internal pocket of ER, at least in the geometry provided by this pyrazine core.

Through an analysis of the transcriptional activity of the higher affinity diazene derivatives, we have identified ligands that show interesting selectivity for ERα and ERβ. Of the four that we studied most fully, all have higher potency and efficacy on ERα. The selectivity in potency is modest, ca. 10-fold in terms of relative EC_{50} values, and is less than that of the best pyrazole or furan that we have investigated earlier.[14,19] The compounds that have the highest ERα efficacy selectivity, being the most agonistic on ERα and most antagonistic on ERβ, are the pyrimidine **27g** and the pyrazine **12b** (Figs 5 and 6); their efficacies on ERα reach 65–80% but on ERβ are less than 10–15%. A structurally novel tetrahydrochrysene, termed by us R,R-THC, is also in this pharmacological class, but is more complete and potent as an antagonist of ERβ.[35]

It is of note that in a recent publication by Henke et al.,[18] a series of 2-amino-4,5-diarylpyridines were prepared and evaluated as ligands for the ERs, with the aim of developing compounds that might have selective antagonist activities. Most of these derivatives had quite low affinities for the ERs, although one analogue had an RBA value of ca. 10% on ERα and ERβ, and another showed higher efficacy on ERα than on ERβ in cell transfection studies. In all cases, selectivity for ERα was modest.

The novel aryl diazenes that we have investigated here have helped us to explore further the structural determinants of binding affinity, potency and efficacy in the alpha and beta subtypes of the estrogen receptor. The additional analogues and derivatives of them that might be prepared could prove to be useful probes of the biological activity of these receptors and might form the basis for the development of novel estrogen pharmaceuticals.

Experimental

Chemical synthesis

General chemical methods. All reactions using water or air sensitive reagents were conducted under a dry inert gas atmosphere with dry solvents. Solvents were distilled under N_2 as follows: 1,2-dichloroethane, DMF, DMSO, acetonitrile, pyridine, triethylamine and hexane from CaH_2 and stored over molecular sieves. THF, dichloromethane, diethyl ether and toluene were obtained dry from solvent delivery system designed by J. C. Meyer using neutral alumina under dry Argon. All of the reagents purchased from Aldrich Chemicals and Lancaster were used without further purification. All reactions were monitored by TLC, supplied by Merck (0.25 mm silica gel glass plates containing F-254 indicator. Visualization on TLC were achieved by UV light (254 nm), I_2 vapor and phosphomolybdic acid indicator. Flash column chromatography was performed using Woelm 32–63 μm silica gel packing.[47]

^1H NMR and ^{13}C NMR spectra were recorded on Varian U400 or U500. NMR spectra chemical shifts (δ) are reported in parts per million (ppm) downfield from internal tetramethylsilane or by reference to proton resonances resulting from incomplete deuteration of NMR solvent. NMR coupling constants are reported in Hertz. Electron ionization (EI) spectra were obtained using a Finnigan-MATCH5 spectrometer at 70 eV and Fast Atomic Bombardment (FAB) spectra were obtained on VG Instrument ZAB-SE mass-spectrometer. Elemental analysis was performed by the Microanalytical service Laboratory at University of Illinois, Urbana-Champaign. Melting points (uncorrected) were recorded on Thomas-Hoover Electrothermal Apparatus. All compounds are chromatographically homogenous and biological sample purities are checked in two different solvent systems by reversed phase HPLC.

A number of starting materials were obtained from Aldrich (**1a–d**, **5c–d**, **8e**, **13a**,**b**,**e**,**f**, **17d**,**e**, **22a**). For the remainder, literature references for their preparation are given in the experimental sections.

General procedure A: synthesis of pyridazines

A stirred solution of 1,4-dione (55.0 mg, 0.12 mmol) in hydrazine hydrate (5 mL) with a minimal amount of ethanol (to dissolve dione), was heated to reflux overnight. The reaction was allowed to cool to room temperature and then diluted with ethyl acetate (15 mL). The solution was transferred to a separatory funnel and the aqueous layer washed with EtOAc. The organic extracts were pooled and washed with H_2O and satd NaCl. Organic extract was dried over Na_2SO_4, filtered and solvent removed under reduced pressure to yield crude 4,5-dihydropyridazine. Flash column chromatography (1:4 EtOAc/hexanes) afforded pure 4,5-dihydropyridazine, which was taken up into CH_2Cl_2 and left exposed to air overnight. Any remaining CH_2Cl_2 was removed under reduced pressure to afford crude pyridazine. Purification by flash column chromatography (1:1 EtOAc/hexanes) followed by recrystallization (EtOAc/Hex) gave pure pyridazine.

4-Ethyl-3,5,6-tris(4′-methoxyphenyl)pyridazine (2a). Dione **1a** (40 mg, 0.092 mmol) was reacted, as outlined in general procedure **A**, to afford **2a** (17 mg, 44% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.75 (3H, t, J = 7.45 Hz, CH_3CH$_2$), 2.63 (2H, q, J = 7.45 Hz, CH$_3$CH_2), 3.77 (3H, s, CH_3OAr), 3.82 (3H, s, CH_3OAr), 3.88 (3H, s, CH_3OAr), 6.76 (2H, AA′XX′, J_{AX} = 8.51, $J_{AA'}$ = 2.59 Hz, Ar*H ortho* to OCH$_3$), 6.88 (2H, AA′XX′, J_{AX} = 8.41, $J_{AA'}$ = 2.37 Hz, Ar*H ortho* to OCH$_3$), 7.03 (2H, AA′XX′, J_{AX} = 8.74, $J_{AA'}$ = 2.46 Hz, Ar*H* ortho to OCH$_3$), 7.05 (2H, AA′XX′, J_{AX} = 9.01, $J_{XX'}$ = 2.50 Hz, Ar*H meta* to OCH$_3$), 7.31 (2H, AA′XX′, J_{AX} = 8.68, $J_{XX'}$ = 2.53 Hz, Ar*H* meta to OCH$_3$), 7.56 (2H, AA′XX′, J_{AX} = 8.58, $J_{XX'}$ = 2.55 Hz, Ar*H meta* to OCH$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 22.3, 55.1, 55.2, 55.3, 113.2(2), 113.8(2), 114.0(2), 128.0, 130.1, 130.5(2), 130.6, 130.8(2), 131.4(2), 138.5, 140.2, 158.4, 159.1, 159.4, 159.9, 160.5; MS (EI, 70 eV) m/z 425.2 (M^+).

3,4,6-Tris(4′-methoxyphenyl)-5-propylpyridazine (2b). Dione **1b** (55 mg, 0.12 mmol) was reacted, as outlined in general procedure **A**, to afford **2b** (30 mg, 57% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.55 (3H, t, J = 7.39 Hz, CH_3CH$_2$CH$_2$), 1.14 (2H, m, CH$_3$CH_2CH$_2$), 2.58 (2H, m, CH$_3$CH$_2$CH_2), 3.78 (3H, s, CH_3OAr), 3.83 (3H, s, CH_3OAr), 3.89 (3H, s, CH_3OAr), 6.76 (2H, AA′XX′, J_{AX} = 8.78, $J_{AA'}$ = 2.58 Hz, Ar*H* ortho to OCH$_3$), 6.87 (2H, AA′XX′, J_{AX} = 8.81, $J_{AA'}$ = 2.56 Hz, Ar*H ortho* to OCH$_3$), 7.04 (4H, overlapping AA′XX′, *2*Ar*H ortho* to and *2*Ar*H meta* to OCH$_3$), 7.31 (2H, AA′XX′, J_{AX} = 9.00, $J_{XX'}$ = 2.58 Hz, Ar*H meta* to OCH$_3$), 7.56 (2H, AA′XX′, J_{AX} = 8.80, $J_{XX'}$ = 2.59 Hz, Ar*H meta* to OCH$_3$).

4-Ethyl-3,5-bis(4′-methoxyphenyl)-6-phenylpyridazine (2c). Dione **1c** (25 mg, 0.06 mmol) was reacted, as outlined in general procedure **A**, to afford **2c** (17 mg, 68% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.76 (3H, t, J = 7.55 Hz, CH_3CH$_2$), 2.66 (2H, q, J = 7.49 Hz, CH$_3$CH_2), 3.81 (3H, s, CH_3OAr), 3.89 (3H, s, CH_3OAr), 6.85 (2H, AA′XX′, J_{AX} = 8.84, $J_{AA'}$ = 2.44 Hz, Ar*H* ortho to OCH$_3$), 7.04 (2H, AA′XX′, J_{AX} = 8.73, $J_{AA'}$ = 2.44 Hz, Ar*H ortho* to OCH$_3$), 7.04 (2H, AA′XX′, J_{AX} = 8.73, $J_{XX'}$ = 2.44 Hz, Ar*H meta* to OCH$_3$), 7.23 (3H, m, Ar*H meta* and *para* to pyridazine), 7.35 (2H, m, Ar*H ortho* to pyridizine), 7.57 (2H, AA′XX′, J_{AX} = 8.76, $J_{XX'}$ = 2.51 Hz, Ar*H meta* to OCH$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 22.3, 55.2, 55.3, 113.80(2), 113.83(2), 127.69, 127.72(2), 127.9, 130.0(2), 130.4, 130.5(2), 130.7(2), 137.7, 138.8, 140.3, 158.9, 159.0, 159.9, 160.8; MS (EI, 70 eV) m/z 395.2 (M^+).

4-Ethyl-3,6-bis(4′-methoxyphenyl)-5-phenylpyridazine (2d). Dione **1d** (35 mg, 0.09 mmol) was reacted, as outlined in general procedure **A**, to afford **2d** (21 mg, 62% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.75 (3H, t, J = 7.50 Hz, CH_3CH$_2$), 2.63 (2H, q, J = 7.48 Hz, CH$_3$CH_2), 3.76 (3H, s, CH_3OAr), 3.89 (3H, s, CH_3OAr), 6.74 (2H, AA′XX′, J_{AX} = 8.82, $J_{AA'}$ = 2.59 Hz, Ar*H ortho* to OCH$_3$), 7.04 (2H, AA′XX′, J_{AX} = 8.60, $J_{AA'}$ = 2.57 Hz, Ar*H* ortho to OCH$_3$), 7.15 (2H, m, Ar*H ortho* to pyridazine), 7.30 (2H, AA′XX′, J_{AX} = 9.01, $J_{XX'}$ = 2.57 Hz, Ar*H meta* to OCH$_3$), 7.35 (3H, m, Ar*H para* and *meta* to pyridazine), 7.57 (2H, AA′XX′, J_{AX} = 8.76, $J_{XX'}$ = 2.53 Hz, Ar*H meta* to OCH$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 22.3, 55.1, 55.3, 113.2(2), 113.8(2), 127.9, 128.5(2), 129.6(2), 129.9, 130.4, 130.5(2), 131.4(2), 135.9, 138.7, 139.9, 158.0, 159.5, 159.9, 160.5; MS (EI, 70 eV) m/z 395.2 (M^+).

General procedure B: deprotection of phenolic methyl ethers

Boron triflouride–dimethylsulfide complex (10 mmol/phenolic group) was added dropwise to a stirred solution 4-methoxyphenylpyrazine (1 mmol) in dichloromethane (5 mL) at room temperature. The reaction mixture was stirred for 24–36 h. Water (2 mL) was added and the organic layer was combined with an ethyl acetate extract (10 mL), washed with satd $NaHCO_3$ solution (5 mL) and brine (5 mL), and dried over anhyd Na_2SO_4. Removal of solvent under vacuum gave the crude product, which was purified by flash column chromatography over silica gel using hexane–ethyl acetate or by direct crystallization.

4-Ethyl-3,5,6-tris(4′-hydroxyphenyl)pyridazine (3a). Pyridazine **2a** (10 mg, 0.02 mmol) was reacted, according to general procedure **B**, to afford crude **3a**. The crude material was purified by recrystallization from EtOAc/CH_2Cl_2 to provide **3a** (6.7 mg, 74% yield). ^{1}H NMR (500 MHz, acetone-d_6) δ 0.73 (3H, t, J = 7.44 Hz, CH_3CH$_2$), 2.69 (2H, q, J = 7.48 Hz, CH$_3$CH_2), 6.71 (2H, AA′XX′, J_{AX} = 8.26, $J_{AA'}$ = 2.73 Hz, Ar*H ortho* to OH), 6.86 (2H, AA′XX′, J_{AX} = 8.24, $J_{AA'}$ = 2.71 Hz, Ar*H* ortho to OH), 7.00 (2H, AA′XX′, J_{AX} = 8.20, $J_{AA'}$ = 2.63 Hz, Ar*H ortho* to OH), 7.07 (2H, AA′XX′, J_{AX} = 8.03, $J_{XX'}$ = 2.34 Hz, Ar*H meta* to OH), 7.23 (2H, AA′XX′, J_{AX} = 8.34, $J_{XX'}$ = 2.48 Hz, Ar*H meta* to OH), 7.50 (2H, AA′XX′, J_{AX} = 8.23, $J_{XX'}$ = 2.45 Hz, Ar*H meta* to OH), 8.47 (1H, bs, O*H*), 8.55 (1H, bs, O*H*), 8.65 (1H, bs, O*H*); ^{13}C NMR (125 MHz, acetone-d_6) δ 13.7,

23.2, 115.6(2), 116.2(2), 116.3(2), 127.0, 128.5, 128.7, 131.5(2), 131.8(2), 132.4(2), 142.0, 143.8, 158.4, 158.9, 159.3, 158.5, 161.3; MS (EI, 70 eV) *m/z* 383.1 (M^+); HRMS calcd for $C_{24}H_{20}N_2O_3$: 383.139568, found: 383.139800.

3,5,6-Tris(4′-hydroxyphenyl)-4-propylpyridazine (3b). Pyridazine **2b** (20 mg, 0.05 mmol) was reacted, according to general procedure **B**, to afford crude **3b**. The crude material was purified by recrystallization from EtOAc/CH_2Cl_2 to provide **3b** (13 mg, 74% yield). ^{1}H NMR (500 MHz, acetone-d_6) δ 0.52 (3H, t, J = 7.38 Hz, $CH_3CH_2CH_2$), 1.16 (2H, m, $CH_3CH_2CH_2$), 2.63 (2H, m, $CH_3CH_2CH_2$), 6.70 (2H, AA′XX′, J_{AX} = 8.73, $J_{AA'}$ = 2.47 Hz, Ar*H ortho* to OH), 6.86 (2H, AA′XX′, J_{AX} = 8.55, $J_{AA'}$ = 2.42 Hz, Ar*H ortho* to OH), 7.00 (2H, AA′XX′, J_{AX} = 8.52, $J_{AA'}$ = 2.47 Hz, Ar*H ortho* to OH), 7.05 (2H, AA′XX′, J_{AX} = 8.54, $J_{XX'}$ = 2.43 Hz, Ar*H meta* to OH), 7.23 (2H, AA′XX′, J_{AX} = 8.75, $J_{XX'}$ = 2.45 Hz, Ar*H meta* to OH), 7.49 (2H, AA′XX′, J_{AX} = 8.68, $J_{XX'}$ = 2.42 Hz, Ar*H meta* to OH), 8.44 (1H, bs, O*H*), 8.54 (1H, bs, O*H*), 8.63 (1H, bs, O*H*); MS (EI, 70 eV) *m/z* 397.2 (M^+); MS (CI, 130 eV) *m/z* 399.2 ($M^+ + H$); HRMS calcd for $C_{25}H_{23}N_2O_3$: 399.170868, found: 399.169900.

4-Ethyl-3,5-bis(4′-hydroxyphenyl)-6-phenylpyridazine (3c). Pyridazine **2c** (10 mg, 0.025 mmol) was reacted, according to general procedure **B**, to afford crude **3c**. The crude material was purified by recrystallization from EtOAc/CH_2Cl_2 to provide **3c** (7 mg, 55% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.75 (3H, t, J = 7.58 Hz, CH_3CH_2), 2.716 (2H, q, J = 7.52 Hz, CH_3CH_2), 6.83 (2H, AA′XX′, J_{AX} = 8.61, $J_{AA'}$ = 2.41 Hz, Ar*H ortho* to OH), 7.01 (2H, AA′XX′, J_{AX} = 8.58, $J_{AA'}$ = 2.44 Hz, Ar*H ortho* to OH), 7.07 (2H, AA′XX′, J_{AX} = 8.583, $J_{XX'}$ = 2.42 Hz, Ar*H meta* to OH), 7.22.27 (3H, overlapping m, Ar*H meta* and *para* to pyridazine), 7.37 (2H, m, Ar*H ortho* to pyridazine), 7.51 (2H, AA′XX′, J_{AX} = 8.42, $J_{XX'}$ = 2.49 Hz, Ar*H meta* to OH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.2, 22.1, 115.2(2), 115.3(2), 126.7, 127.6(2), 127.8, 129.6, 130.0(2), 130.7(2), 131.1(2), 138.4, 139.2, 140.2, 157.3, 158.0, 158.8, 160.9.

4-Ethyl-3,6-bis(4′-hydroxyphenyl)-5-phenylpyridazine (3d). Pyridazine **2d** (12 mg, 0.03 mmol) was reacted, according to general procedure **B**, to afford crude **3d**. The crude material was purified by recrystallization from EtOAc/CH_2Cl_2 to provide **3d** (8 mg, 60% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.72 (3H, t, J = 7.48 Hz, CH_3CH_2), 2.64 (2H, q, J = 7.54 Hz, CH_3CH_2), 6.684 (2H, AA′XX′, J_{AX} = 8.79, $J_{AA'}$ = 2.51 Hz, Ar*H ortho* to OH), 7.00 (2H, AA′XX′, J_{AX} = 8.74, $J_{AA'}$ = 2.43 Hz, Ar*H ortho* to OH), 7.21 (2H, AA′XX′, J_{AX} = 9.00, $J_{XX'}$ = 2.46 Hz, Ar*H meta* to OH), 7.62 (2H, m, Ar*H ortho* to pyridazine), 7.34.41 (3H, overlapping m, Ar*H para* and *meta* to pyridazine), 7.50 (2H, AA′XX′, J_{AX} = 8.88, $J_{XX'}$ = 2.52 Hz, Ar*H meta* to OH), 8.46 (1H, bs, O*H*), 8.65 (1H, bs, O*H*).

General procedure C: synthesis of 2,3-bis-alkyl-5,6-bis-arylpyrazines and 2,3,5,6-tetraarylpyrazines

A stirred solution of the α-diketone (1 mmol) and 1,2-bis-diamine (1 mmol) in glacial acetic acid (2 mL) was refluxed for 4–5 h under dry air. After the completion of reaction, the reaction mixture was cooled, water (5 mL) was added, and the mixture was extracted with ethyl acetate (2 × 10 mL). The organic phase was washed with brine (5 mL) and dried over anhyd Na_2SO_4. Removal of the solvent under vacuum gave the crude product, which was purified by flash column chromatography over silica gel using hexane–ethyl acetate or crystallization.

2-Ethyl-3,5,6-tri-(4′-methoxyphenyl)pyrazine (6a). The reaction of the α-diketone **5a** (71 mg, 0.37 mmol; prepared according to literature methods[29,48,49] with the diamine **4** (100 mg, 0.37 mmol) in glacial acetic acid, following the general procedure B, furnished the corresponding pyrazine **6a** (90 mg, 58%). Mp 127 °C; ^{1}H NMR ($CDCl_3$, 500 MHz). δ 7.64 and 7.01 (4H, AA′XX′, J_{AX} = 8.84 Hz and $J_{AA'}$ = 2.21 Hz), 7.51 and 6.85 (4H, AA′XX′, J_{AX} = 8.84 Hz and $J_{AA'}$ = 2.03 Hz) and 7.49 and 6.83 (4H, AA′XX′, J_{AX} = 8.84 Hz and $J_{AA'}$ = 2.02 Hz) [aromatic], 3.88 (3H, s), 3.82 (3H, s) and 3.81 (3H, s) [3×OCH_3], 3.00 (2H, q, J = 7.55 Hz, CH_2) and 1.33 (3H, t, J = 7.55 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz). δ 159.89, 159.75, 159.64, 151.84, 149.35, 148.25, 147.66, 131.59, 131.26, 131.05, 131.0, 130.56, 113.75, 113.69, 113.58, 55.34, 55.24, 55.22, 27.80 and 13.30. MS (EI, 70 eV). *m/z* 427 (M + 1, 28%), 426 (M^+, 100); HRMS: calcd for $C_{27}H_{26}N_2O_3$: 426.1943, found: 426.1939. Analysis: for $C_{27}H_{26}N_2O_3$ + 0.4 EtOAc: calcd C, 74.39; H, 6.37; N, 6.07, found C, 74.86; H, 6.09; N, 6.35.

