Pyrazolo[1,5-*a*]pyrimidines: Estrogen Receptor Ligands Possessing Estrogen Receptor *β* Antagonist Activity

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In our search for novel subtype-selective estrogen receptor (ER) ligands, we have examined various heterocyclic units as core structural elements. Here, we have investigated the fused, bicyclic pyrazolo[1,5-*a*]pyrimidine core, which is a system that allows for analogues to be readily assembled in a library-like fashion. This series of pyrazolo[1,5-*a*]pyrimidine ER ligands provided us with a new pharmacological profile for an ER ligand: compounds that are passive on both ERs, with a distinct potency selectivity in favor of ER*β*. The most distinctive ligand in this series, 2-phenyl-3-(4-hydroxyphenyl)-5,7-bis(trifluoromethyl)-pyrazolo[1,5-*a*]pyrimidine, was 36-fold selective for ER*β* in binding. Curiously, on the basis of molecular modeling, the ER*β* binding selectivity of compounds in this series appears to be derived from differing orientations that they adapt in the ligand binding pockets of ERα vs ER*β*. In transcription assays this pyrazolopyrimidine was fully effective as an ER*β* antagonist while exhibiting no significant activity on ERα. Thus, this ligand functions as a potency- and efficacy-selective ER*β* antagonist that would abrogate estrogen action through ER*β* with minimal effects on its activity through ERα; as such, it could be used to study the biological function of ER*β*.

Introduction

The estrogen receptor (ER)[1,2] is a member of the superfamily of ligand-regulated nuclear transcription factors that mediates the action of estrogens and has as its primary endogenous ligand 17*β*-OH estradiol (E2). The ER is widely distributed throughout the body, being found in reproductive tissues (uterus and breast) but also in bone, brain, and the cardiovascular system. The ER is a pharmaceutical target of interest for the prevention and treatment of breast cancer, as well as for hormone replacement therapy to prevent osteoporosis and mitigate menopausal symptoms.[3−5] The term selective estrogen receptor modulators (SERMs) has been coined to describe ER ligands that show a desirable balance of tissue-selective effects, being agonists in the brain, liver, bone, and cardiovascular system and being antagonists in the breast and uterus.[1,2,6,7] The ability to optimally target the ER is complicated by the presence of two receptor subtypes, ERα and ER*β*, themselves having differing tissue distributions.[8,9] These subtypes share high sequence homology in the binding pocket, with 24 of the 26 amino acid residues being identical and the two differences being conservative.[10]

The ER is able to accept a wide variety of structurally distinct ligands into its binding pocket, a topic that has recently been reviewed by Anstead,[11] Gao,[12] and Meegan.[13] Among these diverse systems are numerous heterocycles[14−17] including fused bicyclic systems such as benzothiophenes,[18,19] indoles,[20] benzofurans,[21] and indolizines[22,23] (Figure 1), as well as recently reported benzoxazole[24,25] and benzothiazole[25,26] ER*β*-selective ligands. The majority of these fused heterocycles contain only a single heteroatom.

To extend the structural scope of ER ligands, we are exploring fused bicyclic systems that contain multiple heteroatoms. In this search, we sought to design a ligand core structure that could be varied in size and would embody multiple nitrogen atoms to have some polarity while still being largely hydrophobic. To this end, we began exploring pyrazolo[1,5-*a*]pyrimidines as a core scaffold onto which additional substituents could be attached to produce ER ligands. Although a few examples of pyrazolo[1,5-*a*]pyrimidine pharmaceuticals can be found in the literature,[27−30] the substituents thus far described are not appropriate for ER ligands.

Figure 1 illustrates the numbering system used for pyrazolo[1,5-*a*]pyrimidines and our vision of how the pyrazolo[1,5-*a*]pyrimidine system might act as a scaffold for the construction of an ER ligand. Originally, we imagined that it might be possible for the pyrimidine ring of a 6-hydroxypyrazolo[1,5-*a*]pyrimidine to function as the A-ring mimic of estradiol, in a fashion that would be geometrically congruent with the orientation of other [6,5]-fused bicyclic heterocyclic core ER ligands such as raloxifene. However, on the basis of our initial work on this system, described elsewhere, we believe that this is unlikely.[31] Thus, we have pursued an alternative approach, substituting the pyrazolo[1,5-*a*]pyrimidine core with aromatic rings at the 2 and 3 positions. By making at least one of these aromatic rings a phenol, we would provide a functionality that is capable of hydrogen-bonding that can potentially act as an A-ring mimic of the natural ligand E2, in a "pendant phenol" orientation thought to be adopted by certain other fused heterocyclic systems[32−34] and illustrated in certain