2-*n*-Propyl-3,5,6-tri-(4′-methoxyphenyl)pyrazine (6b). The reaction of the α-diketone **5b** (15 mg, 0.073 mmol; prepared according to a literature known method[30] with the diamine, **4** (20 mg, 0.073 mmol) in glacial acetic acid, following the general procedure B, furnished the corresponding pyrazine **6b** (20 mg, 63%). ^{1}H NMR ($CDCl_3$, 500 MHz). δ 7.63 and 7.01 (4H, AA′XX′, J_{AX} = 8.29 Hz and $J_{AA'}$ = 1.47 Hz), 7.50 and 6.85 (4H, AA′XX′, J_{AX} = 8.29 Hz and $J_{AA'}$ = 1.65 Hz) and 7.48 and 6.82 (4H, AA′XX′, J_{AX} = 8.29 Hz and $J_{AA'}$ = 1.66 Hz) [aromatic], 3.88 (3H, s), 3.82 (3H, s) and 3.81 (3H, s) [3×OCH_3], 2.95 (2H, $A_3MM'XX'$, J_{XM} = 7.74 Hz and $J_{XX'}$ = 1.65 Hz, Ar–CH_2), 1.82 (2H, $A_3MM'XX'$, J_{XM} = 7.74 Hz and J_{AM} = 7.37 Hz, CH_2CH_3) and 0.95 (3H, t, J = 7.37 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz). δ 164.51, 159.84, 159.74, 159.64, 150.84, 149.60, 148.19, 147.60, 131.59, 131.54, 131.31, 131.05, 130.99, 130.60, 113.74, 113.69, 113.57, 55.33, 55.24, 55.21, 36.53, 22.36 and 14.07. MS (EI, 70 eV). *m/z* 441 (M + 1, 14%), 440 (M^+, 50), 135 (100); HRMS: calcd for $C_{28}H_{28}N_2O_3$: 440.2099, found: 440.2095.

2,3,5,6-Tetra-(4′-methoxyphenyl)-pyrazine (6c). The reaction of 4,4′-dimethoxybenzil (**5c,** 27 mg, 0.1 mmol) with *meso*-1,2-bis-(4-methoxyphenyl)-ethylenediamine (**4**, 27.2 mg, 0.1 mmol) in glacial acetic acid (2 mL), according to the general procedure C, after careful flash column chromatography (10% EtOAc–hexane) over silica gel and crystallization with ethyl acetate–hexane,

gave the pyrazine **6c** (39 mg, 76%) as a solid. Mp 275–276 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.63 (8H, AA′XX′, J_{AX} = 9.00 and $J_{AA'}$ = 2.14 Hz), 6.88 (8H, AA′XX′, J_{AX} = 9.00 and $J_{AA'}$ = 2.14 Hz), 3.85 (12H, s, 4 × OMe); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.86, 146.81, 131.28, 131.07, 113.66 and 55.24. MS (EI, 70 eV) *m/z* 504 (M^+ 3%), 69 (100%); Analysis for $C_{32}H_{28}N_2O_4$, calcd C, 76.17; H, 5.59; N, 5.55, found C, 76.13; H, 5.56; N, 5.58.

2,3-Bis-ethyl-5,6-bis-(4′-methoxyphenyl)-pyrazine (6d). The reaction of 3,4-hexanedione (**5d**, 45 mg, 0.37 mmol) with *meso*-1,2-bis-(4-methoxyphenyl)-ethylenediamine (**4**, 100 mg, 0.37 mmol) in glacial acetic acid (5 mL), according to the general procedure C, after careful flash column chromatography (15% EtOAc–hexane) over silica gel, gave the pyrazine **6d** (101 mg, 79%) as a solid. Mp 78–79 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.43 (4H, AA′XX′, J_{AX} = 9.00 and $J_{AA'}$ = 2.14 Hz), 6.83 (4H, AA′XX′, J_{AX} = 9.00 and $J_{AA'}$ = 2.14 Hz), 3.81 (6H, s, 2 × OMe), 2.92 (4H, q, J = 7.50 Hz, 2 × CH_2CH_3) and 1.37 (6H, t, J = 7.50 Hz, 2 × CH_2CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.49, 152.69, 148.01, 131.88, 130.92, 113.59, 55.19, 27.12 and 13.01. MS (EI, 70 eV) *m/z* 348 (M^+ 100%), 333 (18%); HRMS calcd for $C_{22}H_{24}N_2O_2$, 348.1838, found: 348.1845.

2,3-Bis-propyl-5,6-bis-(4′-methoxyphenyl)-pyrazine (6e). The reaction of 4,5-octanedione (**5e**, 58 mg, 0.37 mmol; prepared according to a literature method[26]) with *meso*-1,2-bis-(4-methoxyphenyl)-ethylenediamine (**4**, 100 mg, 0.37 mmol) in glacial acetic acid (5 mL), according to the general procedure C, after careful flash column chromatography (15% EtOAc–hexane) over silica gel, gave the pyrazine **6e** (111 mg, 80%) as a solid. Mp 71–72 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40 (4H, AA′XX′, J_{AX} = 8.79 and $J_{AA'}$ = 2.14 Hz), 6.83 (4H, AA′XX′, J_{AX} = 8.79 and $J_{AA'}$ = 2.14 Hz), 3.80 (6H, s, 2 × OMe), 2.86 (4H, t, J = 7.40 Hz, 2 × $CH_2CH_2CH_3$), 1.83 (4H, quint, J = 7.40 Hz, 2 × $CH_2CH_2CH_3$) and 1.05 (6H, t, J = 7.40 Hz, 2 × $CH_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.49, 151.93, 147.98, 131.86, 130.91, 113.59, 55.21, 35.99, 22.29 and 14.19. MS (EI, 70 eV) *m/z* 376 (M^+ 62%), 348 (100%); HRMS calcd for $C_{24}H_{28}N_2O_2$, 376.2151, found: 376.2149.

2-Ethyl-3,5,6-tri-(4′-hydroxyphenyl)pyrazine (7a). Deprotection of the pyrazine **6a** (65 mg, 0.15 mmol) using $BF_3{\cdot}SMe_2$ (595 mg, 4.58 mmol), according to the general procedure **B**, furnished the phenolic pyrazine **7a** (55 mg, 96%). Mp 250 °C; ^{1}*H NMR* ((CD_3)$_2$*CO, 500 MHz*). δ 8.61 (3H, s, 3×OH), 7.59 and 6.97 (4H, AA′XX′, J_{AX} = 8.81 Hz and $J_{AA'}$ = 2.02 Hz), 7.44 and 6.80 (4H, AA′XX′, J_{AX} = 8.81 Hz and $J_{AA'}$ = 2.02 Hz) and 7.40 and 6.78 (4H, AA′XX′, J_{AX} = 8.81 Hz and $J_{AA'}$ = 2.02 Hz) [aromatic], 2.96 (2H, q, J = 7.52 Hz, CH_2) and 1.29 (3H, t, J = 7.52 Hz, CH_3); ^{13}*C NMR* ((CD_3)$_2$*CO, 125 MHz*). δ 158.69, 158.53, 158.44, 151.63, 149.85, 148.60, 148.24, 131.85, 131.52, 131.45, 131.41, 130.90, 115.86, 115.72, 115.69, 28.24 and 13.33. MS (EI, 70 eV). *m/z* 385 (M + 1, 27%), 384 (M^+, 100); *HRMS*: calcd for $C_{24}H_{20}N_2O_3$: 384.1474, found: 384.1469.

2-*n*-Propyl-3,5,6-tri-(4′-hydroxyphenyl)pyrazine (7b). Deprotection of the pyrazine **6b** (10 mg, 0.02 mmol) using $BF_3{\cdot}SMe_2$ (89 mg, 0.68 mmol), according to the general procedure **B**, furnished the phenolic pyrazine **7b** (8 mg, 89%). Mp 239 °C; ^{1}H NMR ((CD_3)$_2$CO, *400 MHz*). δ 7.50 and 6.92 (4H, A_2X_2, J = 8.30 Hz), 7.37 and 6.76 (4H, A_2X_2, J = 8.55 Hz) and 7.37 and 6.73 (4H, A_2X_2, J = 8.79 Hz) [aromatic], 7.33 (1H, s), 7.22 (1H, s) and 7.18 (1H, s) [3×OH], 2.90 (2H, t, J = 7.33 Hz, Ar–CH_2), 1.75 (2H, $A_3MM'XX'$, J_{MX} = 7.33 Hz, J_{AM} = 7.56 Hz, $J_{MM'}$ = 3.12 Hz, CH_2CH_3) and 0.89 (3H, t, J = 7.32 Hz, CH_3); ^{13}C NMR ((CD_3)$_2$CO, 100 MHz). δ 157.70, 157.57, 149.60, 149.12, 147.54, 147.19, 130.87, 130.51, 114.88, 114.71, 36.11, 21.71 and 13.31. MS (EI, 70 eV). *m/z* 399 (M + 1, 29%), 398 (M +, 100); HRMS: calcd for $C_{24}H_{20}N_2O_3$: 398.1630, found: 398.1621.

2,3,5,6-Tetra-(4′-hydroxyphenyl)-pyrazine (7c). The reaction of 2,3,5,6-tetra-(4′-methoxyphenyl)-pyrazine (**6c**, 253 mg, 0.5 mmol) with $BF_3{\cdot}SMe_2$ (2.0 mL, 20 mmol) in dry dichloromethane (10 mL), according to the general procedure **B**, after crystallization with methanol, gave the pyrazine **7c** (201 mg, 90%) as a solid. HPLC purity (reversed phase, C18) in two solvents is: MeOH–H_2O (60:40) 100% and CH_3CN–H_2O (40:60) 100%; mp > 360 °C; ^{1}H NMR (acetone-d_6, 500 MHz) δ 8.59 (4H, s, 4 × OH), 7.51 (8H, AA′XX′, J_{AX} = 8.79 and $J_{AA'}$ = 2.14 Hz), 6.80 (8H, AA′XX′, J_{AX} = 8.79 and $J_{AA'}$ = 2.14 Hz); ^{13}C NMR (acetone-d_6, 125 MHz) δ 158.78, 147.33, 131.94, 131.21 and 115.88. MS (FAB, ZAB) *m/z* 449 (M^+ 31%), 154 (100%); HRMS calcd for $C_{28}H_{20}N_2O_4$, 448.1423, found: 448.1425.

2,3-Bis-ethyl-5,6-bis-(4′-hydroxyphenyl)-pyrazine (7d). The reaction of 2,3-bis-ethyl-5,6-bis-(4′-methoxyphenyl)-pyrazine (**6d**, 80 mg, 0.23 mmol) with $BF_3{\cdot}SMe_2$ (0.48 mL, 4.6 mmol) in dry dichloromethane (5 mL), according to the general procedure **B**, after flash column chromatography (30% EtOAc–hexane) over silica gel, gave the pyrazine **7d** (70 mg, 95%) as a solid. Mp 241–242 °C; HPLC purity (reversed phase, C18) in two solvents is: MeOH–H_2O (70:30) 99.4% and CH_3CN–H_2O (50:50) 99.12%; ^{1}H NMR (acetone-d_6, 500 MHz) δ 8.47 (2H, s, 2 × OH), 7.35 (4H, AA′XX′, J_{AX} = 8.79 and $J_{AA'}$ = 2.14 Hz), 6.76 (4H, AA′XX′, J_{AX} = 8.79 and $J_{AA'}$ = 2.14 Hz), 2.89 (4H, q, J = 7.50 Hz, 2 × CH_2CH_3) and 1.32 (6H, t, J = 7.50 Hz, 2 × CH_2CH_3); ^{13}C NMR (acetone-d_6, 125 MHz) δ 158.39, 152.77, 148.70, 131.88, 115.72, 27.35 and 12.89. MS (EI, 70 eV) *m/z* 320 (M^+ 100%), 75 (92%); HRMS calcd for $C_{20}H_{20}N_2O_2$, 320.1525, found: 320.1519.

2,3-Bis-propyl-5,6-bis-(4′-hydroxyphenyl)-pyrazine (7e). The reaction of 2,3-bis-propyl-5,6-bis-(4′-methoxyphenyl)-pyrazine (**6e**, 85 mg, 0.23 mmol) with $BF_3{\cdot}SMe_2$ (0.48 mL, 4.6 mmol) in dry dichloromethane (5 mL), according to the general procedure **B,** after flash column chromatography (30% EtOAc–hexane) over silica, gave the pyrazine **7e** (70 mg, 89%) as a solid. Mp 175–176 °C; HPLC purity (reversed phase, C18) in two solvents is: MeOH–H_2O (80:20) 98.3% and CH_3CN–H_2O (60:40) 99.9%; ^{1}H NMR (acetone-d_6, 500 MHz) δ 8.49 (2H, s, 2

× OH), 7.34 (4H, AA′XX′, $J_{AX}=8.79$ and $J_{AA'}=2.14$ Hz), 6.77 (4H, AA′XX′, $J_{AX}=8.79$ and $J_{AA'}=2.14$ Hz), 2.84 (4H, t, $J=7.50$ Hz, 2 × $CH_2CH_2CH_3$), 1.81 (4H, quint, $J=7.50$ Hz, 2 × $CH_2CH_2CH_3$) and 1.02 (6H, t, $J=7.40$ Hz, 2 × $CH_2CH_2CH_3$); ^{13}C NMR (acetone-d_6, 125 MHz) δ 158.36, 151.94, 148.64, 131.85, 131.79, 115.66, 36.25, 22.55 and 14.36. MS (EI, 70 eV) m/z 348 (M^+ 46%), 320 (100%); HRMS calcd for $C_{22}H_{24}N_2O_2$, 348.1837, found: 348.1837.

General procedure D: synthesis of α-bromoketone

Bromine (1 mmol) was added dropwise to a stirred solution of ketone (1 mmol) in diethyl ether (5 mL) and glacial acetic acid (0.2 mL) at room temperature. After the reaction was complete, water (5 mL) was added. The organic layer was combined with an ether extract (10 mL), washed with 10% sodium thiosulfate solution (5 mL) and brine (5 mL), and dried over anhyd Na_2SO_4. The solvent was removed under vacuum and the product was purified by crystallization.

2-Bromo-1-(4′-methoxyphenyl)-butan-1-one (9a). To a stirred solution of 1-(4′-methoxyphenyl)-butan-1-one (**8a**, 0.8 g, 4.4 mmol; for preparation, see ref 14) in diethyl ether (25 mL) and glacial acetic acid (0.5 mL) was added dropwise bromine (0.3 mL, 4.5 mmol), according to the general procedure D. Crystallization from hexane, gave the α-bromoketone **9a** (0.9 g, 80%) as a solid. Mp 45–46 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.03 (2H, AA′XX′, $J_{AX}=9.00$ and $J_{AA'}=1.96$ Hz), 6.98 (2H, AA′XX′, $J_{AX}=9.00$ and $J_{AA'}=1.96$ Hz), 5.06 (1H, dd, $J=6.5$ and 6.5 Hz, CH(Br)CH_2), 3.90 (3H, s, OMe), 2.24 (1H, dq, $J=6.6$ and 7.3 Hz, CH(Br)$CH_{AB}CH_3$), 2.14 (1H, dq, $J=6.6$ and 7.3 Hz, CH(Br)$CH_{AB}CH_3$), and 1.09 (3H, t, $J=7.33$ Hz, $CH_2CH_2CH_3$); MS (EI, 70 eV) m/z 258 (M+H, 2.24%), 256 (2.30%), 135 (100%).

2-Bromo-1-(4′-methoxyphenyl)-pentan-1-one (9b). Bromine (0.6 mL, 10 mmol) was added dropwise o a stirred solution of 1-(4′-methoxyphenyl)-pentan-1-one (**8b**, 1.92 g, 10 mmol; for preparation, see ref 14) in diethyl ether (50 mL) and glacial acetic acid (2 mL), according to the general procedure D. Crystallization from hexane gave the α-bromoketone **9b** (2.0 g, 74%) as a solid. Mp 48–49 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.01 (2H, AA′XX′, $J_{AX}=9.00$ and $J_{AA'}=1.96$ Hz), 6.95 (2H, AA′XX′, $J_{AX}=9.00$ and $J_{AA'}=1.96$ Hz), 5.11 (1H, dd, $J=6.5$ and 6.5 Hz, CH(Br)CH_2), 3.88 (3H, s, OMe), 2.19.08 (2H, m, $CH_2CH_2CH_3$), 1.57.40 (2H, m, $CH_2CH_2CH_3$) and 0.98 (3H, t, $J=7.33$ Hz, $CH_2CH_2CH_3$); MS (EI, 70 eV) m/z 271 (M^+ 0.05%), 135 (100%).

2-Bromo-1-(4′-methoxyphenyl)-hexan-1-one (9c). To a stirred solution of 1-(4′-methoxyphenyl)-hexan-1-one (**8c**, 1.3 g, 6.3 mmol; for preparation, see ref 14 in diethyl ether (30 mL) and glacial acetic acid (1.0 mL) was added dropwise bromine (0.4 mL, 6.3 mmol), according to the general procedure D. Crystallization from hexane gave the α-bromoketone **9c** (1.6 g, 89%) as a solid. Mp 51–52 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.03 (2H, AA′XX′, $J_{AX}=9.00$ and $J_{AA'}=2.19$ Hz), 6.97 (2H, AA′XX′, $J_{AX}=9.00$ and $J_{AA'}=2.19$ Hz), 5.12 (1H, dd, $J=6.84$ and 6.59 Hz, CH(Br)CH_2), 3.90 (3H, s, OMe), 2.28.08 (2H, m, CH_2CH_2 CH_2CH_3), 1.53.35 (4H, m, $CH_2CH_2CH_2CH_3$) and 0.94 (3H, t, $J=7.08$ Hz, $CH_2CH_2CH_3$); MS (EI, 70 eV) m/z 286 (M^+H 0.65%), 284 (0.66%), 135 (100%).

2-Bromo-1-(4′-methoxyphenyl)-4-methylpentan-1-one (9d). Bromine (0.1.06 mL, 20 mmol) was added dropwise to a stirred solution of 1-(4′-methoxyphenyl)-4-methylpentan-1-one (**8d**, 4.12 g, 20 mmol; for preparation, see ref 14) in diethyl ether (50 mL) and glacial acetic acid (2 mL), according to the general procedure D. Solvent removal gave the α-bromoketone **9d** (5.3 g, 93%) as an oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.01 (2H, AA′XX′, $J_{AX}=9.00$ and $J_{AA'}=1.96$ Hz), 6.95 (2H, AA′XX′, $J_{AX}=9.00$ and $J_{AA'}=1.96$ Hz), 5.18 (1H, dd, $J=6.59$ and 6.58 Hz, CH(Br)CH_2), 3.89 (3H, s, OMe), 2.12.98 (2H, m, $CH_2CH(CH_3)_2$), 1.86 (1H, septet, $J=6.59$ and 7.32 Hz, $CH_2CH(CH_3)_2$) and 0.96 (6H, dd, $J=6.59$ and 3.66 Hz, CH2CH2$(CH_3)_2$); MS (EI, 70 eV) m/z 286 (M^+ 0.34%), 284 (0.34%), 135 (100%).

2-Bromo-1-(4′-methoxyphenyl)-propan-1-one (9e). Bromine (1.55 mL, 30 mmol) was added dropwise to a stirred solution of 1-(4′-methoxyphenyl)-propan-1-one (**8e**, 5.0 g, 30 mmol) in diethyl ether (60 mL) and glacial acetic acid (2 mL), according to the general procedure D. Crystallization from hexane gave the α-bromoketone **9e** (5.9 g, 81%) as a solid. Mp 66 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.03 (2H, AA′XX′, $J_{AX}=8.79$ and $J_{AA'}=1.96$ Hz), 6.98 (2H, AA′XX′, $J_{AX}=8.79$ and $J_{AA'}=1.96$ Hz), 5.29 (1H, q, $J=6.84$ Hz, CH(Br)CH_3), 3.90 (3H, s, OMe) and 1.89 (3H, d, $J=6.59$ Hz, CH(Br)CH_3); MS (EI, 70 eV) m/z 244 (M^+ 2.30%), 242 (2.47%), 135 (100%).

General procedure E: synthesis of α-azidoketone

Sodium azide (3 mmol) was added to a stirred solution of α-bromoketone (1 mmol) in dry DMF (5 mL) at room temperature, under nitrogen atmosphere. The reaction was complete after stirring for 10 h. Water (5 mL) was added and the aqueous phase extracted with ether (10 mL). The organic phase was washed with brine (5 mL) and dried over anhyd Na_2SO_4. Removal of solvent under vacuum gave the crude product that was purified by flash column chromatography over silica gel using hexane–ethyl acetate.

2-Azido-1-(4′-methoxyphenyl)-butan-1-one (10a). NaN_3 (0.97 g, 15 mmol) was added to a stirred solution of bromo-1-(4′-methoxyphenyl)-butan-1-one (**9a**, 1.28 g, 4.9 mmol) in DMF (20 mL), according to the general procedure E, after flash column chromatography over silica gel using 15% ethyl acetate/hexane, gave α-azidoketone **10a** (0.98 g, 92%) as an oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.95 (2H, AA′XX′, $J_{AX}=9.00$ and $J_{AA'}=1.96$ Hz), 6.98 (2H, AA′XX′, $J_{AX}=9.00$ and $J_{AA'}=1.96$ Hz), 4.89 (1H, dd, $J=5.13$ Hz, CH(Br)CH_2), 3.90 (3H, s, OMe), 2.06.85 (2H, m, CH(Br)$CH_{AB}CH_3$),

and 1.09 (3H, t, $J=7.33$ Hz, $CH_2CH_2CH_3$); MS (EI, 70 eV) m/z 271 (M^+-N_2 1.2%), 135 (100%).