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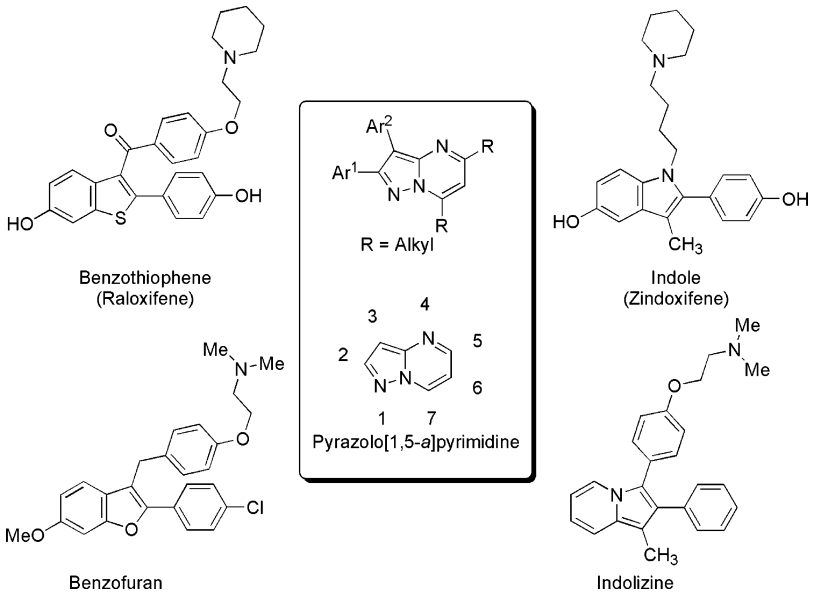


Figure 1. Fused heterocyclic systems as ER ligands. Numbering system of pyrazolo[1,5-*a*]pyrimidine rings and structural design for use as an ER ligand.

crystal structures, at least in ERβ.[10,35] In addition to orienting the phenolic hydroxyl group para to the heterocyclic core, we wanted to examine systems with two para hydroxyl groups, as well as systems having one para and one meta hydroxyl group. Changing the size of the substituents at the 5 and 7 positions would vary the hydrophobicity and the size of the system, which might lead to improved binding. The pyrazolo-[1,5-*a*]pyrimidine core itself would act as a hydrophobic, although somewhat polar, portion of the ligand to assist in filling the central space within the binding pocket.

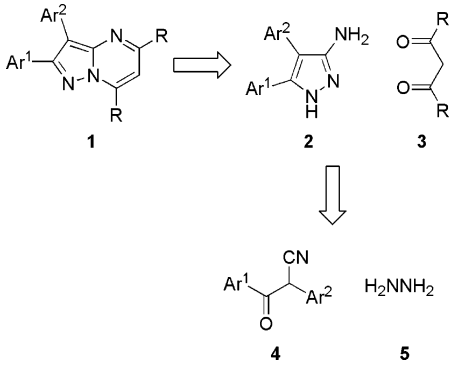
In this study we evaluated the ERα and ERβ binding affinities of 44 pyrazolo[1,5-*a*]pyrimidines and studied the transcriptional efficacy of 11 of the most interesting of these. In this series, we have observed compounds having binding affinities as high as 2% that of E_2, as well as ligands that exhibited an ERα binding selectivity as high as 41-fold and an ERβ binding selectivity as high as 36-fold. The latter of these compounds is fully effective as an ERβ antagonist while exhibiting no significant activity on ERα, a pharmacological profile that might be useful in evaluating the role of ERβ in mediating the diverse biological effects of estrogens.