2-Azido-1-(4′-methoxyphenyl)-pentan-1-one (10b). NaN_3 (0.75 g, 10 mmol) was added to a stirred solution of 2-bromo-1-(4′-methoxyphenyl)-pentan-1-one (**9b**, 1.0 g, 3.7 mmol) in DMF (15 mL), according to the general procedure E, after flash column chromatography over silica gel using 15% ethyl acetate/hexane, gave α-azidoketone **10b** (0.83 g, 96%) as an oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.95 (2H, AA′XX′, $J_{AX}=9.00$ and $J_{AA'}=1.96$ Hz), 6.99 (2H, AA′XX′, $J_{AX}=9.00$ and $J_{AA'}=1.96$ Hz), 4.55 (1H, dd, $J=5.43$ Hz, $CH(N_3)CH_2$), 3.91 (3H, s, OMe), 1.91.82 (2H, m, $CH_2CH_2CH_3$), 1.61.47 (2H, m, $CH_2CH_2CH_3$) and 1.00 (3H, t, $J=7.33$ Hz, $CH_2CH_2CH_3$); MS (EI, 70 eV) m/z 205 (M^+-N_2 1.3%), 135 (100%).

2-Azido-1-(4′-methoxyphenyl)-hexan-1-one (10c). NaN_3 (1.03 g, 16 mmol) was added to a stirred solution of 2-bromo-1-(4′-methoxyphenyl)-hexan-1-one (**9c**, 1.5 g, 5.3 mmol) in DMF (20 mL), according to the general procedure E, after flash column chromatography over silica gel using 15% ethyl acetate/hexane, gave α-azidoketone **10c** (1.25 g, 95%) as an oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.92 (2H, AA′XX′, $J_{AX}=9.00$ and $J_{AA'}=2.19$ Hz), 6.96 (2H, AA′XX′, $J_{AX}=9.00$ and $J_{AA'}=2.19$ Hz), 4.51 (1H, dd, $J=4.88$ and 5.13 Hz, $CH(Br)CH_2$), 3.90 (3H, s, OMe), 1.93.78 (2H, m, $CH_2CH_2CH_2CH_3$), 1.58.27 (4H, m, $CH_2CH_2CH_2CH_3$) and 0.91 (3H, t, $J=7.33$ Hz, $CH_2CH_2CH_3$); MS (EI, 70 eV) m/z 206 (M^+-N_3 0.55%), 135 (100%).

2-Azido-1-(4′-methoxyphenyl)-4-methylpentan-1-one (10d). NaN_3 (1.95 g, 30 mmol) was added to a stirred solution of **2**-bromo-1-(4′-methoxyphenyl)-4-methylpentan-1-one (**9d**, 2.85 g, 10 mmol) in DMF (20 mL), according to the general procedure E, after flash column chromatography over silica gel using 15% ethyl acetate/hexane, gave α-azidoketone **10d** (2.10 g, 87%) as an oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.01 (2H, AA′XX′, $J_{AX}=9.00$ and $J_{AA'}=1.96$ Hz), 6.95 (2H, AA′XX′, $J_{AX}=9.00$ and $J_{AA'}=1.96$ Hz), 4.54 (1H, dd, $J=4.15$ and 10.0 Hz, $CH(Br)CH_2$), 3.88 (3H, s, OMe), 1.92.84 (1H, m, $CH(N_3)CH_{AB}CH(CH_3)_2$), 1.79 (1H, septet, $J=8.79$ and 4.15 Hz, $CH(N_3)CH_{AB}CH(CH_3)_2$), 1.65 (1H, septet, $J=8.79$ and 4.15 Hz, $CH_2CH(CH_3)_2$), 1.04 (3H, dd, $J=6.59$ and 3.66 Hz, $CH_2CH_2(CH_3)_2$) and 0.98 (3H, dd, $J=6.59$ and 3.66 Hz, $CH_2CH_2(CH_3)_2$); MS (EI, 70 eV) m/z 205 (M^+-N_3 0.21%), 135 (100%).

2-Azido-1-(4′-methoxyphenyl)-propan-1-one (10e). NaN_3 (1.95 g, 30 mmol) was added to a stirred solution of 2-bromo-1-(4′-methoxyphenyl)-propan-1-one (**9e**, 2.43 g, 10 mmol) in DMF (20 mL), according to the general procedure E, after flash column chromatography over silica gel using 15% ethyl acetate/hexane, gave α-azidoketone **10e** (1.68 g, 86%) as an oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.95 (2H, AA′XX′, $J_{AX}=9.00$ and $J_{AA'}=1.96$ Hz), 6.95 (2H, AA′XX′, $J_{AX}=8.79$ and $J_{AA'}=1.96$ Hz), 4.66 (1H, q, $J=7.08$ Hz, $CH(Br)CH_3$), 3.88 (3H, s, OMe) and 1.56 (3H, d, $J=7.08$ Hz, $CH(Br)CH_3$); MS (EI, 70 eV) m/z 163 (M^+-N_2 0.17%), 135 (100%).

General procedure F: synthesis of 2,5-bis-alkyl-3,6-bis-arylpyrazines. A solution of the α-azidoketone (1 mmol) and Ph_3P (1.2 mmol) in dry THF (5 mL) was stirred for 0.5 h under dry air. Water (0.4 mL) was added and stirring continued overnight. THF and water were removed with a toluene azeotrope. Hexane (2×10 mL) was added and the precipitated Ph_3P=O was removed by filtration and washing with 10% ethyl acetate/hexane. Solvent was removed under vacuum, and ethanol (10 mL) and acetic acid (0.2 mL) were added. The mixture was refluxed for 4 h, cooled, and water (5 mL) was added. The mixture was extracted with ethyl acetate (2×10 mL) and the organic phase was washed with brine (5 mL) and dried over anhyd Na_2SO_4. Removal of solvent under vacuum gave the crude product, which was purified by flash column chromatography over silica gel using hexane-ethyl acetate or directly by crystallization.

2,5-Bis-ethyl-3,6-bis-(4′-methoxyphenyl)-pyrazine (11a). The reaction of 2-azido-1-(4′-methoxyphenyl)-butan-1-one (**10a**, 1.1 g, 5 mmol) and Ph_3P (1.45 g, 5.5 mmol) in dry THF (15 mL) followed by hydrolysis, dimerization and oxidation according to the general procedure F, after flash column chromatography (15% EtOAc–hexane) over silica gel, gave the pyrazine **11a** (0.7 g, 80%) as a solid. Mp 127–128 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.58 (4H, AA′XX′, $J_{AX}=8.79$ and $J_{AA'}=2.14$ Hz), 7.02 (4H, AA′XX′, $J_{AX}=8.79$ and $J_{AA'}=2.14$ Hz), 3.88 (6H, s, 2 × OMe), 2.94 (4H, q, $J=7.50$ Hz, 2 × CH_2CH_3) and 1.28 (6H, t, $J=7.50$ Hz, 2 × CH_2CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.80, 151.85, 150.09, 131.54, 130.39, 113.80, 55.35, 27.78 and 13.56. MS (EI, 70 eV) m/z 348 (M^+ 100%), 333 (18%); HRMS calcd for $C_{22}H_{23}N_2O_2$, 347.1757, found: 347.1759.

2,5-Bis-propyl-3,6-bis-(4′-methoxyphenyl)-pyrazine (11b). The reaction of 2-azido-1-(4′-methoxyphenyl)-pentan-1-one (**10b**, 0.5 g, 2.15 mmol) and Ph_3P (0.62 g, 2.4 mmol) in dry THF (10 mL) followed by hydrolysis, dimerization and oxidation according to the general procedure F, after flash column chromatography (15% EtOAc–hexane) over silica gel, gave the pyrazine **11b** (334 mg, 82%) as a solid. Mp 116–117 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.56 (4H, AA′XX′, $J_{AX}=8.79$ and $J_{AA'}=2.14$ Hz), 7.01 (4H, AA′XX′, $J_{AX}=8.79$ and $J_{AA'}=2.14$ Hz), 3.88 (6H, s, 2 × OMe), 2.87 (4H, t, $J=7.40$ Hz, 2 × $CH_2CH_2CH_3$), 1.75 (4H, quint, $J=7.40$ Hz, 2 × $CH_2CH_2CH_3$) and 0.90 (6H, t, $J=7.40$ Hz, 2 × $CH_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.73, 150.77, 150.28, 132.63, 131.57, 130.40, 114.18, 113.77, 55.31, 36.50, 22.56 and 14.02. MS (EI, 70 eV) m/z 376 (M^+ 65%), 348 (100%); HRMS calcd for $C_{24}H_{27}N_2O_2$, 375.2072, found: 375.2072.

2,5-Bis-butyl-3,6-bis-(4′-methoxyphenyl)-pyrazine (11c). The reaction of 2-azido-1-(4′-methoxyphenyl)-hexan-1-one (**10c**, 1.0 g, 4.01 mmol) and Ph_3P (1.17 g, 4.45 mmol) in dry THF (15 mL) followed by hydrolysis, dimerization and oxidation according to the general procedure F, after flash column chromatography (15% EtOAc–hexane) over silica gel, gave the pyrazine **11c** (0.66 g, 78%) as a solid. Mp 102–103 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.56 (4H, AA′XX′, $J_{AX}=8.79$ and

$J_{AA'}$ = 2.14 Hz), 7.02 (4H, AA′XX′, J_{AX} = 8.79 and $J_{AA'}$ = 2.14 Hz), 3.88 (6H, s, 2 × OMe), 2.89 (4H, t, J = 7.40 Hz, 2 × CH_2CH_2 CH_2CH_3), 1.73.67 (4H, m, 2 × $CH_2CH_2CH_2CH_3$), 1.31 (4H, quint, J = 7.50 and 14.79 Hz, 2 × $CH_2CH_2CH_3$) and 0.86 (6H, t, J = 7.50 Hz, 2 × $CH_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.78, 150.97, 150.23, 131.54, 130.44, 113.80, 55.35, 34.25, 31.49, 22.61 and 13.89. MS (EI, 70 eV) m/z 404 (M^+ 7%), 362 (53%), 121 (100%); HRMS calcd for $C_{26}H_{32}N_2O_2$, 404.2464, found: 404.2466.

2,5-Bis-isopropyl-3,6-bis-(4′-methoxyphenyl)-pyrazine (11d). The reaction of 2-azido-1-(4′-methoxyphenyl)-4-methylpentan-1-one (**10d**, 2.47 g, 10 mmol) and Ph_3P (2.80 g, 12 mmol) in dry THF (20 mL) followed by hydrolysis, dimerization and oxidation according to the general procedure F, after flash column chromatography (15% EtOAc–hexane) over silica gel, gave the pyrazine **11d** (1.7 g, 84%) as a solid. Mp 108–109 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.56 (4H, AA′XX′, J_{AX} = 8.79 and $J_{AA'}$ = 2.14 Hz), 7.02 (4H, AA′XX′, J_{AX} = 8.79 and $J_{AA'}$ = 2.14 Hz), 3.89 (6H, s, 2 × OMe), 2.86 (4H, d, J = 7.07 Hz, 2 × $CH_2CH(CH_3)_2$), 2.19 (2H, septet, J = 6.66 and 13.72 Hz, 2 × $CH_2CH(CH_3)_2$)) and 0.89 (12H, d, J = 6.65 Hz, 2 × $CH_2CH(CH_3)_2$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.75, 150.64, 149.93, 130.62, 133.80, 55.33, 42.90, 28.48 and 22.29. MS (EI, 70 eV) m/z 404 (M^+ 17%), 362 (48%), 84 (100%); HRMS calcd for $C_{26}H_{32}N_2O_2$, 404.2464, found: 404.2466.

2,5-Bis-methyl-3,6-bis-(4′-methoxyphenyl)-pyrazine (11e). The reaction of 2-azido-1-(4′-methoxyphenyl)-propan-1-one (**10e**, 1.0 g, 5 mmol) and Ph_3P (1.6 g, 6 mmol) in dry THF (10 mL) followed by hydrolysis, dimerization and oxidation according to the general procedure F, after crystallization of crude, gave the pyrazine **11e** (0.61 g, 75%) as a solid. Mp 190–191 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.62 (4H, AA′XX′, J_{AX} = 9.00 and $J_{AA'}$ = 2.14 Hz), 7.04 (4H, AA′XX′, J_{AX} = 9.00 and $J_{AA'}$ = 2.14 Hz), 3.89 (6H, s, 2 × OMe) and 2.66 (6H, s, 2 × CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.87, 150.18, 147.49, 131.23, 130.39, 113.84, 55.35 and 22.79. MS (EI, 70 eV) m/z 320 (M^+ 100%), 319 (81%), 135 (55%); HRMS calcd for $C_{20}H_{19}N_2O_2$, 319.1446, found: 319.1446.

2,5-Bis-ethyl-3,6-bis-(4′-hydroxyphenyl)-pyrazine (12a). The reaction of 2,5-bis-ethyl-3,6-bis-(4′-methoxyphenyl)-pyrazine (**11a**, 697 mg, 2 mmol) with $BF_3{\cdot}SMe_2$ (0.42 mL, 40 mmol) in dry dichloromethane (10 mL), according to the general procedure **B**, after crystallization with MeOH–acetone gave the pyrazine **12a** (535 mg, 86%) as a solid. Mp > 300 °C (dec.); HPLC purity (reversed phase, C18) in two solvents is: MeOH–H_2O (70:30) 99.6% and CH_3CN–H_2O (40:60) 100%; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 9.78 (2H, s, 2×OH), 7.47 (4H, AA′XX′, J_{AX} = 8.79 and $J_{AA'}$ = 2.14 Hz), 6.89 (4H, AA′XX′, J_{AX} = 8.79 and $J_{AA'}$ = 2.14 Hz), 2.84 (4H, q, J = 7.50 Hz, 2 × CH_2CH_3) and 1.19 (6H, t, J = 7.50 Hz, 2 × CH_2CH_3); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 157.83, 150.76, 149.32, 130.39, 129.14, 115.08, 27.14 and 13.10. MS (EI, 70 eV) m/z 320 (M^+ 61.7%), 319 (57.3%), 57 (100%); HRMS calcd for $C_{20}H_{19}N_2O_2$, 319.1443, found: 319.1443.

2,5-Bispropyl-3,6-bis-(4′-hydroxyphenyl)-pyrazine (12b). The reaction of 2,5-bis-propyl-3,6-bis-(4′-methoxyphenyl)-pyrazine (**11b**, 377 mg, 1 mmol) with $BF_3{\cdot}SMe_2$ (0.23 mL, 20 mmol) in dry dichloromethane (5 mL), according to the general procedure **B**, after crystallization with MeOH–acetone, gave the pyrazine **12b** (289 mg, 83%) as a solid. Mp 272–274 °C; HPLC purity (reversed phase, C18) in two solvents is: MeOH–H_2O (70:30) 99.3% and CH_3CN–H_2O (50:50) 99.8%; ^{1}H NMR (acetone-d_6, 500 MHz) δ 8.61 (2H, s, 2×OH), 7.54 (4H, AA′XX′, J_{AX} = 8.58 and $J_{AA'}$ = 1.93 Hz), 6.97 (4H, AA′XX′, J_{AX} = 8.54 and $J_{AA'}$ = 1.93 Hz), 2.87 (4H, t, J = 7.28 Hz, 2 × $CH_2CH_2CH_3$), 1.76 (4H, quint, J = 7.50 and 7.28 Hz, 2 × $CH_2CH_2CH_3$) and 0.87 (6H, t, J = 7.50 Hz, 2 × $CH_2CH_2CH_3$); ^{13}C NMR (acetone-d_6, 125 MHz) δ 158.61, 150.83, 150.78, 131.48, 131.33, 115.85, 37.13, 22.79 and 14.27. MS (EI, 70 eV) m/z 348 (M^+ 60%), 347 (47%), 320 (100%); HRMS calcd for $C_{22}H_{23}N_2O_2$, 347.1757, found: 347.1757.

2,5-Bis-butyl-3,6-bis-(4′-hydroxyphenyl)-pyrazine (12c). The reaction of 2,5-bis-butyl-3,6-bis-(4′-methoxyphenyl)-pyrazine (**11c**, 90 mg, 0.22 mmol) with $BF_3{\cdot}SMe_2$ (0.48 mL, 4.4 mmol) in dry dichloromethane (5 mL), according to the general procedure **B**, after crystallization with ethyl acetate–hexane, gave the pyrazine **12c** (67 mg, 81%) as a solid. Mp 242–243 °C; HPLC purity (reversed phase, C18) in two solvents is: MeOH–H_2O (75:25) 100% and CH_3CN–H_2O (75:25) 100%; ^{1}H NMR (acetone-d_6, 500 MHz) δ 8.62 (2H, s, 2×OH), 7.53 (4H, AA′XX′, J_{AX} = 8.58 and $J_{AA'}$ = 1.93 Hz), 6.96 (4H, AA′XX′, J_{AX} = 8.58 and $J_{AA'}$ = 1.93 Hz), 2.89 (4H, t, J = 7.72 Hz, 2 × CH_2CH_2 CH_2CH_3), 1.75.67 (4H, m, 2 × $CH_2CH_2CH_2CH_3$), 1.31 (4H, quint, J = 7.50 and 14.79 Hz, 2 × $CH_2CH_2CH_3$) and 0.84 (6H, t, J = 7.50 Hz, 2 × $CH_2CH_2CH_3$); ^{13}C NMR (acetone-d_6, 125 MHz) δ 158.61, 151.02, 150.76, 131.46, 131.34, 115.84, 34.77, 31.80, 23.16 and 14.13. MS (EI, 70 eV) m/z 376 (M^+ 7%), 375 (9%), 334 (100%); HRMS calcd for $C_{24}H_{27}N_2O_2$, 375.2072, found: 375.2074.

2,5-Bis-isopropyl-3,6-bis-(4′-hydroxyphenyl)-pyrazine (12d). The reaction of 2,5-bis-isopropyl-3,6-bis-(4′-methoxyphenyl)-pyrazine (**11d**, 405 mg, 1 mmol)) with $BF_3{\cdot}SMe_2$ (2.6 mL, 20 mmol) in dry dichloromethane (10 mL), according to the general procedure **B**, after crystallization with acetone-hexane gave the pyrazine **12d** (321 mg, 85%) as a solid. Mp 277–278 °C; HPLC purity (reversed phase, C18) in two solvents is: MeOH–H_2O (75:25) 100% and CH_3CN–H_2O (60:40) 100%; ^{1}H NMR (acetone-d_6, 500 MHz) δ 8.61 (2H, s, 2 × OH), 7.53 (4H, AA′XX′, J_{AX} = 8.58 and $J_{AA'}$ = 1.93 Hz), 6.97 (4H, AA′XX′, J_{AX} = 8.58 and $J_{AA'}$ = 1.93 Hz), 2.83 (4H, d, J = 7.29 Hz, 2 × $CH_2CH(CH_3)_2$), 2.19 (2H, septet, J = 6.66 and 13.51 Hz, 2 × $CH_2CH(CH_3)_2$) and 0.79 (12H, d, J = 6.65 Hz, 2 × $CH_2CH(CH_3)_2$)); ^{13}C NMR (acetone-d_6, 125 MHz) δ 158.58, 151.14, 150.07, 131.61, 131.43, 115.85, 115.77,

43.79, 28.78 and 22.66. MS (EI, 70 eV) *m/z* 376 (M^+ 33%), 375 (31%), 334 (100%); HRMS calcd for $C_{24}H_{27}N_2O_2$, 375.2072, found: 375.2072.

2,5-Bis-methyl-3,6-bis-(4′-hydroxyphenyl)-pyrazine (12e). The reaction of 2,5-bis-methyl-3,6-bis-(4′-methoxyphenyl)-pyrazine (**11e**, 200 mg, 0.62 mmol)) with $BF_3{\cdot}SMe_2$ (1.3 mL, 12.6 mmol) in dry dichloromethane (10 mL), according to the general procedure **B**, after crystallization with acetone–hexane, gave the pyrazine **12e** (160 mg, 88%) as a solid. Mp >360 (dec.) °C; HPLC purity (reversed phase, C18) in two solvents is: MeOH–H_2O (70:30) 99.14% and CH_3CN–H_2O (60:40) 100%; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 9.73 (2H, s, 2 × OH), 7.51 (4H, AA′XX′, J = 8.58 Hz), 6.87 (4H, AA′XX′, J = 8.58 Hz) and 2.54 (6H, s, 2 × CH_3); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 157.82, 149.24, 146.63, 130.49, 129.03, 115.01 and 22.67. MS (EI, 70 eV) *m/z* 292 (M^+ 97%), 291 (100%), 91 (24%); HRMS calcd for $C_{18}H_{16}N_2O_2$, 292.1212, found: 292.1211.

General procedure G: synthesis of pyrimidines from vinyl triflates. Triflic anhydride (1.1 mmol) was added dropwise over 10 min at RT under nitrogen atmosphere to a stirred solution of the ketone (1 mmol) and anisonitrile (14, 2.2 mmol) in dry 1,2-dichloroethane (5 mL). The reaction mixture was stirred for 24 h, and satd $NaHCO_3$ solution (5 mL) was added. The organic phase was washed with brine (5 mL) and dried over anhyd Na_2SO_4. Solvent was removed under vacuum and the product purified by flash column chromatography over silica gel using hexane–ethyl acetate.

2,4-Di-(4′-methoxyphenyl)-5-ethyl-6-phenylpyrimidine (15a). The reaction of butyro-phenone (**13a**) (148 mg, 1 mmol) with anisonitrile (**14**) (293 mg, 2.2 mmol) and Tf_2O (310 mg, 1.1 mmol), according to the general procedure G, furnished the corresponding pyrimidine **15a** (300 mg, 78%) as white solid which as recrystallized using hexane–CH_2Cl_2 as solvent. Mp 132 °C; ^{1}H NMR ($CDCl_3$, 500 MHz). δ 8.48 and 6.95 (4H, AA′XX′, J_{AX} = 8.96 Hz and $J_{AA'}$ = 2.02 Hz, C-2 aryl H), 7.63 and 7.03 (4H, AA′XX′, J_{AX} = 8.78 Hz and $J_{AA'}$ = 2.02 Hz, C-4 aryl H), 7.45.55 (5H, m, phenyl), 3.89 (3H, s) and 3.86 (3H, s) [2×OCH_3], 2.85 (2H, q, J = 7.50 Hz, CH_2) and 0.78 (3H, t, J = 7.50 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz). δ 166.91, 166.38, 161.38, 160.79, 159.99, 139.75, 132.04, 130.54, 130.17, 129.72, 128.69, 128.62, 128.53, 128.19, 113.62, 113.51, 55.19, 55.14, 21.49 and 14.35. MS (EI, 70 eV). *m/z* 397 (M + 1, 19%), 396 (M^+, 74), 395 (100); HRMS: calcd for $C_{26}H_{24}N_2O_2$: 396.1838, found: 396.1832. Analysis: for $C_{26}H_{24}N_2O_2$: calcd C, 78.76; H, 6.10; N, 7.07, found C, 78.37; H, 6.11; N, 6.74.

2,4-Di-(4′-methoxyphenyl)-6-phenyl-5-n-propylpyrimidine (15b). The reaction of valero-phenone (**13b**) (162 mg, 1 mmol) with anisonitrile (**14**) (293 mg, 2.2 mmol) and Tf_2O (310 mg, 1.1 mmol), according to the general procedure G, furnished the corresponding pyrimidine **15b** (400 mg, quantitative) as white solid which as recrystallized using hexane–CH_2Cl_2 as solvent. Mp 128°; ^{1}H NMR ($CDCl_3$, 400 MHz). δ 8.51 and 6.97 (4H, AA′XX′, J_{AX} = 9.04 Hz and $J_{AA'}$ = 2.20 Hz, C-2 aryl H), 7.64 and 7.04 (4H, AA′XX′, J_{AX} = 8.79 Hz and $J_{AA'}$ = 2.20 Hz, C-4 aryl H), 7.40.50 (5H, m, phenyl), 3.90 (3H, s) and 3.86 (3H, s) [2×OCH_3], 2.82 (2H, $A_3MM'XX'$, J_{XM} = 7.81 Hz and $J_{XX'}$ = 1.95 Hz, $CH_2CH_2CH_3$), 1.19 (2H, $A_3MM'XX'$, J_{MX} = 7.81 Hz, J_{AM} = 7.33 Hz and $J_{MM'}$ = 2.20 Hz, $CH_2CH_2CH_3$) and 0.59 (3H, t, J = 7.33 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz). δ 167.11, 166.58, 161.39, 160.01, 139.88, 132.23, 130.57, 130.28, 129.77, 128.74, 128.58, 128.23, 127.29, 113.66, 113.56, 55.31, 55.27, 30.33, 23.09 and 13.89. MS (EI, 70 eV). *m/z* 411 (M + 1, 29%), 410 (M^+, 87), 381 (100); HRMS: calcd for $C_{27}H_{26}N_2O_2$: 410.1994, found: 410.1988. Analysis: for $C_{27}H_{26}N_2O_2$: calcd C, 79.00; H, 6.38; N, 6.82, found C, 78.69; H, 6.59; N, 6.97.

5-Ethyl-2,4,6-tri-(4′-methoxyphenyl)pyrimidine (15c). The reaction of 4′-methoxy-butyrophenone (**13c**, which is the same compound as **8a**) (178 mg, 1 mmol) with anisonitrile (**14**) (293 mg, 2.2 mmol) and Tf_2O (310 mg, 1.1 mmol), according to the general procedure G, furnished the corresponding pyrimidine **15c** (300 mg, 73%) as a solid which was contaminated with ~10% of unreacted anisonitrile. A portion of the sample was then recrystallized using hexane–CH_2Cl_2 as solvent. Mp 147 °C; ^{1}H NMR ($CDCl_3$, 500 MHz). δ 8.49 and 6.96 (4H, AA′XX′, J_{AX} = 8.95 Hz and $J_{AA'}$ = 1.95 Hz, C-2 aryl H), 7.63 and 7.03 (8H, AA′XX′, J_{AX} = 8.66 Hz, C-4 and C-6 aryl H), 3.89 (6H, s) and 3.86 (3H, s) [3×OCH_3], 2.89 (2H, q, J = 7.55 Hz, CH_2) and 0.79 (3H, t, J = 7.55 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz). δ 166.47, 161.41, 160.81, 132.30, 130.70, 130.27, 129.97, 113.70, 113.58, 55.32, 55.28, 21.67 and 14.37. MS (EI, 70 eV). *m/z* 427 (M + 1, 5%), 426 (M^+, 19), 133 (100); HRMS: calcd for $C_{27}H_{26}N_2O_3$: 426.1943, found: 426.1940.

5-*n*-Propyl-2,4,6-tri-(4′-methoxyphenyl)pyrimidine (15d). The reaction of 4′-methoxy-valerophenone (**13d**, which is the same compound as **8b**) (192 mg, 1 mmol) with anisonitrile (**14**) (293 mg, 2.2 mmol) and Tf_2O (310 mg, 1.1 mmol), according to the general procedure G, furnished the corresponding pyrimidine **15d** (306 mg, 72%) as a solid which was contaminated with ~10% of unreacted anisonitrile. A portion of the sample was then recrystallized using hexane–CH_2Cl_2 as solvent. Mp 135 °C; ^{1}H NMR ($CDCl_3$, 400 MHz). δ 8.49 and 6.95 (4H, AA′XX′, J_{AX} = 9.03 Hz and $J_{AA'}$ = 1.95 Hz, C-2 aryl H), 7.62 and 7.03 (8H, AA′XX′, J_{AX} = 8.79 Hz and $J_{AA'}$ = 1.95 Hz, C-2 and C-4 aryl H), 3.90 (6H, s) and 3.86 (3H, s) [3×OCH_3], 2.84 (2H, $A_3MM'XX'$, J_{XM} = 7.81 Hz and $J_{XX'}$ = 1.95 Hz, $CH_2CH_2CH_3$), 1.16 (2H, $A_3MM'XX'$, J_{MX} = 7.81 Hz, J_{AM} = 7.57 Hz and $J_{MM'}$ = 2.20 Hz, $CH_2CH_2CH_3$) and 0.59 (3H, t, J = 7.57 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz). δ 166.51, 162.99, 162.71, 161.29, 159.91, 133.86, 132.29, 130.59, 130.23, 129.65, 127.10, 114.63, 113.73, 113.58, 55.41, 55.24, 55.20, 30.29, 22.92 and 13.84. MS (EI, 70 eV). *m/z* 441 (M + 1, 16%), 440 (M^+, 58), 369 (100). HRMS: calcd for $C_{28}H_{28}N_2O_3$: 440.2099, found: 440.2094.

5-Ethyl-2,6-bis-(4′-methoxyphenyl)-4-methylpyrimidine (15e). The reaction of 2-pentanone (172.26 mg, 2 mmol) with anisonitrile (**14**, 585 mg, 4.4 mmol) and Tf_2O

(620 mg, 2.2 mmol), according to the general procedure G, gave the corresponding pyrimidine (**15e**) after flash column chromatography (15% EtOAc–hexane) over silica gel. Residual anisonitrile was removed by distillation, and crystallization of the remainder from ethanol gave **15e** (220 mg, 33%) as a solid. Mp 114–115 °C, ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.43 (2H, AA′XX′, J_{AX} = 9.00 and $J_{AA'}$ = 2.00 Hz), 7.53 (2H, AA′XX′, J_{AX} = 9.00 and $J_{AA'}$ = 2.00 Hz), 7.01 (2H, AA′XX′, J_{AX} = 9.00 and $J_{AA'}$ = 2.00 Hz), 6.96 (2H, AA′XX′, J_{AX} = 9.00 and $J_{AA'}$ = 2.00 Hz), 3.88 (3H, s, OMe), 3.86 (3H, s, OMe), 2.72 (2H, q, J = 7.50 Hz, CH_2CH_3), 2.67 (3H, s, CH_3) and 1.14 (3H, t, J = 7.50 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.23, 164.99, 161.41, 160.93, 160.07, 132.07, 130.93, 130.26, 129.68,129.35, 113.73, 113.71, 55.42, 55.38, 22.47, 21.68 and 14.24. MS (EI, 70 eV) m/z 334 (M^+, 68%), 333 (100%); HRMS calcd for $C_{21}H_{22}N_2O_2$, 334.1681, found: 334.1671.

2,6-Bis-(4′-methoxyphenyl)-4-methyl-5-propylpyrimidine (15f). The reaction of 2-hexanone (200 mg, 2 mmol) with anisonitrile (**14**, 585 mg, 4.4 mmol) and Tf_2O (620 mg, 2.2 mmol), according to the general procedure G, gave the corresponding pyrimidine (**15f**) after flash column chromatography (15% EtOAc–hexane) over silica gel. Residual anisonitrile was removed by distillation, and crystallization of the remainder from ethanol gave **15f** (238 mg, 34%) as a solid. Mp 89–90 °C, ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.42 (2H, AA′XX′, J_{AX} = 9.00 and $J_{AA'}$ = 2.00 Hz), 7.52 (2H, AA′XX′, J_{AX} = 9.00 and $J_{AA'}$ = 2.00 Hz), 7.00 (2H, AA′XX′, J_{AX} = 9.00 and $J_{AA'}$ = 2.00 Hz), 6.95 (2H, AA′XX′, J_{AX} = 9.00 and $J_{AA'}$ = 2.00 Hz), 3.88 (3H, s, OMe), 3.86 (3H, s, OMe), 2.69.65 (2H, m, CH_2CH_2), 2.64 (3H, s, CH_3), 1.53.45 (2H, m, CH_2CH_3) and 0.88 (3H, t, J = 7.50 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.29, 165.22, 161.45, 160.85, 160.05, 132.17, 130.87, 130.33, 129.68,129.72, 128.09, 113.75, 113.71, 55.43, 55.39, 30.60, 23.19 and 14.29. MS (EI, 70 eV) m/z 348 (M^+, 100%), 333 (38%), 319 (98%); HRMS calcd for $C_{22}H_{24}N_2O_2$, 348.1838, found: 348.1840.

2,4-Di-(4′-hydroxyphenyl)-5-ethyl-6-phenylpyrimidine (16a). Deprotection of the pyrimidine **15a** (125 mg, 0.33 mmol) using $BF_3{\cdot}SMe_2$ (640 mg, 4.89 mmol), according to the general procedure **B**, furnished the phenolic pyrimidine **16a** (110 mg, 95%). Mp 197 °C; ^{1}H NMR ($(CD_3)_2CO$, 400 MHz). δ 8.19 and 6.70 (4H, AA′XX′, J_{AX} = 8.54 Hz and $J_{AA'}$ = 1.46 Hz, C-2 aryl H), 8.10 (2H, br s, 2×OH), 7.41 (2H, dd, J = 8.06 and 1.46 Hz) and 7.20.30 (3H, m) [phenyl], 7.35 and 6.78 (4H, AA′XX′, J_{AX} = 8.55 Hz and $J_{AA'}$ = 1.46 Hz, C-4 aryl H), 2.65 (2H, q, J = 7.33 Hz, CH_2) and 0.57 (3H, t, J = 7.32 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz). δ 166.54, 166.30, 160.58, 158.63, 157.23, 139.47, 130.79, 129.98, 129.53, 129.40, 128.33, 128.22, 128.19, 127.86, 114.89, 21.21 and 13.99. MS (EI, 70 eV). m/z 369 (M + 1, 17%), 368 (M^+, 71), 367 (100); *HRMS*: calcd for $C_{24}H_{20}N_2O_2$: 368.1525, found: 368.1516. Analysis: for $C_{24}H_{20}N_2O_2$ + 0.2 EtOAc: calcd C, 77.16; H, 5.64; N, 7.26, found C, 77.10; H, 5.55; N, 7.11.

2,4-Di-(4′-hydroxyphenyl)-6-phenyl-5-*n*-propylpyrimidine (16b). Deprotection of the pyrimidine **15b** (100 mg, 0.25 mmol) using $BF_3{\cdot}SMe_2$ (490 mg, 3.77 mmol), according to the general procedure **B**, furnished the phenolic pyrimidine **16b** (88 mg, 95%). Mp 189 °C; ^{1}H NMR ($CDCl_3 + (CD_3)_2CO$, 400 MHz). δ 8.28 and 6.78 (4H, AA′XX′, J_{AX} = 8.79 Hz and $J_{AA'}$ = 1.95 Hz, C-2 aryl H), 8.07 (1H, br s) and 7.97 (1H, br s) [2×OH], 7.49 (2H, dd, J = 8.06 and 1.71 Hz) and 7.30.40 (3H, m) [phenyl], 7.43 and 6.86 (4H, AA′XX′, J_{AX} = 8.55 Hz and $J_{AA'}$ = 1.95 Hz, C-4 aryl H), 2.69 (2H, $A_3MM'XX'$, J_{XM} = 7.81 Hz and $J_{XX'}$ = 1.95 Hz, $CH_2CH_2CH_3$), 1.03 (2H, $A_3MM'XX'$, J_{MX} = 7.81 Hz, J_{AM} = 7.57 Hz and $J_{MM'}$ = 2.44 Hz, $CH_2CH_2CH_3$) and 0.45 (3H, t, J = 7.57 Hz, CH_3); ^{13}C NMR ($CDCl_3 + (CD_3)_2CO$, 100 MHz). δ 166.75, 166.63, 160.61, 158.68, 157.28, 139.69, 131.07, 130.14, 129.63, 129.51, 128.51, 127.93, 126.82, 114.97, 30.07, 22.77 and 13.57. MS (EI, 70 eV). m/z 383 (M + 1, 20%), 382 (M^+, 75), 353 (100). HRMS: calcd for $C_{25}H_{22}N_2O_2$: 382.1681, found: 382.1674. Analysis: for $C_{25}H_{22}N_2O_2$ + 0.4 EtOAc: calcd C, 76.49; H, 6.08; N, 6.74, found C, 76.18; H, 5.58; N, 6.71.

5-Ethyl-2,4,6-tri-(4′-hydroxyphenyl)pyrimidine (16c). Deprotection of the pyrimidine **15c** (165 mg, 0.4 mmol) using $BF_3{\cdot}SMe_2$ (1.4 g, 11.41 mmol), according to the general procedure **B**, furnished the phenolic pyrimidine **16c** (145 mg, 97%). Mp 276 °C; ^{1}H NMR ($CDCl_3 + (CD_3)_2CO$, 400 MHz). δ 8.13 and 6.63 (4H, A_2X_2, J = 8.54 Hz, C-2 aryl H), 8.10 (2H, s) and 8.04 (1H, s) [3×OH], 7.27 and 6.71 (8H, A_2X_2, J = 8.54 Hz, C-4 and C-6 aryl H), 2.65 (2H, q, J = 7.33 Hz, CH_2) and 0.50 (3H, t, J = 7.33 Hz, CH_3); ^{13}C NMR ($CDCl_3 + (CD_3)_2CO$, 100 MHz). δ 166.3, 160.54, 158.53, 157.18, 131.24, 130.57, 130.14, 129.64, 128.23, 115.26, 114.99, 21.47 and 14.08. MS (EI, 70 eV). m/z 385 (M + 1, 15%), 384 (M^+, 62), 383 (100); HRMS: calcd for $C_{24}H_{20}N_2O_3$: 384.1474, found: 384.1477.

5-*n*-Propyl-2,4,6-tri-(4′-hydroxyphenyl)pyrimidine (16d). Deprotection of the pyrimidine **15d** (60 mg, 0.14 mmol) using $BF_3{\cdot}SMe_2$ (486 mg, 3.74 mmol), according to the general procedure **B**, furnished the phenolic pyrimidine **16d** (45 mg, 84%). Mp 264 °C; ^{1}H NMR ($CDCl_3 + (CD_3)_2CO$, 400 MHz). δ 8.29 and 6.78 (4H, A_2X_2, J = 8.55 Hz, C-2 aryl H), 7.99 (2H, s) and 7.90 (1H, s) [3×OH], 7.42 and 6.86 (8H, A_2X_2, J = 8.18 Hz, C-4 and C-6 aryl H), 2.73 (2H, t, J = 8.06 Hz, Ar–CH_2), 1.03 (2H, $A_3MM'XX'$, J_{AM} = 7.08 Hz, J_{MX} = 7.81 Hz, CH_2CH_3) and 0.45 (3H, t, J = 7.33 Hz, CH_3); ^{13}C NMR ($(CD_3)_2CO$, 125 MHz). δ 167.69, 161.33, 160.47, 158.94, 132.34, 131.69, 131.36, 130.63, 130.47, 127.67, 115.93, 115.83, 31.24, 23.42 and 14.12. MS (EI, 70 eV). m/z 399 (M + 1, 25%), 398 (M^+, 27), 369 (100); HRMS: calcd for $C_{25}H_{22}N_2O_3$: 398.1630, found: 398.1639. Analysis: for $C_{25}H_{22}N_2O_3$ + 0.4 EtOAc + 0.3 CH_2Cl_2: calcd C, 70.36; H, 5.66; N, 6.10, found C, 70.62; H, 5.25; N, 6.10.

5-Ethyl-2,6-bis-(4′-hydroxyphenyl)-4-methylpyrimidine (16e). The reaction of 5-ethyl-2,6-bis-(4′-methoxyphenyl)-4-methylpyrimidine (**15e**, 90 mg, 0.27 mmol) with $BF_3{\cdot}SMe_2$ (0.56 mL, 5.4 mmol) in dry dichloromethane (10 mL), according to the general procedure **B**,

after flash column chromatography (45% EtOAc–hexane) over silica gel, gave the pyrimidine **16e** (78 mg, 94%) as a solid. HPLC purity (reversed phase, C18) in two solvents is: MeOH–H_2O (70:30) 99.8% and CH_3CN–H_2O (40:60) 100%. Mp 160–161 °C; ^{1}H NMR (acetone-d_6, 500 MHz) δ 8.66 (2H, s, OH), 8.35 (2H, AA′XX′, J_{AX} = 9.00 and $J_{AA'}$ = 2.14 Hz), 7.47 (2H, AA′XX′, J_{AX} = 8.79 and $J_{AA'}$ = 2.14 Hz), 6.96 (2H, AA′XX′, J_{AX} = 8.79 and $J_{AA'}$ = 2.14 Hz), 6.91 (2H, AA′XX′, J_{AX} = 9.00 and $J_{AA'}$ = 2.14 Hz), 2.75 (2H, q, J = 7.50 Hz, CH_2CH_3), 2.60 (3H, s, CH_3) and 1.13 (3H, t, J = 7.50 Hz, CH_2CH_3); ^{13}C NMR (acetone-d_6, 125 MHz) δ 166.80, 165.92, 161.35, 160.35, 158.83, 131.87, 131.11, 130.68, 130.38, 129.86, 115.88, 115.75, 22.51, 22.07 and 14.31. MS (EI, 70 eV) m/z 306 (M^+, 59%), 305 (100%); HRMS calcd for $C_{19}H_{18}N_2O_2$, 306.1368, found: 306.1368.