Results and Discussion

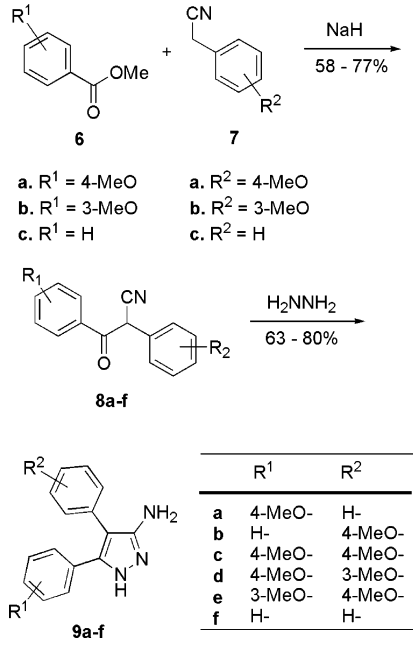
1. Chemistry. The desired pyrazolo[1,5-*a*]pyrimidine systems **1** can be readily assembled in just a few steps from simple starting materials. The retrosynthetic analysis in Scheme 1 shows how pyrazolo[1,5-*a*]pyrimidine **1** can be formed by the condensation of 3-amino-4,5-diarylpyrazole **2** and a diketone **3**, the key 3-aminopyrazole intermediate **2** then being produced by a condensation of a 2,3-diaryl-3-oxopropiontirile **4** and hydrazine **5**. Utilizing pyrazole **2** and a series of commercially available diketones, we were able to prepare a library of compounds for screening.

As shown in Scheme 2, a Claisen condensation between a methyl benzoate **6a**−**c** and a benzyl cyanide **7a**−**c** gave the 4,5-diaryl-3-oxopropionitriles[36] **8a**−**f**. These systems were then reacted with excess hydrazine to yield the diaryl-3-aminopyrazoles **9a**−**f**. We found

Scheme 1



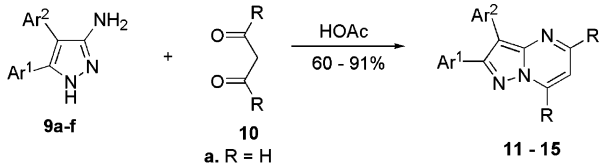
Scheme 2



	R^1	R^2
a	4-MeO-	H-
b	H-	4-MeO-
c	4-MeO-	4-MeO-
d	4-MeO-	3-MeO-
e	3-MeO-	4-MeO-
f	H-	H-

that the hydrazine condensation worked best with the addition of a small amount of concentrated hydrochloric acid[37] to facilitate proton transfer and dehydration. With

Scheme 3



	11 R = H	12 R = Me	13 R = Et	14 R = CF_3	15 R = *i*-Pr
a. Ar^1	4-MeOPh	4-MeOPh	4-MeOPh	4-MeOPh	4-MeOPh
Ar^2	Ph	Ph	Ph	Ph	Ph
b. Ar^1	Ph	Ph	Ph	Ph	Ph
Ar^2	4-MeOPh	4-MeOPh	4-MeOPh	4-MeOPh	4-MeOPh
c. Ar^1	4-MeOPh	4-MeOPh	4-MeOPh	4-MeOPh	4-MeOPh
Ar^2	4-MeOPh	4-MeOPh	4-MeOPh	4-MeOPh	4-MeOPh
d. Ar^1	4-MeOPh	4-MeOPh	4-MeOPh	4-MeOPh	4-MeOPh
Ar^2	3-MeOPh	3-MeOPh	3-MeOPh	3-MeOPh	3-MeOPh
e. Ar^1	3-MeOPh	3-MeOPh	3-MeOPh	3-MeOPh	3-MeOPh
Ar^2	4-MeOPh	4-MeOPh	4-MeOPh	4-MeOPh	4-MeOPh
f. Ar^1	Ph	Ph	Ph	Ph	
Ar^2	Ph	Ph	Ph	Ph	

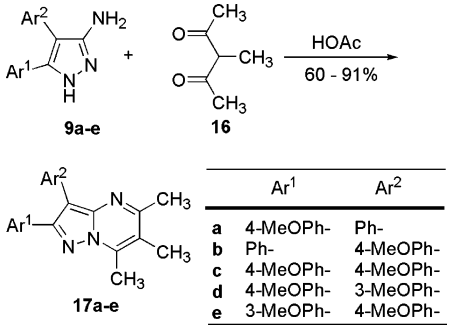
this intermediate available, we were able to assemble a library of pyrazolo[1,5-*a*]pyrimidines.

Historically, the pyrazolo[1,5-*a*]pyrimidines have been formed by reacting 3-aminopyrazoles with diketones or α,*β*-unsaturated ketones under acidic conditions.[38−40] As shown in Scheme 3, a series of commercially available diketones **10a**−**e** were reacted with the 3-aminopyrazoles **9a**−**f** to yield the pyrazolo[1,5-*a*]pyrimidines containing a variety of alkyl substituents at the 5 and 7 positions. To determine the most suitable reaction conditions, the first systems we chose for examination where those utilizing 1,3-propanedial **10a**. Because this simple dialdehyde (**10a)** is not stable, we used the tetramethyl bis-acetal as a the synthetic equivalent for 1,3-propanedial. The generation of **10a** in situ, by deprotection of the acetal, gave material for reaction with the 3-aminopyrazoles **9a**−**f**. Since acetals are sensitive to acidic conditions, acetic acid was chosen as the solvent; it is sufficiently acidic to generate the 1,3-propanedial and sufficiently polar to dissolve the 3-aminopyrazoles, which are quite polar. Once this method was found to be successful, it was then extended to diketones **10b**−**f** with good success to produce an initial library of 29 compounds that are substituted with alkyl groups at the C-5 and C-7 positions (Scheme 3).

In addition to examining the effects of increasing the size of the C-5 and C-7 substituents, we prepared a smaller series of pyrazolo[1,5-*a*]pyrimidines containing a substituent at C-6 by reacting **9a**−**e** with 3-methyl-2,4-pentanedione **16** (Scheme 4). These reactions were found to proceed well in acetic acid to give five additional pyrazolo[1,5-*a*]pyrimidines with methyl substituents at positions 5, 6, and 7.

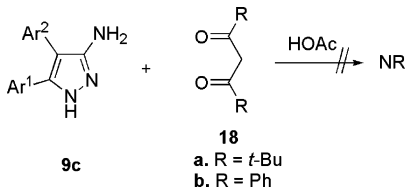
After the initial binding affinity studies (see below) indicated that the heterocycles were binding to the ER, we wanted to investigate how large of a group would be tolerated at the 5 and 7 positions. We wished to incorporate *tert*-butyl and phenyl substituents, which would allow us to determine how large of a substitution

Scheme 4



	Ar^1	Ar^2
a	4-MeOPh-	Ph-
b	Ph-	4-MeOPh-
c	4-MeOPh-	4-MeOPh-
d	4-MeOPh-	3-MeOPh-
e	3-MeOPh-	4-MeOPh-

Scheme 5



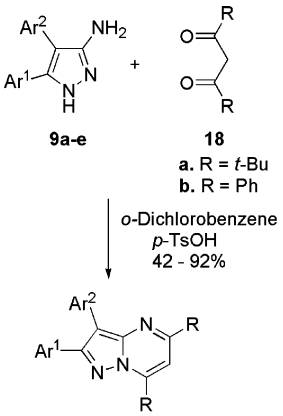
could be incorporated onto the pyrazolopyrimidine core. When the more hindered diketones **18a**,**b** where reacted with **9c** in acetic acid (Scheme 5), however, we found that the pyrazolo[1,5-*a*]pyrimidines did not form; starting material was recovered, even when the reaction times were extended to 48 h. To overcome these limitations, we examined new reaction conditions, but we encountered some difficulty because of the poor solubility of the 3-aminopyrazoles in simple aromatic solvents such as benzene and toluene. The 3-aminopyrazoles were found to be soluble in anhydrous *o*-dichlorobenzene above 100 °C. Thus, reaction of diketones **18a**,**b** with the 3-aminopyrazoles **9a**−**e** using 1.2 equiv of *p*-toluenesulfonic acid in *o*-dichlorobenzene (Scheme 6) provided good yields of the pyrazolo[1,5-*a*]pyrimidines **19a**−**e** and **20a**−**e** containing the larger substituents. This alternative synthesis allowed us to examine a larger, more diverse library of ligands, allowing us to explore the effect of size of the substituents at the 5 and 7 positions on ER binding.