2,6-Bis-(4′-hydroxyphenyl)-4-methyl-5-propylpyrimidine (16f). The reaction of 2,6-bis-(4′-methoxyphenyl)-4-methyl-5-propylpyrimidine (**15f**, 70 mg, 0.20 mmol) with $BF_3{\cdot}SMe_2$ (0.42 mL, 4.0 mmol) in dry dichloromethane (5 mL), according to the general procedure **B**, after careful flash column chromatography (45% EtOAc–hexane) over silica gel, gave the pyrimidine **16f** (58 mg, 91%) as a solid. HPLC purity (reversed phase, C18) in two solvents is: MeOH–H_2O (70:30) 98.9% and CH_3CN–H_2O (40:60) 99.4%. Mp 110–111 °C, ^{1}H NMR (acetone-d_6, 500 MHz) δ 8.63 (2H, s, OH), 8.32 (2H, AA′XX′, J_{AX} = 8.79 and $J_{AA'}$ = 2.14 Hz), 7.42 (2H, AA′XX′, J_{AX} = 8.58 and $J_{AA'}$ = 2.14 Hz), 6.92 (2H, AA′XX′, J_{AX} = 8.79 and $J_{AA'}$ = 2.14 Hz), 6.86 (2H, AA′XX′, J_{AX} = 9.00 and $J_{AA'}$ = 2.14 Hz), 2.69.65 (2H, m, CH_2CH_2), 2.55 (3H, s, CH_3), 1.50.45 (2H, m, CH_2CH_3) and 0.88 (3H, t, J = 7.20 Hz, CH_2CH_3); ^{13}C NMR (acetone-d_6, 125 MHz) δ 166.95, 166.09, 161.32, 160.34, 158.76, 131.95, 131.14, 130.65, 130.36, 128.52, 115.87, 115.73, 31.05, 23.61, 22.66 and 14.39. MS (EI, 70 eV) m/z 320 (M^+, 59%), 319 (32%), 291 (100%); HRMS calcd for $C_{20}H_{20}N_2O_2$, 320.1524, found: 320.1522.

General procedure H: preparation of *N*-methoxy-*N*-methylacetamide

Pyridine (2.2 mol) was added dropwise at 0 °C to a stirred solution of acid chloride (1 mol) and *N*-methoxy-*N*-methylammonium chloride (1.2 mol) in CH_2Cl_2 (10 mL). After the addition of pyridine, the reaction was stirred at rt for 1 h, then water (5 mL) was added. The organic phase was washed with 2 N HCl (5 mL) followed by satd $NaHCO_3$ soln and brine, at 0 °C dried over anhyd Na_2SO_4. Solvent removal gave the corresponding amides.

***N* - Methoxy - *N* - methyl - phenylacetamide.** Pyridine (7.0 mL, 0.08 mol) was added dropwise to a stirred solution of phenylacetyl chloride [prepared from phenylacetic acid and oxalyl chloride (5.72 g, 0.037 mol)] and *N*-methoxy-*N*-methylammonium chloride (4.0 g, 0.041 mol) in CH_2Cl_2 (50 mL), according to the general procedure H. Solvent removal and flash column chromatography with 15% EtOAc/hexane gave the title compound (5.4 g, 82%) as an oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.32.28 (3H, m, Ph), 7.25.24 (2H, m, Ph), 3.77 (2H, s, CH_2Ph), 3.60 (3H, s, OCH_3) and 3.19 (3H, s, CH_3); MS (EI, 70 eV) m/z 179 (M^+, 8%), 118 (33%), 91 (100%).

***N*-Methoxy-*N*-methyl-4′-methoxyphenylacetamide.** Pyridine (20.0 mL, 0.25 mol) was added dropwise to a stirred solution of 4-methoxyphenylacetyl chloride (20.0 g, 0.11 mol) and *N*-methoxy-*N*-methyl ammonium chloride (13.0 g, 0.13 mol) in CH_2Cl_2 (150 mL), according to the general procedure H. Solvent removal gave the title compound (23.0 g, 100%) as an oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.24 (2H, AA′XX′, J_{AX} = 9.00 and $J_{AA'}$ = 2.00 Hz), 6.88 (2H, AA′XX′, J_{AX} = 9.00 and $J_{AA'}$ = 2.00 Hz), 3.83 (3H, s, OMe), 3.82 (2H, s, CH_2), 3.65 (3H, s, OCH_3) and 3.22 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 130.34, 113.96, 161.33, 55.26 and 38.46. MS (EI, 70 eV) m/z 209 (M^+, 10%), 148 (20%), 121 (100%).

General procedure I: preparation of 1-aryl-alkan-2-ones (17a–e)

Grignard's reagent (1.2 mol) was added dropwise at 0 °C to a stirred solution of *N*-methoxy-*N*-methyl-arylamide (1 mol) in THF (8 mL). After the addition, the reaction was stirred for 3 h, and for 1 h at rt, and then poured over cooled 6 N HCl and extracted with diethyl ether. The organic phase was washed with brine and dried over anhyd Na_2SO_4. Solvent removal and flash column chromatography (EtOAc–hexane) over silica gel gave corresponding ketone as an oil.

1-Phenyl-pentan-2-one (17a). *n*-PrMgBr (30 mL, 0.038 mol, prepared from C_3H_7Br and Mg in ether) was added dropwise to a stirred solution of *N*-methoxy-*N*-methyl-phenylacetamide (5.0 g, 0.027 mol) in THF (30 mL) at 0 °C, according to the general procedure I. Flash column chromatography (10% EtOAc–hexane), over silica gel, gave ketone **17a** (2.88 g, 64%) as an oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34.19 (5H, m, Ph), 3.67 (2H, s, CH_2Ph), 2.42 (2H, t, J = 7.33 Hz, CH_2CH_2), 1.58 (2H, quint, J = 7.33 and 7.57 Hz, $CH_2CH_2CH_3$) and 0.86 (3H, t, J = 7.57 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 208.68, 134.61, 129.63, 128.91, 127.17, 50.39, 44.12, 17.39 and 13.85. MS (EI, 70 eV) m/z 162 (M^+, 16%), 91 (47%), 71 (100%).

1-(4′-Methoxyphenyl)-butan-2-one (17b). EtMgBr (3M) (40.0 mL, 0.12 mol) was added dropwise to a stirred solution of *N*-methoxy-*N*-methyl-4′-methoxyphenylacetamide (20.9 g, 0.10 mol) in THF (80 mL) at 0 °C, according to the general procedure I. Flash column chromatography (10% EtOAc–hexane) over silica gel gave **17b** (14.5 g, 81%) as an oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.12 (2H, AA′XX′, J_{AX} = 8.79 and $J_{AA'}$ = 2.00 Hz), 6.85 (2H, AA′XX′, J_{AX} = 8.79 and $J_{AA'}$ = 2.00 Hz), 3.79 (3H, s, OMe), 3.61 (2H, s, CH_2Ar), 2.45 (2H, q, J = 7.2 Hz, CH_2) and 1.02 (3H, t, J = 7.2 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 130.44, 126.58, 114.17, 55.32, 48.98, 35.09 and 7.86. MS (EI, 70 eV) m/z 178 (M^+, 10%), 135 (5%), 121 (100%).

1-(4′-Methoxyphenyl)-pentan-2-one (17c or 22b). *n*-PrMgBr (30 mL, 0.038 mol, prepared from C_3H_7Br and Mg in ether) was added dropwise to a stirred solution of *N*-methoxy-*N*-methyl-4′-methoxyphenylacetamide (6.0 g, 0.028 mol) in THF (30 mL) at 0 °C, according to the general procedure I. Flash column chromatography (10% EtOAc–hexane) over silica gel gave **17c** (3.8 g, 71%) as an oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.12 (2H, AA′XX′, J_{AX} = 8.79 and $J_{AA'}$ = 1.95 Hz), 6.87 (2H, AA′XX′, J_{AX} = 8.79 and $J_{AA'}$ = 1.95 Hz), 3.81 (3H, s, OMe), 3.63 (2H, s, CH_2Ar), 2.43 (2H, q, J = 7.33 Hz, CH_2CH_2), 1.57 (2H, quint, J = 7.33 and 7.57 Hz, $CH_2CH_2CH_3$) and 0.88 (3H, t, J = 7.57 Hz, CH_3 and 1.02 (3H, t, J = 7.2 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 208.91, 158.53, 130.35, 126.37, 114.04, 55.21, 49.20, 43.68,17.15 and 13.61. MS (EI, 70 eV) *m*/*z* 192 (M^+, 15%), 135 (55%), 121 (100%).

4-Ethyl-2,6-bis-(4′-methoxyphenyl)-5-phenylpyrimidine (18a) and 4-benzyl-2,6-bis-(4′methoxyphenyl)-5-methylpyrimidine (19a). The reaction of 1-phenylbutan-2-one (**17a**) (148 mg, 1 mmol) with anisonitrile (**14**, 293 mg, 2.2 mmol) and Tf_2O (310 mg, 1.1 mmol), according to the general procedure G, gave the corresponding pyrimidines **18a** and **19a** in the ratio of ~1:1. Careful flash column chromatography (15% EtOAc–hexane) over silica gel and crystallization from ethanol gave the first required pyrimidine (**18a**) 148 mg, 37%), followed by the isomeric pyrimidine (**19a**) 156 mg, 39%), as solids. *4-Ethyl-2,6-bis-(4′-methoxyphenyl)-5-phenylpyrimidine* (**18a**). Mp 130–131 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.57 (2H, AA′XX′, J_{AX} = 9.00 and $J_{AA'}$ = 2.14 Hz), 7.39 (2H, AA′XX′, J_{AX} = 9.00 and $J_{AA'}$ = 2.14 Hz), 7.38.31 (3H, m), 7.16 (2H, AA′XX′, J_{AX} = 9.00 and $J_{AA'}$ = 2.14 Hz), 7.02 (2H, AA′XX′, J_{AX} = 9.00 and $J_{AA'}$ = 2.14 Hz), 6.73 (2H, AA′XX′, J_{AX} = 9.00 and $J_{AA'}$ = 2.14 Hz), 3.89 (3H, s, OMe), 3.76 (3H, s, OMe), 2.70 (2H, q, J = 7.50 Hz, CH_2CH_3) and 1.24 (3H, t, J = 7.50 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.00, 162.63, 162.32, 161.55, 159.92, 137.36, 131.55, 131.24, 130.96, 130.23, 129.83, 128.57, 128.53, 127.35, 113.67, 113.67, 113.08, 55.32, 55.14, 28.83 and 12.85. MS (EI, 70 eV) *m*/*z* 396 (M^+, 52%), 395 (100%); HRMS calcd for $C_{26}H_{23}N_2O_2$, 395.1759, found: 395.1760. Analysis for $C_{26}H_{24}N_2O_2$, calcd C,78.75; H, 6.10; N, 7.07, found C,78.56; H, 6.06; N, 7.10. *4-Benzyl-2,6-bis-(4′methoxyphenyl)-5-methylpyrimidine* (**19a**). Mp 127–128 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.51 (2H, AA′XX′, J_{AX} = 9.00 and $J_{AA'}$ = 2.14 Hz), 7.62 (2H, AA′XX′, J_{AX} = 8.79 and $J_{AA'}$ = 2.14 Hz), 7.37.31 (4H, m), 7.26.24 (1H, m), 7.01 (4H, AA′XX′, J_{AX} = 9.00, 8.79 and $J_{AA'}$ = 2.14 Hz), 4.28 (2H, s, CH_2Ph), 3.90 (3H, s, OMe), 3.89 (3H, s, OMe) and 2.32 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.69, 165.25, 161.36, 160.95, 160.16, 137.89, 131.56, 130.86, 129.62, 128.94, 128.49, 126.42, 122.97, 113.64, 113.53, 55.33, 55.31, 42.36 and 15.36. MS (EI, 70 eV) *m*/*z* 396 (M^+, 57%), 395 (100%); HRMS calcd for $C_{26}H_{23}N_2O_2$, 395.1759, found: 395.1763; Analysis for $C_{26}H_{24}N_2O_4$, calcd C,78.75; H, 6.10; N, 7.07, found C,78.61; H, 6.05; N, 7.18.

2,6-Bis-(4′-methoxyphenyl)-5-phenyl-4-propylpyrimidine (18b) and 4-benzyl-5-ethyl-2,6-bis-(4′methoxyphenyl)-pyrimidine (19b). The reaction of 1-phenylpentan-2-one (**3b**) (324 mg, 2 mmol) with anisonitrile (**14**, 585 mg, 4.4 mmol) and Tf_2O (620 mg, 2.2 mmol), according to the general procedure G, gave the corresponding pyrimidines **18b** and **19b** in a ~1:1 ratio. Careful flash column chromatography (15% EtOAc–hexane) over silica gel and crystallization from ethanol gave the first required isomeric pyrimidine (**18b**) (280 mg, 34%), followed by the pyrimidine (**19b**) (260 mg, 32%, as solids. *2,6-Bis-(4′-methoxyphenyl)-5-phenyl-4-propylpyrimidine* (**18b**). Mp 107–108 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.56 (2H, AA′XX′, J_{AX} = 8.79 and $J_{AA'}$ = 1.95 Hz), 7.40.30 (5H, m, Ph), 7.15 (2H, AA′XX′, J_{AX} = 9.00 and $J_{AA'}$ = 1.95 Hz), 7.00 (2H, AA′XX′, J_{AX} = 9.00 and $J_{AA'}$ = 1.95 Hz), 6.72 (2H, AA′XX′, J_{AX} = 8.79 and $J_{AA'}$ = 1.95 Hz), 3.89 (3H, s, OMe), 3.76 (3H, s, OMe), 2.64 (2H, t, J = 7.57 Hz, $CH_2CH_2CH_3$), 1.77 (2H, quint, J = 7.57 Hz, $CH_2CH_2CH_3$ and 0.89 (3H, t, J = 7.39 Hz, $CH_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.95, 162.71, 162.19, 161.54, 159.89, 137.39, 131.53, 131.29, 130.98, 130.30, 129.82, 128.85, 128.50, 127.31, 113.66, 113.06, 55.29, 55.11, 37.33, 21.88 and 14.02. MS (EI, 70 eV) *m*/*z* 410 (M^+,38%), 409 (33%), 381(100%); HRMS calcd for $C_{27}H_{25}N_2O_2$, 409.1915, found: 409.1910. Analysis for $C_{27}H_{26}N_2O_2$, calcd C,78.99; H, 6.39; N, 6.83, found C, 78.86; H, 6.32; N, 6.93. *4-Benzyl-5-ethyl-2,6-bis-(4′methoxyphenyl)-pyrimidine* (**19b**). Mp 102–103 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.44 (2H, AA′XX′, J_{AX} = 8.82 and $J_{AA'}$ = 1.95 Hz), 7.53 (2H, AA′XX′, J_{AX} = 8.79 and $J_{AA'}$ = 1.95 Hz), 7.40.22 (5H, m, Ar), 7.00.93 (4H, m, Ar), 4.28 (2H, s, CH_2Ph), 3.87 (3H, s, OMe), 3.86 (3H, s, OMe), 2.73 (2H, q, J = 7.57 Hz, CH_2CH_3) and 1.02 (3H, t, J = 7.57 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.21, 166.02, 161.39, 160.93, 159.96, 138.59, 132.05, 130.86, 130.09, 129.69, 129.39, 128.97, 128.44, 126.41, 113.64, 55.32, 55.31, 41.38, 21.10 and 14.69. MS (EI, 70 eV) *m*/*z* 410 (M^+,73%), 409 (100%); HRMS calcd for $C_{27}H_{25}N_2O_2$, 409.1915, found: 409.1908. Analysis for $C_{27}H_{26}N_2O_4$, calcd C,78.99; H, 6.39; N, 6.83, found C,78.46; H, 6.16; N, 6.80.

4-(4′-Methoxybenzyl)-2,6-di-(4′-methoxyphenyl)-5-methylpyrimidine (19c). The reaction of 1-(4′methoxyphenyl)butan-2-one (**17c**) (210 mg, 1.18 mmol) with anisonitrile (**14**) (346 mg, 2.59 mmol) and Tf_2O (366 mg, 1.3 mmol), according to the general procedure G, furnished the corresponding pyrimidines **18c** and **19c** (21%). Column chromatography over silica gel furnished first the required isomer, **18c** in only trace amounts (and very much contaminated with the unreacted anisonitrile (**14**), followed by the isomer, the benzyl pyrimidine **19c** (105 mg, 21%) as a solid. Mp 218 °C; ^{1}H NMR ($CDCl_3$, 500 MHz). δ 8.49 and 6.99 (4H, A_2X_2, J_{AX} = 8.48 Hz, C-2 aryl H), 7.59 and 6.99 (4H, A_2X_2, J_{AX} = 8.11 Hz, C-6 aryl H), 7.27 and 6.85 (4H, A_2X_2, J_{AX} = 8.11 Hz, C-4 aryl H), 4.20 (2H, s, CH_2Ar), 3.87 (6H, s) and 3.78 (3H, s) [3×OCH_3] and 2.30 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz). δ 167.96, 165.13, 161.28, 160.84, 160.08, 158.12, 131.51, 130.80, 130.64, 129.84, 129.55, 113.81, 113.58, 113.45, 55.27, 55.17, 41.43 and 15.31. MS (EI, 70 eV). *m*/*z* 427 (M + 1, 4%), 426 (M^+, 13), 133 (100); HRMS: calcd for $C_{27}H_{26}N_2O_3$: 426.1943, found: 426.1939.

4,5-Bis-ethyl-2,6-bis-(4′-methoxyphenyl)-pyrimidine (18d) and 2,6-bis-(4′-methoxyphenyl)-5-methyl-4-propylpyrimidine (19d). The reaction of 3-hexanone (200 mg, 2 mmol) with anisonitrile (**14**, 585 mg, 4.4 mmol) and Tf_2O (620 mg, 2.2 mmol), according to the general procedure F, gave after flash column chromatography (10% EtOAc–hexane) over silica gel an inseparable mixture of isomeric pyrimidines **18d** and **19d** (298 mg, 43%) as solids. Mp 109–110 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.48 (2H, AA′XX′, J_{AX} = 9.00 and $J_{AA'}$ = 2.14 Hz), 7.62 and 7.54 (2H, AA′XX′, J_{AX} = 8.78 and $J_{AA'}$ = 1.93 Hz), 7.05.00 (2H, m, Ar), 6.99.96 (2H, m, Ar), 3.90, 3.89 and 3.88 (6H, s, OMe), 2.93 and 2.75 (2H, q, J = 7.5 Hz,CH_2CH_3), 2.86 (2H, t, J = 7.5 Hz, CH_2CH_2), 2.35 (3H, s, CH_3), 1.92 (2H, quint, J = 7.5 Hz, $CH_2CH_2CH_3$), 1.45 (3H, t, J = 7.5 Hz, CH_2CH_3) and 1.15.09 (6H, overlapping t, J = 7.50 Hz, CH_2CH_3); ratio of two isomers by ^{1}H NMR is (65:35). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.14, 169.47, 165.09, 164.49, 161.23, 160.76, 160.08, 159.88, 132.26, 131.87, 131.15, 130.83, 130.12, 129.60, 129.54, 128.66, 122.41, 113.66, 113.58, 113.53, 55.33, 55.31, 55.28, 37.39, 27.60, 21.11, 20.99, 15.12, 14.89, 14.18 and 12.83. MS (EI, 70 eV) m/z 348 (M^+, 10%), 347 (17%), 135 (100%); HRMS calcd for $C_{22}H_{23}N_2O_2$, 347.1759, found: 347.1762.

4-Butyl-2,6-bis-(4′-methoxyphenyl)-5-methylpyrimidine (18e) and 2,6-bis-(4′-methoxyphenyl)-4-ethyl-5-propylpyrimidine (19e). The reaction of 3-heptanone (228 mg, 2 mmol) with anisonitrile (**14**) (585 mg, 4.4 mmol) and Tf_2O (620 mg, 2.2 mmol), according to the general procedure F, gave after flash column chromatography (15% EtOAc–hexane) over silica gel an inseparable mixture of pyrimidines **18e** and **19e** (445 mg, 61%) as solids. Mp 109–110 °C, ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.50 (2H, AA′XX′, J_{AX} = 8.79 Hz), 7.62 and 7.54 (2H, AA′XX′, J_{AX} = 8.58 and 8.36 Hz), 7.05.98 (4H, m, Ar), 3.90, 3.89 and 3.88 (6H, s, OMe), 2.90.85 (2H, m, CH_2CH_3 and $CH_2CH_2CH_3$), 2.35 (3H, s, CH_3), 1.55.46 (2H, m, $CH_2CH_2CH_3$), 1.45 (3H, t, J = 7.5 Hz, CH_2CH_3), 1.04 (3H, t, J = 7.50 Hz, CH_2CH_3) and 0.94 (3H, t, J = 7.50 Hz, CH_2CH_3); ratio of two isomers by ^{1}H NMR is (59:41). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.51, 169.77, 165.52, 164.77, 161.54, 161.52, 161.07, 161.04, 160.36, 160.12, 132.63, 132.14, 131.43, 131.37, 131.11, 130.46, 129.87, 129.83, 127.62, 122.62, 113.86, 113.80, 55.59, 55.57, 55.55, 35.47, 30.23, 27.99, 24.10, 23.04, 15.38, 14.51, 14.31 and 13.11. MS (EI, 70 eV) m/z 62 (M^+, 50%), 361 (55%), 320 (70%), 84 (100%); HRMS calcd for $C_{23}H_{25}N_2O_2$, 361.1916, found: 361.1919.

4-Ethyl-2,6-bis-(4′-hydroxyphenyl)-5-phenylpyrimidine (20a). The reaction of 4-ethyl-2,6-bis-(4′-methoxyphenyl)-5-phenylpyrimidine (**18a**, 60 mg, 0.15 mmol) with $BF_3{\cdot}SMe_2$ (0.32 mL, 3.0 mmol) in dry dichloromethane (5 mL), according to the general procedure **B**, after flash column chromatography (35% EtOAc–hexane) over silica gel, gave the pyrimidine **20a** (50 mg, 89%) as a solid. HPLC purity (reversed phase, C18) in two solvents is: MeOH–H_2O (75:25) 100% and CH_3CN–H_2O (60:40) 99.9%. Mp 107 °C, ^{1}H NMR (acetone-d_6, 400 MHz) δ 8.64 (2H, s, OH), 8.50 (2H, AA′XX′, J_{AX} = 9.00 and $J_{AA'}$ = 2.14 Hz), 7.39.32 (5H, m, Ph), 7.24 (2H, AA′XX′, J_{AX} = 8.79 and $J_{AA'}$ = 2.14 Hz), 6.97 (2H, AA′XX′, J_{AX} = 8.79 and $J_{AA'}$ = 2.14 Hz), 6.68 (2H, AA′XX′, J_{AX} = 9.00 and $J_{AA'}$ = 2.14 Hz), 2.63 (2H, q, J = 7.50 Hz, CH_2CH_3) and 1.21 (3H, t, J = 7.50 Hz, CH_2CH_3); ^{13}C NMR (acetone-d_6, 100 MHz) δ 170.41, 163.68, 162.91, 160.62, 158.82, 138.41, 132.45, 131.13, 130.69, 130.63, 129.36, 129.22, 128.19, 115.97, 115.25, 29.22 and 12.96. MS (EI, 70 eV) m/z 368 (M^+, 61%), 367 (100%); HRMS calcd for $C_{24}H_{20}N_2O_2$, 367.1446, found: 367.1442.

4-Benzyl-2,6-bis-(4-′hydroxyphenyl)-5-methylpyrimidine (21a). The reaction of 4-benzyl-2,6-bis-(4′-methoxyphenyl)-5-methylpyrimidine (**19a**, 80 mg, 0.20 mmol) with $BF_3{\cdot}SMe_2$ (0.42 mL, 4.0 mmol) in dry dichloromethane (5 mL), according to the general procedure **B**, after flash column chromatography (35% EtOAc–hexane) over silica gel, gave the pyrimidine **21a** (70 mg, 95%) as a solid. HPLC purity (reversed phase, C18) in two solvents is: MeOH–H_2O (75:25) 99.9% and CH_3CN–H_2O (60:40) 99.9%. Mp 115–116 °C; ^{1}H NMR (acetone-d_6, 400 MHz) δ 8.67 (2H, s, OH), 8.40 (2H, AA′XX′, J_{AX} = 8.79 and $J_{AA'}$ = 1.95 Hz), 7.56 (2H, AA′XX′, J_{AX} = 8.79 and $J_{AA'}$ = 1.95 Hz), 7.36 (2H, AA′XX′, J_{AX} = 7.60 Hz), 7.29 (2H, AA′XX′, J_{AX} = 7.30 and $J_{AA'}$ = 1.95 Hz), 7.20 (1H, AA′XX′, J_{AX} = 7.30 Hz), 6.79.91 (4H, AA′XX′, J_{AX} = 9.00, 8.79 and $J_{AA'}$ = 2.14 Hz), 4.27 (2H, s, CH_2Ph) and 2.32 (3H, s, CH_3); ^{13}C NMR (acetone-d_6, 100 MHz) δ 168.66, 166.23, 161.53, 160.37, 159.06, 139.15, 131.84, 131.36, 130.69, 130.39, 129.78, 129.26, 127.13, 123.58, 123.21, 115.89, 115.67, 42.66 and 15.59. MS (EI, 70 eV) m/z 368 (M^+, 67%), 367 (100%); HRMS calcd for $C_{24}H_{20}N_2O_2$, 367.1446, found: 367.1443.

2,6-Bis-(4′-hydroxyphenyl)-5-phenyl-4-propylpyrimidine (20b). The reaction of 2,6-bis-(4′-methoxyphenyl)-5-phenyl-4-propylpyrimidine (**18b**, 150 mg, 0.36 mmol) with $BF_3{\cdot}SMe_2$ (0.76 mL, 7.2 mmol) in dry dichloromethane (5 mL), according to the general procedure **B**, after careful flash column chromatography (30% EtOAc–hexane) over silica gel, gave the pyrimidine **20b** (125 mg, 89%) as a solid. HPLC purity (reversed phase, C18) in two solvents is: MeOH–H_2O (75:25) 100% and CH_3CN–H_2O (60:40) 99.9%. Mp 208–209 °C; ^{1}H NMR (acetone-d_6, 500 MHz) δ 8.69 (2H, s, OH), 8.49 (2H, AA′XX′, J_{AX} = 9.00 and $J_{AA'}$ = 2.40 Hz), 7.40.32 (5H, m, Ph), 7.23 (2H, AA′XX′, J_{AX} = 9.00 and $J_{AA'}$ = 2.4 Hz), 6.97 (2H, AA′XX′, J_{AX} = 8.79 and $J_{AA'}$ = 1.95 Hz), 6.67 (2H, AA′XX′, J_{AX} = 8.79 and $J_{AA'}$ = 1.95 Hz), 2.62 (2H, t, J = 7.57 Hz, $CH_2CH_2CH_3$), 1.73 (2H, quint, J = 7.57 Hz, $CH_2CH_2CH_3$ and 0.85 (3H, t, J = 7.32 Hz, $CH_2CH_2CH_3$); ^{13}C NMR (acetone-d_6, 125 MHz) δ 169.39, 163.79, 162.83, 160.65, 158.85, 138.46, 132.49, 131.23, 131.15, 130.69, 130.66, 129.56, 129.34, 128.19, 116.00, 115.26, 37.94, 22.32 and 14.27. MS (EI, 70 eV) m/z 382 (M^+, 51%), 381 (53%), 353(100%); HRMS calcd for $C_{25}H_{21}N_2O_2$, 381.1603, found: 381.1604.

4-Benzyl-5-ethyl-2,6-bis-(4′-hydroxyphenyl)-pyrimidine (21b). The reaction of 4-benzyl-5-ethyl-2,6-bis-

(4′methoxyphenyl)-pyrimidine (**19b**, 90 mg, 0.21 mmol) with $BF_3{\cdot}SMe_2$ (0.43 mL, 4.2 mmol) in dry dichloromethane (5 mL), according to the general procedure **B**, after careful flash column chromatography (30% EtOAc–hexane) over silica gel, gave the pyrimidine **21b** (78 mg, 93%) as a solid. HPLC purity (reversed phase, C18) in two solvents is: MeOH–H_2O (75:25) 100% and CH_3CN–H_2O (60:40) 99.4%. Mp 197–198 °C; ^{1}H NMR (acetone-d_6, 500 MHz) δ 8.68 (2H, s, OH), 8.36 (2H, AA′XX′, $J_{AX}=9.00$ and $J_{AA'}=2.14$ Hz), 7.47 (2H, AA′XX′, $J_{AX}=9.00$ and $J_{AA'}=2.14$ Hz), 7.40.38 (2H, m, Ar), 7.22.19 (1H, m, Ar), 6.96 (2H, AA′XX′, $J_{AX}=8.79$ and $J_{AA'}=2.14$ Hz), 6.90 (2H, AA′XX′, $J_{AX}=8.79$ and $J_{AA'}=2.14$ Hz), 4.29 (2H, s, CH_2Ph), 2.80 (2H, q, $J=7.50$ Hz, CH_2CH_3) and 1.00 (3H, t, $J=7.50$ Hz); ^{13}C NMR (acetone-d_6, 125 MHz) δ 168.18, 167.16, 161.55, 160.45, 158.83, 139.81, 131.88, 131.05, 130.62, 130.46, 129.99, 129.84, 129.84, 129.21, 127.13, 115.93, 115.77, 41.75, 21.65 and 14.90. MS (EI, 70 eV) *m*/*z* 382 (M^+, 42%), 381 (77%), 73 (100%); HRMS calcd for $C_{25}H_{21}N_2O_2$, 381.1603, found: 381.1607.

4-(4′-Hydroxybenzyl)-2,6-di-(4′-hydroxyphenyl)-5-methylpyrimidine (21c). Deprotection of the pyrimidine **19c** (22 mg, 0.052 mmol) using $BF_3{\cdot}SMe_2$ (20 mg, 1.55 mmol), according to the general procedure **B**, furnished the phenolic pyrimidine **21c** (18 mg, 91%). Mp 252 °C; ^{1}H NMR ($(CD_3)_2CO$, 400 MHz). δ 8.679 (1H, s), 8.677 (1H, s) and 8.17 (1H, s) [3×OH], 8.40 and 6.92 (4H, A_2X_2, $J=8.55$ Hz, C-2 aryl H), 7.55 and 6.95 (4H, A_2X_2, $J=8.55$ Hz, C-6 aryl H), 7.19 and 6.77 (4H, A_2X_2, $J=8.55$ Hz, C-4 aryl H), 4.16 (2H, s, CH_2Ar) and 2.33 (3H, s, CH_3); ^{13}C NMR ($(CD_3)_2CO$, 100 MHz). δ 169.13, 166.04, 161.41, 160.31, 159.00, 156.76, 131.81, 131.34, 130.69, 130.35, 129.61, 123.42, 116.05, 115.87, 115.63, 41.86 and 15.54. MS (EI, 70 eV). *m*/*z* 385 (M+1, 17%), 384 (M^+, 69), 383 (100); HRMS: calcd for $C_{24}H_{19}N_2O_3$ (M−1). 383.1396, found: 383.1393.

4,5-Bis-ethyl-2,6-bis-(4′-hydroxyphenyl)-pyrimidine (20d) and 2,6-bis-(4′-hydroxyphenyl)-5-methyl-4-propylpyrimidine (21d). The reaction of 4,5-bis-ethyl-2,6-bis-(4′-methoxyphenyl)-pyrimidine (**18d**) and 2,6-bis-(4′-methoxyphenyl)-5-methyl-4-propylpyrimidine (**19d**, 220 mg, 0.63 mmol) with $BF_3{\cdot}SMe_2$ (1.23 mL, 12.6 mmol) in dry dichloromethane (15 mL), according to the general procedure **B**, after careful flash column chromatography (40% EtOAc–hexane) over silica gel, gave an inseparable mixture of pyrimidines **20d** and **21d** (180 mg, 89%) as solids. HPLC purity (reversed phase, C18) in two solvents showed that the pyrimidine isomers are separable. MeOH–H_2O (70:30) (65.95 + 33.89 = 98.9%) and CH_3CN–H_2O (40:60) (66.25 + 33.48 = 99.4%). Mp 104–106 °C, ^{1}H NMR (acetone-d_6, 500 MHz) δ 8.66 (2H, s, OH), 8.38 (2H, AA′XX′, $J_{AX}=9.00$ and $J_{AA'}=2.14$ Hz), 7.57 and 7.46 (2H, AA′XX′, $J_{AX}=8.79$ and $J_{AA'}=1.93$ Hz), 6.96 (2H, AA′XX′, $J_{AX}=8.79$ and $J_{AA'}=1.93$ Hz), 6.90 (2H, AA′XX′, $J_{AX}=8.79$ and $J_{AA'}=2.14$ Hz), 2.90 and 2.76 (2H, q, $J=7.50$ Hz,CH_2CH_3), 2.83 (2H, t, $J=7.50$ Hz, CH_2CH_2), 2.35 (3H, s, CH_3), 1.88 (2H, quint, $J=7.50$ Hz, $CH_2CH_2CH_3$), 1.39 and 1.09 (3H, t, $J=7.50$ Hz, CH_2CH_3) and 1.05 (3H, t, $J=7.50$ Hz, CH_2CH_3); ratio of two isomers by ^{1}H NMR is (65.15:34.85). ^{13}C NMR (acetone-d_6, 125 MHz) δ 170.71, 170.04, 166.24, 165.47, 161.45, 161.33, 160.28, 158.99, 158.75, 132.07, 131.85, 131.63, 131.08, 130.94, 130.87, 129.32, 123.16, 115.86, 115.74, 115.66, 37.81, 28.03, 21.59, 21.48, 15.32, 15.26, 14.35, 12.99 and 12.94. MS (EI, 70 eV) *m*/*z* 320 (M^+, 47%), 319 (100%), 291 (75%); HRMS calcd for $C_{20}H_{19}N_2O_2$ 319.1446, found: 319.1441.

4-Butyl-2,6-bis-(4′-hydroxyphenyl)-5-methylpyrimidine (20e) and 2,6-bis-(4′-hydroxyphenyl)-4-ethyl-5-propylpyrimidine (21e). The reaction of 4-butyl-2,6-bis-(4′-methoxyphenyl)-5-methylpyrimidine (**18e**) and 2,6-bis-(4′-methoxyphenyl)-4-ethyl-5-propylpyrimidine (**19e**, 300 mg, 0.83 mmol) with $BF_3{\cdot}SMe_2$ (1.64 mL, 16.6 mmol) in dry dichloromethane (15 mL), according to the general procedure **B**, after careful flash column chromatography (30% EtOAc–hexane) over silica gel, gave an inseparable mixture of pyrimidines **20e** and **21e** (244 mg, 88%) as solids. HPLC purity (reversed phase, C18) in two solvents showed that the pyrimidine isomers are separable. MeOH–H_2O (70:30) (65.95 + 33.89 = 98.9%) and CH_3CN–H_2O (40:60) (66.25 + 33.48 = 99.4%). Mp 96–98 °C, ^{1}H NMR (acetone-d_6, 500 MHz) δ 8.67, 8.65, 8.64 and 8.63 (2H, s, OH), 8.38 (2H, AA′XX′, $J_{AX}=8.79$ Hz), 7.56 and 7.45 (2H, AA′XX′, $J_{AX}=8.58$ and $J_{AA'}=2.14$ Hz), 6.92.90 (2H, m, Ar), 2.92.85 (4H, m, CH_2CH_3 and $CH_2CH_2CH_3$), 2.73.70 (2H, m, $CH_2CH_2CH_3$), 2.36 (3H, s, CH_3), 1.86.80 (2H, m, $CH_2CH_2CH_3$), 1.53.47 (4H, m, $CH_2CH_2CH_2CH_3$), 1.38 and 0.86 (3H, t, $J=7.50$ Hz, CH_2CH_3 and $CH_2CH_2CH_3$) and 0.86 (3H, t, $J=7.50$ Hz, $CH_2CH_2CH_2CH_3$); ratio of two isomers by ^{1}H NMR is (60.56:39.44). ^{13}C NMR (acetone-d_6, 125 MHz) δ 170.81, 170.26, 166.41, 165.49, 161.44, 161.33, 160.35, 160.29, 159.02, 158.74, 132.19, 131.86, 131.64, 131.13, 130.94, 130.87, 130.35, 127.97, 123.11, 115.88, 115.79, 115.74, 115.68, 115.59, 35.60, 28.16, 24.37, 23.33, 15.32, 15.25, 14.31 and 13.02. MS (EI, 70 eV) *m*/*z* 62 (M^+, 50%), 361 (55%), 320 (70%), 84 (100%); HRMS calcd for $C_{21}H_{21}N_2O_2$, 333.1603, found: 333.1609.

General procedure J: preparation of *p*-nitrophenyl esters

The acid chloride (1 mmol) was added dropwise at 0 °C to a stirred solution of *p*-nitrophenol (1 mmol) and pyridine (1.5 mmol) in dichloromethane (5 mL). Stirring was continued for 3 h and water (5 mL) was added. The organic phase was washed with 2 N HCl, brine and dried over anhyd Na_2SO_4. Solvent removal and crystallization from dry ether gave the corresponding ester.

4-Nitrophenyl-4′-methoxybenzoate (23a). *p*-Anisoyl chloride (5.10 g, 30 mmol) was added dropwise to a stirred solution of *p*-nitrophenol (4.17 g, 30 mmol) and pyridine (3.6 mL, 45 mmol) in dichloromethane (100 mL), according to the general procedure J. Crystallization from dry ether gave the ester **23a** (8.0 g, 98%). Mp 165 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.34 (2H, AA′XX′, $J_{AX}=9.00$ Hz), 8.19 (2H, AA′XX′, $J_{AX}=8.79$ Hz), 7.40 (2H, AA′XX′, $J_{AX}=9.00$ Hz), 6.92

(2H, AA′XX′, J_{AX} = 9.00 Hz), 3.86 (3H, s, OMe); MS (EI, 70 eV) *m*/*z* 273 (M^+, 27%), 135 (100%).

4-Nitrophenylacetate (23b). Acetyl chloride (7.8 g, 0.10 mol) was added dropwise to a stirred solution of *p*-nitrophenol (14.0 g, 0.11 mol) and pyridine (10 mL, 0.13 mol) in dichloromethane (60 mL), according to the general procedure J. Crystallization from dry ether gave the ester **23b** (14 g, 76%). Mp 78–79 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.23 (2H, AA′XX′, J_{AX} = 9.00 Hz and $J_{AA'}$ = 2.14 Hz), 7.24 (2H, AA′XX′, J_{AX} = 9.00 Hz and $J_{AA'}$ = 2.14 Hz) and 2.31 (3H, s, CH_3); MS (EI, 70 eV) *m*/*z* 181 (M^+, 75%), 139 (100%).

4-Nitrophenylpropionate (23c). Propionyl chloride (14.0 g, 0.15 mol) was added dropwise to a stirred solution of *p*-nitrophenol (23.1 g, 0.16 mol) and pyridine (20 mL, 0.24 mol) in dichloromethane (100 mL), according to the general procedure J. Crystallization from dry ether gave the ester **23c** (27.0 g, 93%). Mp 63–64 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.27 (2H, AA′XX′, J_{AX} = 9.00 Hz and $J_{AA'}$ = 2.14 Hz), 7.27 (2H, AA′XX′, J_{AX} = 9.00 Hz and $J_{AA'}$ = 2.14 Hz), 2.63 (2H, q, *J* = 7.50 Hz, CH_2CH_3) and 1.28 (3H, t, *J* = 7.50 Hz, CH_2CH_3); MS (EI, 70 eV) *m*/*z* 195 (M^+, 4%), 57 (100%).

4-Nitrophenyl-*n*-butanoate (23d). *n*-Butanoyl chloride (10.6 g, 0.10 mol) was added dropwise to a stirred solution of *p*-nitrophenol (14.0 g, 0.11 mol) and pyridine (10 mL, 0.13 mol) in dichloromethane (60 mL), according to the general procedure J. Removal of solvent under vacuum and product purification by flash column chromatography over silica gel using 10% ethyl acetate in hexane gave the ester **23d** (20.1 g, 99%) as an oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.29 (2H, AA′XX′, J_{AX} = 9.00 Hz and $J_{AA'}$ = 1.95 Hz), 7.28 (2H, AA′XX′, J_{AX} = 9.00 Hz and $J_{AA'}$ = 1.95 Hz), 2.60 (2H, q, *J* = 7.33 Hz, $CH_2CH_2CH_3$), 1.82 (2H, quint, *J* = 7.33 Hz, CH_2 CH_2CH_3) and 1.07 (3H, t, *J* = 7.33 Hz, CH_2CH_3); MS (EI, 70 eV) *m*/*z* 209 (M^+, 2%), 71 (100%).

General procedure K: synthesis of 1,3-diones

Ketone (1 mmol) and dibenzo-18-crown-6-ether (5 mg) dissolved in THF (2 mL) was added dropwise over 10 min at rt to a stirred mixture of NaH (2 mmol, 60% dispersion washed with dry hexane) and ester (1.2 mmol) in THF (5 mL) under dry inert atmosphere. The reaction mixture was refluxed for 3–4 h and reaction progress was monitored by TLC. The reaction mixture was cooled, poured over cool 10% HCl (10 mL) with stirring, and extracted with ethyl acetate. The organic layer was washed with water, satd $NaHCO_3$ soln, brine (5 mL) and dried over anhyd Na_2SO_4. Removal of solvent under vacuum gave the crude product that was purified by flash column chromatography over silica gel using hexane–ethyl acetate or was directly crystallized.