The final step to yield testable compounds requires their conversion from the methyl ethers to the corresponding free phenols (Scheme 7). Although there are many possible methods for this transformation, the use of boron trifluoride/methyl sulfide complex was chosen as a mild deprotection agent. After all deprotections were performed, a library of 44 compounds **11f**−**14f** and **21a**−**e** through **28a**−**e** was obtained, and their relative binding affinities were measured.

2. Estrogen Receptor Binding Affinity. The relative binding affinities (RBAs) of the pyrazolo[1,5-*a*]-pyrimidine systems were measured in purified full-length human ERα and ER*β* receptors using a competitive radiometric binding assay, according to our published procedure.[41] The RBA values are listed in Table 1; E2 has a RBA of 100%.

The first trend to note in the series is the RBA of compounds **11f**−**14f**. These compounds contain only the unsubstituted phenyl rings at the 2 and 3 positions, and as might have been predicted, they show no measurable binding to the receptor because they lack the hydroxyl group that is believed to be a necessary hydrogen-bonding partner for the ER. The low affinity of these

Scheme 6



	19 R = *t*-Bu	20 R = Ph
a. Ar^1	4-MeOPh	4-MeOPh
Ar^2	Ph	Ph
b. Ar^1	Ph	Ph
Ar^2	4-MeOPh	4-MeOPh
c. Ar^1	4-MeOPh	4-MeOPh
Ar^2	4-MeOPh	4-MeOPh
d. Ar^1	4-MeOPh	4-MeOPh
Ar^2	3-MeOPh	3-MeOPh
e. Ar^1	3-MeOPh	3-MeOPh
Ar^2	4-MeOPh	4-MeOPh

compounds is consistent with the low affinity of 3-deoxyestradiol[11] and that of other ligands in which the hydroxyl group is removed from the phenol that mimics the A-ring of estradiol.[12,42] This indicates that the ER binding found in the rest of the series is due to the appropriate placement of the hydroxyl groups to enable hydrogen-bonding in the binding pocket, with the pyrazolo[1,5-*a*]pyrimidine system acting as a hydrophobic core unit to occupy space in the pocket. It was found that the addition of hydroxyl groups in appropriate orientations, as well as the addition of substituents at the 5 and 7 positions, did lead to ligands having good binding affinity to the ERs, with pyrazolo[1,5-*a*]pyrimidine **24c** having the highest overall RBA for ERα and ERβ, 1.9% and 1.7%, respectively.

The nature of the substituent at the 5 and 7 positions proved to be very important for binding. Compounds **24a**−**e** showed the highest overall binding to the receptor, and comparison with other analogues suggests a beneficial effect of the trifluoromethyl group for receptor interaction that may be derived from factors other than its hydrophobic character. For example, when substituents of comparable size are examined (**25a**−**e** and **27a**−**e**), only **27a** has an RBA on ERα comparable to that of the series **24a**−**e**. When **25c** is compared to **27c**, a greater than 2-fold increase in binding affinity is observed for **27c** on ERβ and **27a** shows a 6-fold increase over **25a** for ERα. These results were not anticipated because the larger *tert*-butyl substituent was expected to reduce the binding affinity of the ligands, especially for ERβ with its smaller binding pocket.[10]

Although **24c** was found to have the highest RBA of the series, it showed no selectivity between ERα and ERβ. Nonetheless, with this series there seems to be an overall preference for ERβ, with **24b** being 36-fold selective for ERβ over ERα. This is not universally the case, however, because **27a** showed 41-fold selectivity for ERα over ERβ. Although neither **24b** nor **27a** is the highest binding ligand, they did show very good affinity selectivity for ERβ and ERα, respectively.

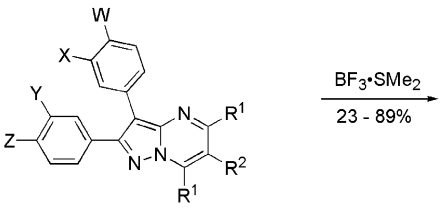
In addition to examination of substituents at the 5 and 7 positions, a smaller series of compounds was developed with an additional methyl substituent at the 6 position (**26a**−**e**). The binding data for this system are best understood when compared to the data of the dimethyl-substituted compounds **22a**−**e**. When a third methyl substituent was placed at the 6 position (**26a**−**e**), there was a significant decrease in the RBA compared to that of the corresponding dimethyl-substituted analogues (**22a**−**e**), in all cases where the RBA was measurable. Because substitution of a 6-hydrogen with a 6-methyl group is not well tolerated, we chose not to explore other systems substituted with larger alkyl groups at the 6 position.