1,2-Bis-(4′-methoxyphenyl)-pentane-1,3-dione (24a). 1-(4′-Methoxyphenyl)-butan-2-one (**22b**, 712 mg, 4 mmol) and dibenzo-18-crown-6-ether (20 mg) dissolved in THF (20 mL) was added dropwise to a stirred mixture of NaH (320 mg, 8 mmol, 60% dispersion washed with dry hexane) and 4-nitrophenyl 4′-methoxybenzoate (**23a**, 1.1 g, 4.2 mmol) in THF (20 mL) under dry inert atmosphere, according to the general procedure K. Crystallization from ethyl acetate gave **24a** (525 mg, 42%). Mp 145–146 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.92 (2H, AA′XX′, J_{AX} = 8.79 and $J_{AA'}$ = 1.95 Hz), 7.25 (2H, AA′XX′, J_{AX} = 8.79 and $J_{AA'}$ = 1.95 Hz), 6.91 (4H, AA′XX′, J_{AX} = 9.00 and $J_{AA'}$ = 1.22 Hz), 5.62 (1H, s, CHAr), 3.85 (3H, s, OMe), 3.79 (3H, s, OMe), 2.63 (1H, dq, *J* = 7.33 and 3.66 Hz, $CH_{AB}CH_3$), 2.51 (1H, dq, *J* = 7.33 and 3.66 Hz, $CH_{AB}CH_3$) and 1.06 (3H, t, *J* = 7.33 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 206.29, 193.93, 163.69, 159.20, 131.19, 130.39, 128.98, 125.79, 114.38, 113.87, 66.12, 55.47, 55.20, 35.32 and 7.86. MS (EI, 70 eV) *m*/*z* 312 (M^+, 28%), 135 (100%). HRMS calcd for $C_{19}H_{20}O_4$, 312.1365, found: 312.1365. Analysis for $C_{19}H_{20}O_4$, calcd C,73.06; H, 6.45; found C,72.74; H, 6.40.

1,2-Bis-(4′-methoxyphenyl)-hexane-1,3-dione (24b). 1-(4′-Methoxyphenyl)-pentan-2-one (**22c**, 960 mg, 5 mmol; prepared according to a literature method)[50] and dibenzo-18-crown-6-ether (25 mg) dissolved in THF (20 mL) were added dropwise to a stirred mixture of NaH (400 mg, 10 mmol, 60% dispersion washed with dry hexane) and 4-nitrophenyl 4′-methoxybenzoate (**23a**, 1.63 g, 6 mmol) in THF (20 mL) under dry inert atmosphere, according to the general procedure K. Flash column chromatography over silica gel using 15% ethyl acetate/hexane and crystallization with ethyl acetate gave **24b** (570 mg, 35%). Mp 107–109 °C, ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.90 (2H, AA′XX′, J_{AX} = 9.00 and $J_{AA'}$ = 2.14 Hz), 7.23 (2H, AA′XX′, J_{AX} = 9.00 and $J_{AA'}$ = 2.14 Hz), 6.88 (4H, AA′XX′, J_{AX} = 9.00 and $J_{AA'}$ = 2.14 Hz), 5.58 (1H, s, CHAr), 3.83 (3H, s, OMe), 3.79 (3H, s, OMe), 2.57 (1H, dq, *J* = 7.72 and 2.78 Hz, $CH_{AB}CH_2$), 2.47 (1H, dq, *J* = 7.72 and 2.78 Hz, $CH_{AB}CH_2$), 1.63.55 (2H, m, $CH_2CH_2CH_3$) and 0.86 (3H, t, *J* = 7.50 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 205.64, 193.92, 163.75, 159.27, 131.21, 130.46, 129.10, 125.73, 114.41, 113.91, 66.36, 55.48, 55.22, 43.90, 17.12 and 13.53. MS (EI, 70 eV) *m*/*z* 326 (M^+, 13%), 256 (20), 139 (100%). HRMS calcd for $C_{20}H_{22}O_4$, 326.1518, found: 326.1515. Analysis for $C_{20}H_{22}O_4$, calcd C, 73.60; H, 6.79; found C, 73.34; H, 6.25.

3-(4′-Methoxyphenyl)-hexane-2,4-dione (24c). 4-Methoxyphenylacetone (**22a**, 5.0 g, 0.03 mol) and dibenzo-18-crown-6-ether (150 mg) dissolved in THF (50 mL) was added dropwise to a stirred mixture of NaH (**23c**, 2.4 g, 0.06 mol, 60% dispersion washed with dry hexane) and 4-nitrophenyl propionate (6.9 g, 0.035 mol) in THF (50 mL) under dry inert atmosphere, according to general procedure K. Flash column chromatography over silica gel using 10% ethyl acetate/hexane gave **24c** (3.5 g, 52%) as oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 16.85 (1H, s, OH), 7.08 (2H, AA′XX′, J_{AX} = 8.79 and $J_{AA'}$ = 2.14 Hz), 6.93 (2H, AA′XX′, J_{AX} = 8.79 and $J_{AA'}$ = 2.14 Hz), 3.85 (3H, s, OMe), 2.17 (2H, q,

$J=7.50$ Hz CH_2CH_3), 1.88 (3H, s, Me), and 1.03 (3H, t, $J=7.50$ Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 196.02, 189.55, 158.88, 132.21, 130.36, 128.81,114.47, 114.12, 113.95, 113.66, 55.19, 30.19, 23.65 and 9.39. MS (EI, 70 eV) m/z 220 (M^+, 98%), 191 (64%), 163 (100%). HRMS calcd for $C_{13}H_{16}O_3$; 220.1106, found: 220.1106.

3-(4′-Methoxyphenyl)-pentane-2,4-dione (24d). 4-Methoxyphenylacetone (**22a**, 5.0 g, 0.03 mol) and dibenzo-18-crown-6-ether (150 mg) dissolved in THF (50 mL) was added dropwise to a stirred mixture of NaH (2.4 g, 0.06 mol, 60% dispersion washed with dry hexane) and 4-nitrophenyl acetate (**23b**, 6.0 g, 0.033 mol) in THF (50 mL) under dry inert atmosphere, according to the general procedure K. Flash column chromatography over silica gel using 10% ethyl acetate/hexane gave **24d** (3.5 g, 57%) as a solid. Mp 70 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 16.67 (1H, s, OH), 7.08 (2H, AA′XX′, $J_{AX}=8.79$ and $J_{AA'}=2.14$ Hz), 6.92 (2H, AA′XX′, $J_{AX}=8.79$ and $J_{AA'}=2.14$ Hz), 3.84 (3H, s, OMe) and 1.89 (3H, s, Me); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 191.18, 158.83, 132.07, 130.31, 129.03, 114.55, 114.11, 55.19 and 24.09. MS (EI, 70 eV) m/z 206 (M^+, 100%), 164 (98%), 121 (84%). HRMS calcd for $C_{12}H_{14}O_3$; 206.0937, found: 206.0938. Analysis for $C_{12}H_{14}O_3$, calcd C,69.88; H, 6.84; found C,70.22; H, 6.89.

3-(4′-Methoxyphenyl)-heptane-2,4-dione (24e). 4-Methoxyphenylacetone (**22a**, 5.0 g, 0.03 mol) and dibenzo-18-crown-6-ether (150 mg) dissolved in THF (50 mL) was added dropwise to a stirred mixture of NaH (2.4 g, 0.06 mol, 60% dispersion washed with dry hexane) and 4-nitrophenyl butanoate (**23c**, 6.5 g, 0.033 mol) in THF (50 mL) under dry inert atmosphere, according to the general procedure K. Flash column chromatography over silica gel using 10% ethyl acetate/hexane gave **24e** (6.2 g, 88%) as an oil, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 16.77 (1H, s, OH), 7.32.96 (2H, m, Ar), 6.94.82 (2H, m, Ar), 6.19 and 5.90 (1H, s, C*H*Ar Z/E isomers), 3.85, 3.82 and 3.80 (3H, s, OMe, Z/E isomers of keto and enol), 2.79.26 (2H, dt, $J=7.32$ and 5.37 Hz, $CH_{AB}CH_2CH_3$, Z/E isomers), 2.07 and 1.88 (3H, s, CH_3, Z/E isomers), 1.77.51 (2H, quint, $J=7.32$ Hz, $CH_2CH_2CH_3$, Z/E isomers) and 1.04.82 (3H, overlapping t, $J=7.32$ Hz, CH_2CH_3, Z/E isomers); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 193.69, 191.35, 171.26, 158.79, 158.36, 146.65, 144.78, 132.25, 130.33, 129.86, 129.36, 128.84, 127.15, 118.03, 115.79, 114.39, 114.06, 113.70, 113.66, 55.19, 55.16, 38.16, 36.29, 36.19, 24.24, 20.57, 18.86, 18.44, 18.27, 17.11, 13.77 and 13.62. MS (EI, 70 eV) m/z 234 (M^+, 73%), 191 (47%), 164 (100%). HRMS calcd for $C_{14}H_{18}O_3$, 234.1256, found: 234.1252.

4-(4′-Methoxyphenyl)-heptane-3,5-dione (24f). 1-(4′-Methoxyphenyl)-butan-2-one (**22b**, which is the same compound as **17c**; 2.5 g, 0.014 mol) and dibenzo-18-crown-6-ether (70 mg) dissolved in THF (20 mL) was added dropwise to a stirred mixture of NaH (1.12 g, 0.028 mol, 60% dispersion washed with dry hexane) and 4-nitrophenyl propionate (**23c**, 3.2 g, 0.016 mol) in THF (25 mL) under dry inert atmosphere, according to the general procedure K. Flash column chromatography over silica gel using 10% ethyl acetate/hexane gave **24f** (2.2 g, 67%) as an oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 16.68 (1H, s, OH), 7.32.07 (2H, m, Ar), 6.94.82 (2H, m, Ar), 6.12 and 5.62 (1H, s, C*H*Ar Z/E isomers), 3.83, 3.80, 3.79 and 3.78 (3H, s, OMe Z/E isomers of keto and enol), 2.79.26 (2H, dq, $J=7.56$ and 3.41 Hz, $CH_{AB}CH_3$ of Z/E isomers), 2.13 (2H, q, $J=7.56$ Hz, CH_2CH_3), 1.25.05 (3H, m, $CH_{AB}CH_3$) and 1.02 (3H, t, $J=7.56$ Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 217.88, 194.44, 158.83, 149.83, 132.29, 130.34, 129.79, 129.41, 128.52, 127.50, 127.49, 127.14, 117.72, 114.12, 114.07, 113.71, 113.68, 113.62, 113.24, 75.85, 55.19, 55.17, 39.21, 29.87, 27.79, 27.31, 26.29, 23.18, 1135, 9.62 and 9.06. MS (EI, 70 eV) m/z 234 (M^+, 22%), 178 (81%), 121 (100%). HRMS calcd for $C_{14}H_{18}O_3$, 234.1256, found: 234.1261.

4-(4′-Methoxyphenyl)-octane-3,5-dione (24g). 1-(4′-Methoxyphenyl)-butan-2-one (**22b**, which is the same compound as **17c**; 2.5 g, 0.014 mol) and dibenzo-18-crown-6-ether (70 mg) dissolved in THF (20 mL) was added dropwise to a stirred mixture of NaH (1.12 g, 0.028 mol, 60% dispersion washed with dry hexane) and 4-nitrophenylbutanoate (**23d**, 3.7 g, 0.016 mol) in THF (25 mL) under dry inert atmosphere, according to the general procedure K. Flash column chromatography over silica gel using 10% ethyl acetate/hexane gave **24g** (3.0 g, 89%) as an oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 16.76 (1H, s, OH), 7.08 (2H, AA′XX′, $J_{AX}=8.79$ and $J_{AA'}=2.19$ Hz), 6.92 (2H, AA′XX′, $J_{AX}=8.79$ and $J_{AA'}=2.19$ Hz), 3.85, 3.82 and 3.79 (3H, s, OMe, Z/E isomers of keto and enol), 2.14 (2H, q, $J=7.33$, CH_2CH_3), 2.09 (2H, t, $J=7.33$ Hz, $CH_2CH_2CH_3$), 1.54 (2H, quint, $J=7.33$ and 7.57 Hz, $CH_2CH_2CH_3$), 1.57 (3H, t, $J=7.57$ Hz, CH_2CH_3) and 0.86 (3H, t, $J=7.57$ Hz, $CH_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 196.22, 192.01, 158.79, 132.39, 128.58, 114.04, 113.77, 113.65, 55.21, 37.83, 30.37, 19.03, 13.81 and 9.45. MS (EI, 70 eV) m/z 248 (M^+, 100%), 219 (60%), 178 (70%). HRMS calcd for $C_{15}H_{20}O_3$, 248.1412, found: 248.1411.

General procedure L: synthesis of pyrimidines from 1,3-diones

Glacial acetic acid (0.2 mL), followed by anhyd ammonium acetate (0.8 g, 10 mmol) at rt was added to a stirred solution of the 1,3-dione (1 mmol) and *p*-anisaldehyde (**25**, 1 mmol) in dry DMSO (2 mL). The reaction mixture was heated to 80–90 °C under dry air atmosphere for 10–12 h. Dichloromethane (10 mL) and water (5 mL) were added to the cooled reaction mixture. The organic phase was washed with brine (5 mL) and dried over anhyd Na_2SO_4. Solvent was removed under vacuum and the crude product was purified by flash column chromatography over silica gel using hexane–ethyl acetate.

4-Ethyl-2,5,6-tris-(4′-methoxyphenyl)-pyrimidine (26a). The reaction of 1,2-bis-(4′-methoxyphenyl)-pentane-1,3-dione (**24a**, 200 mg, 0.64 mmol) with *p*-anisaldehyde (**25**, 87 mg, 0.64 mmol) in dry DMSO (2 mL), glacial acetic acid (0.15 mL) and anhyd ammonium acetate (0.5 g, 6.5 mmol), according to the general procedure L, after

careful flash column chromatography (10% EtOAc–hexane) over silica gel and crystallization from ethanol, gave the pyrimidine **26a** (48 mg, 18%) as solids. Mp 152–153 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.58 (2H, AA′XX′, J_{AX} = 9.00 and $J_{AA'}$ = 2.19 Hz), 7.43 (2H, AA′XX′, J_{AX} = 9.00 and $J_{AA'}$ = 2.19 Hz), 7.06 (2H, AA′XX′, J_{AX} = 9.00 and $J_{AA'}$ = 2.19 Hz), 6.92 (2H, AA′XX′, J_{AX} = 8.79 and $J_{AA'}$ = 2.19 Hz), 6.83 (2H, AA′XX′, J_{AX} = 8.79 and $J_{AA'}$ = 2.19 Hz), 6.77 (2H, AA′XX′, J_{AX} = 8.79 and $J_{AA'}$ = 1.95 Hz), 3.91 (3H, s, OMe), 3.86 (3H, s, OMe), 3.81 (3H, s, OMe), 2.71 (2H, q, J = 7.50 Hz, CH_2CH_3) and 1.27 (3H, t, J = 7.50 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.32, 162.77, 162.09, 161.45, 159.80, 158.76, 131.52, 131.37, 131.28, 130.99, 129.77, 129.32, 128.16, 113.99, 113.63, 113.08, 55.31, 55.19, 55.15, 28.83 and 12.89. MS (EI, 70 eV) m/z 426 (M^+, 87%), 425 (100%); HRMS calcd for $C_{27}H_{26}N_2O_3$, 426.1943, found: 426.1931.

4-Propyl-2,5,6-tris-(4′-methoxyphenyl)-pyrimidine (26b). The reaction of 1,2-bis-(4′-methoxyphenyl)-hexane-1,3-dione (**24b**, 240 mg, 0.73 mmol) with *p*-anisaldehyde (**25**, 100 mg, 0.73 mmol) in dry DMSO (2 mL), glacial acetic acid (0.15 mL) and anhyd ammonium acetate (0.6 g, 8 mmol), according to the general procedure L, after careful flash column chromatography (10% EtOAc–hexane) over silica gel and crystallization from ethanol, gave the pyrimidine **26b** (70 mg, 22%) as a solid. Mp 130–131 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.56 (2H, AA′XX′, J_{AX} = 9.00 and $J_{AA'}$ = 1.93 Hz), 7.41 (2H, AA′XX′, J_{AX} = 8.79 and $J_{AA'}$ = 1.94 Hz), 7.05 (2H, AA′XX′, J_{AX} = 8.79 and $J_{AA'}$ = 2.14 Hz), 7.00 (2H, AA′XX′, J_{AX} = 8.79 and $J_{AA'}$ = 1.93 Hz), 6.89 (2H, AA′XX′, J_{AX} = 8.79 and $J_{AA'}$ = 1.95 Hz), 6.76 (2H, AA′XX′, J_{AX} = 9.00 and $J_{AA'}$ = 2.14 Hz), 3.88 (3H, s, OMe), 3.86 (3H, s, OMe), 3.85 (3H, s, OMe), 2.65 (2H, t, J = 7.50 Hz, CH_2CH_2), 1.78 (2H, quint, J = 7.5 and 7.3 Hz, $CH_2CH_2CH_3$) and 0.91 (3H, t, J = 7.30 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.33, 162.91, 162.02, 161.49, 159.85, 158.78, 131.54, 131.47, 131.38, 131.06, 129.79, 129.41, 128.52, 113.98, 113.66, 113.10, 55.13, 55.14, 37.33, 21.90 and 14.05. MS (EI, 70 eV) m/z 440 (M^+, 65%), 412 (100%); HRMS calcd for $C_{28}H_{28}N_2O_3$, 440.2097, found: 440.2097.

4-Ethyl-2,5-bis-(4′-methoxyphenyl)-6-methylpyrimidine (26c). The reaction of 3-(4′-methoxyphenyl)-hexane-1,3-dione (**24c**, 1.1 g, 5 mmol) with *p*-anisaldehyde (**25**, 680 mg, 5 mmol) in dry DMSO (10 mL), glacial acetic acid (1 mL) and anhyd ammonium acetate (4 g, 53 mmol), according to the general procedure L, after careful flash column chromatography (10% EtOAc–hexane) over silica gel and crystallization from ethanol, gave the pyrimidine **26c** (65 mg, 4%) as a solid. Mp 132–133 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.48 (2H, AA′XX′, J_{AX} = 9.00 and $J_{AA'}$ = 2.14 Hz), 7.13 (2H, AA′XX′, J_{AX} = 8.79 and $J_{AA'}$ = 1.93 Hz), 7.01 (4H, AA′XX′, J_{AX} = 8.79 and $J_{AA'}$ = 2.14 Hz), 3.90 (3H, s, OMe), 3.89 (3H, s, OMe), 2.59 (2H, q, J = 7.50 Hz, CH_2CH_3), 2.32 (3H, s, CH_3) and 1.27 (3H, t, J = 7.50 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.87, 164.85, 162.12, 161.42, 159.03, 131.04, 130.29, 130.05, 129.67, 129.13, 114.16, 113.72, 55.31, 55.25, 28.64, 23.32 and 12.82. MS (EI, 70 eV) m/z 334 (M^+, 82%), 333 (100%); HRMS calcd for $C_{21}H_{22}N_2O_2$, 333.1603, found: 333.1602.

4,6-Bis-methyl-2,5-bis-(4′-methoxyphenyl)-pyrimidine (26d). The reaction of 3-(4′-methoxyphenyl)-pentane-2,4-dione (**24d**, 2.06 g, 10 mmol) with *p*-anisaldehyde (**25**, 1.36 mg, 10 mmol) in dry DMSO (15 mL), glacial acetic acid (2 mL) and anhyd ammonium acetate (8 g, 0.11 mol), according to the general procedure L, after careful flash column chromatography (10% EtOAc–hexane) over silica gel and crystallization from ethanol, gave the pyrimidine **26d** (160 mg, 5%) as a solid. Mp 120–121 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.43 (2H, AA′XX′, J_{AX} = 9.00 and $J_{AA'}$ = 2.14 Hz), 7.11 (2H, AA′XX′, J_{AX} = 8.79 and $J_{AA'}$ = 2.14 Hz), 6.99 (4H, AA′XX′, J_{AX} = 9.00 and $J_{AA'}$ = 2.14 Hz), 3.88 (3H, s, OMe), 3.87 (3H, s, OMe) and 2.31 (6H, s, 2×CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.76, 161.99, 161.46, 159.06, 130.81, 130.59, 130.18, 129.65, 129.28, 114.25, 113.76, 55.31, 55.26 and 23.26. MS (EI, 70 eV) m/z 320 (M^+ 100%), 146 (30%); HRMS calcd for $C_{20}H_{20}N_2O_2$, 320.1525, found: 320.1519.

2,5-Bis-(4′-methoxyphenyl)-6-methyl-4-propylpyrimidine (26e). The reaction of 3-(4′-methoxyphenyl)-heptane-2,4-dione (**24e**, 2.34 g, 10 mmol) with and *p*-anisaldehyde (**25**, 1.36 mg, 10 mmol) in dry DMSO (15 mL), glacial acetic acid (2 mL) and anhyd ammonium acetate (8 g, 0.11 mol), according to the general procedure L, after careful flash column chromatography (10% EtOAc–hexane) over silica gel and crystallization from ethanol gave the pyrimidine **26e** (300 mg, 9%) as a solid. Mp 136–137 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.47 (2H, AA′XX′, J_{AX} = 8.79 and $J_{AA'}$ = 1.93 Hz), 7.12 (2H, AA′XX′, J_{AX} = 8.58 and $J_{AA'}$ = 1.93 Hz), 7.01 (4H, AA′XX′, J_{AX} = 8.58 and $J_{AA'}$ = 2.14 Hz), 3.90 (3H, s, OMe), 3.89 (3H, s, OMe), 2.54 (2H, t, J = 7.50 Hz, $CH_2CH_2CH_3$), 2.34 (3H, s, CH_3), 1.74 (2H, quint, J = 7.50 Hz, $CH_2CH_2CH_3$) and 0.89 (3H, t, J = 7.50 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.79, 164.92, 162.01, 161.39, 158.98, 131.05, 130.41. 130.36, 129.66, 129.18, 114.10, 113.72, 55.31, 55.25, 37.15, 23.40, 21.84 and 14.00. MS (EI, 70 eV) m/z 348 (M^+ 45%), 320 (100%); HRMS calcd for $C_{22}H_{24}N_2O_2$, 348.1838, found: 348.1828. Analysis for $C_{22}H_{24}N_2O_2$, calcd C,75.83; H, 6.94; N, 8.04, found C,75.85; H, 6.95; N, 7.89.

4,6-Bis-ethyl-2,5-bis-(4′-methoxyphenyl)-pyrimidine (26f). The reaction of 4-(4′-methoxyphenyl)-heptane-3,5-dione (**24f**, 1.17 g, 5 mmol) with *p*-anisaldehyde (**25**, 680 mg, 5 mmol) in dry DMSO (10 mL), glacial acetic acid (1 mL) and anhyd ammonium acetate (4 g, 53 mmol), according to the general procedure L, after careful flash column chromatography (10% EtOAc–hexane) over silica gel and crystallization from ethanol, gave the pyrimidine **26f** (170 mg, 10%) as a solid. Mp 142–143 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.52 (2H, AA′XX′, J_{AX} = 9.00 and $J_{AA'}$ = 2.14 Hz), 7.14 (2H, AA′XX′, J_{AX} = 8.79 and $J_{AA'}$ = 1.93 Hz), 7.01 (4H, AA′XX′, J_{AX} = 8.79 and $J_{AA'}$ = 2.14 Hz), 3.90 (3H, s, OMe), 3.89 (3H, s, OMe), 2.56 (4H, q, J = 7.72 Hz,

2×CH_2CH_3) and 1.22 (6H, t, J = 7.72 Hz, 2×CH_2CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.98, 162.25, 161.38, 158.98, 131.29, 130.47, 130.37, 129.69, 129.51, 128.94, 114.04, 113.68, 55.31, 55.24, 28.72 and 12.86. MS (EI, 70 eV) m/z 348 (M^+ 15%), 347 (28%), 121 (100%); HRMS calcd for $C_{22}H_{24}N_2O_2$, 347.1761, found: 347.1761.

6-Ethyl-2,5-bis-(4′-methoxyphenyl)-4-propylpyrimidine (26g). The reaction of 4-(4′-methoxyphenyl)-octan-3,5-dione (**24g**, 2.48 g, 10 mmol) with *p*-anisaldehyde (**25**, 1.36 mg, 10 mmol) in dry DMSO (15 mL), glacial acetic acid (2 mL) and anhyd ammonium acetate (8 g, 0.11 mol), according to the general procedure L, after careful flash column chromatography (10% EtOAc –hexane) over silica gel and crystallization from ethanol, gave the pyrimidine **26g** (220 mg, 6%) as a solid. Mp 120–121 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.42 (2H, AA′XX′, J_{AX} = 8.79 and $J_{AA'}$ = 1.93 Hz), 7.13 (2H, AA′XX′, J_{AX} = 8.58 and $J_{AA'}$ = 1.93 Hz), 7.02.79 (4H, m, Ar), 3.90 (3H, s, OMe), 3.89 (3H, s, OMe), 2.53 (2H, q, J = 7.40 Hz, CH_2CH_3), 2.52 (2H, t, J = 7.50 Hz, $CH_2CH_2CH_3$), 1.74 (2H, quint, J = 7.50 Hz, $CH_2CH_2CH_3$), 1.21 (3H, t, J = 7.40 Hz, CH_2CH_3) and 0.89 (3H, t, J = 7.50 Hz, $CH_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.03, 167.89, 162.12, 161.36, 158.95, 131.29, 130.52, 130.36, 129.85, 129.68, 128.99, 113.99, 113.67, 55.31, 55.23, 37.24, 28.78, 21.87, 14.02 and 12.84. MS (EI, 70 eV) m/z 362 (M^+ 62%), 334 (100%); HRMS calcd for $C_{23}H_{26}N_2O_2$, 362.1994, found: 362.1989. Analysis for $C_{23}H_{26}N_2O_2$, calcd C,76.21; H, 7.23; N, 7.73, found C,76.18; H, 7.22; N, 7.69.

4-Ethyl-2,5,6-tris-(4′-hydroxyphenyl)-pyrimidine (27a). The reaction of 4-ethyl-2,5,6-tris-(4′-methoxyphenyl)-pyrimidine (**26a**, 60 mg, 0.14 mmol) with $BF_3{\cdot}SMe_2$ (0.43 mL, 4.2 mmol) in dry dichloromethane (5 mL), according to the general procedure **B**, after careful flash column chromatography (30% EtOAc–hexane) over silica gel, gave the pyrimidine **27a** (78 mg, 93%) as a solid. HPLC purity (reversed phase, C18) in two solvents: MeOH–H_2O (70:30) 100% and CH_3CN–H_2O (40:60) 100%. Mp 234–235 °C; ^{1}H NMR (acetone-d_6, 500 MHz) δ 8.59 (3H, bs, OH), 8.48 (2H, AA′XX′, J_{AX} = 9.00 and $J_{AA'}$ = 2.14 Hz), 7.38 (2H, AA′XX′, J_{AX} = 8.79 and $J_{AA'}$ = 2.14 Hz), 7.04 (2H, AA′XX′, J_{AX} = 8.57 and $J_{AA'}$ = 2.14 Hz), 6.96 (2H, AA′XX′, J_{AX} = 9.00 and $J_{AA'}$ = 2.14 Hz), 6.87 (2H, AA′XX′, J_{AX} = 8.57 and $J_{AA'}$ = 2.14 Hz), 6.70 (2H, AA′XX′, J_{AX} = 9.00 and $J_{AA'}$ = 2.14 Hz), 2.66 (2H, q, J = 7.50 Hz, CH_2CH_3) and 1.21 (3H, t, J = 7.50 Hz, CH_2CH_3); ^{13}C NMR (acetone-d_6, 125 MHz) δ 170.92, 163.88, 162.64, 160.57, 158.79, 157.68, 132.50, 132.25, 131.38, 130.82, 130.60, 129.19, 129.06, 116.35, 115.97, 115.25, 29.29 and 13.01. MS (EI, 70 eV) m/z 384 (M^+, 75%), 383 (100%), 135 (34%); HRMS calcd for $C_{24}H_{20}N_2O_3$, 384.1474, found: 384.1475.

4-Propyl-2,5,6-tris-(4′-hydroxyphenyl)-pyrimidine (27b). The reaction of 4-propyl-2,5,6-tris-(4′-methoxyphenyl)-pyrimidine (**26b**, 120 mg, 0.27 mmol) with $BF_3{\cdot}SMe_2$ (0.83 mL, 8.1 mmol) in dry dichloromethane (10 mL), according to the general procedure **B**, after careful flash column chromatography (30% EtOAc–hexane) over silica gel, gave the pyrimidine **27b** (98 mg, 90%) as a solid. HPLC purity (reversed phase, C18) in two solvents is: MeOH–H_2O (70:30) 100% and CH_3CN–H_2O (40:60) 100%. Mp 170–171 °C; ^{1}H NMR (acetone-d_6, 500 MHz) δ 8.58 (3H, s, OH), 8.48 (2H, AA′XX′, J_{AX} = 8.79 and $J_{AA'}$ = 2.14 Hz), 7.37 (2H, AA′XX′, J_{AX} = 8.79 and $J_{AA'}$ = 1.94 Hz), 7.05 (2H, AA′XX′, J_{AX} = 8.57 and $J_{AA'}$ = 2.14 Hz), 6.97 (2H, AA′XX′, J_{AX} = 8.79 and $J_{AA'}$ = 2.14 Hz), 6.87 (2H, AA′XX′, J_{AX} = 8.57 and $J_{AA'}$ = 2.14 Hz), 6.69 (2H, AA′XX′, J_{AX} = 9.00 and $J_{AA'}$ = 2.14 Hz), 2.63 (2H, t, J = 7.50 Hz, CH_2CH_2), 1.75 (2H, quint, J = 7.5 and 7.3 Hz, $CH_2CH_2CH_3$) and 0.87 (3H, t, J = 7.30 Hz, CH_2CH_3); ^{13}C NMR (acetone-d_6, 125 MHz) δ 169.82, 163.95, 162.52, 160.52, 158.75, 157.60, 132.49, 132.30, 131.41, 130.82, 130.59, 129.49, 129.08, 116.29, 115.29, 115.96, 115.23, 37.93, 22.36 and 14.31. MS (EI, 70 eV) m/z 398 (M^+, 55%), 397 (43%), 370 (100%); HRMS calcd for $C_{25}H_{21}N_2O_3$, 397.1552, found: 397.1553.

4-Ethyl-2,5-bis-(4′-hydroxyphenyl)-6-methylpyrimidine (27c). The reaction of 4-ethyl-2,5-bis-(4′-methoxyphenyl)-6-methylpyrimidine (**26c**, 80 mg, 0.24 mmol) with $BF_3{\cdot}SMe_2$ (0.85 mL, 8.4 mmol) in dry dichloromethane (10 mL), according to general the procedure, after careful flash column chromatography (30% EtOAc–hexane) over silica gel, gave the pyrimidine **27c** (65 mg, 89%) as a solid. HPLC purity (reversed phase, C18) in two solvent is: MeOH–H_2O (70:30) 100% and CH_3CN–H_2O (40:60) 100%. Mp 178–179 °C; ^{1}H NMR (acetone-d_6, 500 MHz) δ 8.62 (2H, s, OH), 8.42 (2H, AA′XX′, J_{AX} = 8.79 and $J_{AA'}$ = 2.14 Hz), 7.12 (2H, AA′XX′, J_{AX} = 8.79 and $J_{AA'}$ = 1.93 Hz), 7.00 (4H, AA′XX′, J_{AX} = 8.79 and $J_{AA'}$ = 2.14 Hz), 2.54 (2H, q, J = 7.50 Hz, CH_2CH_3), 2.23 (3H, s, CH_3) and 1.17 (3H, t, J = 7.50 Hz, CH_2CH_3); ^{13}C NMR (acetone-d_6, 125 MHz) δ 169.29, 165.51, 162.49, 160.49, 157.89, 131.25, 131.06, 130.71, 130.52, 128.65, 116.48, 115.94, 23.42 and 12.99. MS (EI, 70 eV) m/z 306 (M^+, 45%), 305 (100%); HRMS calcd for $C_{19}H_{17}N_2O_2$, 305.1289, found: 305.1289.

4,6-Bis-methyl-2,5-bis-(4′-hydroxyphenyl)-pyrimidine (27d). The reaction of 4,6-bis-methyl-2,5-bis-(4′-methoxyphenyl)-pyrimidine (**26d**, 120 mg, 0.38 mmol) with $BF_3{\cdot}SMe_2$ (0.78 mL, 7.6 mmol) in dry dichloromethane (10 mL), according to the general procedure **B**, after careful flash column chromatography (30% EtOAc–hexane) over silica gel, gave the pyrimidine **27d** (102 mg, 92%) as a solid. HPLC purity (reversed phase, C18) in two solvent is: MeOH–H_2O (60:40) 99.86% and CH_3CN–H_2O (40:60) 100%. Mp 195–196 °C; ^{1}H NMR (acetone-d_6, 500 MHz) δ 8.63 (2H, s, OH), 8.39 (2H, AA′XX′, J_{AX} = 8.79 and $J_{AA'}$ = 2.14 Hz), 7.13 (2H, AA′XX′, J_{AX} = 8.79 and $J_{AA'}$ = 2.14 Hz), 6.97 (2H, AA′XX′, J_{AX} = 8.79 and $J_{AA'}$ = 2.14 Hz), 6.92 (2H, AA′XX′, J_{AX} = 9.00 and $J_{AA'}$ = 2.14 Hz) and 2.25 (6H, s, 2×CH_3); ^{13}C NMR (acetone-d_6, 125 MHz) δ 165.25, 162.23, 160.50, 157.89, 131.53, 131.14, 130.50, 128.87, 116.51, 115.94 and 23.33. MS (EI, 70 eV) m/z 292 (M^+ 100%), 132 (42%), 291 (28%); HRMS calcd for $C_{18}H_{15}N_2O_2$, 291.1133, found: 291.1133.

2,5-Bis-(4′-hydroxyphenyl)-6-methyl-4-propylpyrimidine (27e). The reaction of 2,5-bis-(4′-methoxyphenyl)-6-methyl-4-propylpyrimidine (**26e**, 200 mg, 0.57 mmol) with $BF_3{\cdot}SMe_2$ (1.15 mL, 11.4 mmol) in dry dichloromethane (10 mL), according to the general procedure **B**, after careful flash column chromatography (30% EtOAc–hexane) over silica gel, gave the pyrimidine **27e** (168 mg, 92%) as a solid. HPLC purity (reversed phase, C18) in two solvent is: MeOH–H_2O (70:30) 99.19% and CH_3CN–H_2O (50:50) 99.76%. Mp 140–141 °C; ^{1}H NMR (acetone-d_6, 500 MHz) δ 8.69 (1H, s, OH), 8.54 (1H, s, OH), 8.40 (2H, AA′XX′, $J_{AX}=9.00$ and $J_{AA'}=2.14$ Hz), 7.10 (2H, AA′XX′, $J_{AX}=8.58$ and $J_{AA'}=2.14$ Hz), 6.96 (4H, AA′XX′, $J_{AX}=8.58$ and $J_{AA'}=2.14$ Hz), 6.94 (4H, AA′XX′, $J_{AX}=8.79$ and $J_{AA'}=2.14$ Hz), 2.51 (2H, t, $J=7.72$ Hz, $CH_2CH_2CH_3$), 2.24 (3H, s, CH_3), 1.71 (2H, quint, $J=7.72$ Hz, $CH_2CH_2CH_3$) and 0.84 (3H, t, $J=7.72$ Hz, CH_2CH_3); ^{13}C NMR (acetone-d_6, 125 MHz) δ 168.18, 165.59, 162.37, 160.50, 157.88, 131.42, 131.32, 130.71, 130.51, 128.69, 116.44, 115.94, 37.73, 23.49, 22.33 and 14.25. MS (EI, 70 eV) m/z 320 (M^+ 32%), 319 (25%), 291 (100%); HRMS calcd for $C_{20}H_{19}N_2O_2$, 319.1447, found: 319.1447.

4,6-Bis-ethyl-2,5-bis-(4′-hydroxyphenyl)-pyrimidine (27f). The reaction of 4,6-bis-ethyl-2,5-bis-(4′-methoxyphenyl)-pyrimidine (**26f**, 150 mg, 0.36 mmol) with $BF_3{\cdot}SMe_2$ (0.68 mL, 6.7 mmol) in dry dichloromethane (10 mL), according to the general procedure **B**, after careful flash column chromatography (30% EtOAc–hexane) over silica gel, gave the pyrimidine **27f** (130 mg, 92%) as a solid. HPLC purity (reversed phase, C18) in two solvent is: MeOH–H_2O (70:30) 100% and CH_3CN–H_2O (40:60) 100%. Mp 203–204 °C; ^{1}H NMR (acetone-d_6, 500 MHz) δ 8.63 (2H, s, OH), 8.44 (2H, AA′XX′, $J_{AX}=8.79$ and $J_{AA'}=2.14$ Hz), 7.11 (2H, AA′XX′, $J_{AX}=8.79$ and $J_{AA'}=2.14$ Hz), 7.01 (4H, AA′XX′, $J_{AX}=8.79$ and $J_{AA'}=2.14$ Hz), 2.53 (4H, q, $J=7.72$ Hz, $2\times CH_2CH_3$) and 1.17 (6H, t, $J=7.72$ Hz, $2\times CH_2CH_3$); ^{13}C NMR (acetone-d_6, 125 MHz) δ 169.51, 162.69, 160.47, 157.87, 131.39, 130.86, 130.55, 130.52, 128.33, 116.39, 115.93, 29.17 and 12.99. MS (EI, 70 eV) m/z 320 (M^+ 43%), 319 (100%); HRMS calcd for $C_{20}H_{19}N_2O_2$, 319.1446, found: 319.1440.

6-Ethyl-2,5-bis-(4′-hydroxyphenyl)-4-propylpyrimidine (27g). The reaction of 6-ethyl-2,5-bis-(4′-methoxyphenyl)-4-propylpyrimidine (**26g**, 400 mg, 1.1 mmol) with $BF_3{\cdot}SMe_2$ (2.2 mL, 22 mmol) in dry dichloromethane (10 mL), according to the general procedure **B**, after careful flash column chromatography (30% EtOAc–hexane) over silica gel, gave the pyrimidine **27g** (330 mg, 89%) as a solid. HPLC purity (reversed phase, C18) in two solvent is: MeOH–H_2O (70:30) 99.91% and CH_3CN–H_2O (40:60) 99.90%. Mp 160–161 °C; ^{1}H NMR (acetone-d_6, 500 MHz) δ 8.70 (1H, s, OH), 8.55 (1H, s, OH), 8.43 (2H, AA′XX′, $J_{AX}=8.79$ and $J_{AA'}=1.93$ Hz), 7.09 (2H, AA′XX′, $J_{AX}=8.58$ and $J_{AA'}=2.14$ Hz), 6.99.92 (4H, m, Ar), 2.55.48 (4H, m, CH_2CH_3 and $CH_2CH_2CH_3$), 1.70 (2H, quint, $J=7.50$ Hz, $CH_2CH_2CH_3$), 1.65 (3H, t, $J=7.50$ Hz, CH_2CH_3) and 0.84 (3H, t, $J=7.50$ Hz, $CH_2CH_2CH_3$); ^{13}C NMR (acetone-d_6, 125 MHz) δ 169.61, 168.43, 162.59, 160.50, 157.89, 133.15, 131.48, 130.94, 130.86, 130.53, 128.39, 116.92, 116.38, 116.29, 115.95, 115.85, 37.85, 37.85, 29.24, 22.34, 14.27 and 12.99. MS (EI, 70 eV) m/z 334 (M^+ 19%), 284 (55%), 58 (100%); HRMS calcd for $C_{21}H_{22}N_2O_2$, 334.1681, found: 334.1672.

Biological methods

General biological methods. Cell culture media were purchased from Gibco BRL (Grand Island, NY, USA). Calf serum was obtained from Hyclone Laboratories, Inc. (Logan, UT, USA), and fetal calf serum was purchased from Atlanta Biologicals (Atlanta, GA, USA). The luciferase assay system was from Promega (Madison, WI, USA). The expression vector for human ERα (pCMV5-hERα) was constructed previously as described.[51] The expression vector pCMV5-ERβ was constructed by inserting the cDNA encoding the full length human ERβ (530 residues;[7] into the *Bam*HI site of pCMV5. The estrogen responsive reporter plasmid was $(ERE)_2$-pS2-Luc, and was constructed by inserting the $(ERE)_2$-pS2 fragment from $(ERE)_2$-pS2-CAT into the *Mlu*I/*Bgl*II sites of pGL3-Basic vector (Promega, Madison, WI, USA). The plasmid pCMVβ (Clontech, Palo Alto, CA, USA), which contains the β-galactosidase gene, was used as an internal control for transfection efficiency.

Hormone binding assays. Binding affinities of each compound for ERα and ERβ were determined in a radiometric competitive binding assay, using [^{3}H]estradiol as tracer and hydroxylapatite to adsorb ligand–receptor complex.[14,36] Receptor preparations were human ERα and ERβ, expressed in baculovirus and purified (PanVera, Madison, WI, USA). Values given represent the mean of 2–3 repeat determinations which have a coefficient of variation of 0.3.

Cell culture and transient transfections. Human endometrial cancer (HEC-1) cells were maintained in culture as described.[37] Transfection of HEC-1 cells in 24-well plates used a mixture of 0.35 mL of serum-free IMEM medium and 0.15 mL of HBSS containing 5 μL of lipofectin (Life Technologies, Rockville, MD, USA), 1.6 μg of transferrin (Sigma, St. Louis, MO, USA), 0.5 μg of pCMVβ-galactosidase as internal control, 1 or 2 μg of the reporter gene plasmid, 100 or 250 ng of ER expression vector, and carrier DNA to a total of 3 μg DNA per well. The cells were incubated at 37 °C in a 5% CO_2 containing incubator for 6 h. The medium was then replaced with fresh medium containing the desired concentrations of ligands. Reporter gene activity was assayed at 24 h after ligand addition. Luciferase activity, normalized for the internal control β-galactosidase activity, was assayed as described.[37]

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