One can compare the two monophenol series to determine whether there is a preference for the *p*-hydroxyphenyl at position 2 (Ar^1) or 3 (Ar^2) to act as the A-ring mimic of E2 (series **21a**−**28a** vs **21b**−**28b**). The overall trend indicates that a *p*-hydroxyphenyl at position 2 is the preferred A-ring mimic; however, a comparison of **24a** to **24b** indicates an interesting interaction. While **24a** shows a higher affinity than **24b**, there is a greater change in the ERα values than that of the ERβ values; in ERα there was a 40-fold decrease in RBA when going from a 4-hydroxyphenyl at C-2 (**24a)** to a 4-hydroxyphenyl at C-3 (**24b)**, whereas there is only a 12% decrease in the ERβ RBA. This seems to indicate that when binding to ERβ, **24b** is able to compensate for the loss of the preferred A-ring mimic; however, because this compensation does not occur in ERα, **24b** is a compound that has a 36-fold affinity preference for ERβ over ERα.

In further attempts to increase the RBA, one of the hydroxyl groups was moved from the para to the meta position while the other hydroxyl was left in the para position (**24d**,**e** and **28d**,**e**). This led, however, to a loss of binding affinity, with compounds **24d**,**e** being the only systems to have measurable RBAs. The diphenols **24c**−**e** were compared, and additional support for Ar^1 (i.e., at C-2) being the A-ring mimic was found. When the *p*-hydroxyl remains on Ar^1 (**24d**), the RBA for both ERα and ERβ is higher than for **24e**, where Ar^1 has a *m*-hydroxyl group. Although both **24d** and **24e** have significantly lower affinity than the initial diphenol **24c**, the information obtained still supports a 4-hydroxyphenyl at the C-2 position as being the A-ring mimic of estradiol.

The general trends in RBAs indicate that within a subset of R groups, the systems with *p*-hydroxyphenyls at both positions 2 and 3 were superior to those with other hydroxyl substitution patterns. Two notable exceptions are **25a** and **27a**, both of which show significantly higher ERα binding over the corresponding diphenols **25c** and **27c**, respectively. The majority of systems were shown to be ERβ selective or to have no significant preference for either receptor. Again, **27a** proved to be a noticeable exception, being 40-fold more selective for ERα. Despite the modest binding affinity

Scheme 7



	R^1	R^2
11	H-	H-
12	Me-	H-
13	Et-	H-
14	CF_3-	H-
15	*i*-Pr	H-
17	Me-	Me-
19	*t*-Bu	H-
20	Ph	H-

	W	X	Y	Z
a	H-	H-	H-	MeO-
b	MeO-	H-	H-	H-
c	MeO-	H-	H-	MeO-
d	H-	MeO-	H-	MeO-
e	MeO-	H-	MeO-	H-

	R^1	R^2
21	H-	H-
22	Me-	H-
23	Et-	H-
24	CF_3-	H-
25	*i*-Pr	H-
26	Me-	Me-
27	*t*-Bu	H-
28	Ph	H-

	W	X	Y	Z
a	H-	H-	H-	HO-
b	HO-	H-	H-	H-
c	HO-	H-	H-	HO-
d	H-	HO-	H-	HO-
e	HO-	H-	HO-	H-

of the pyrazolo[1,5-*a*]pyrimidines, we were able to study meaningful structure−affinity relationships.

3. Activity of Selected Pyrazolo[1,5-*a*]pyrimidines on Gene Transcription. Eleven compounds that showed good relative binding affinities or interesting selectivity between ERα and ER*β* (**21c**, **22a**, **22c**, **23c**, **24a**−**c**, **25a**, **25c**, **27a**, and **27c**) were tested for their agonistic or antagonistic character as regulators of transcription by cotransfection assays in human endometrial cancer cells (HEC-1), using expression plasmids for either ERα or ER*β* and an estrogen-responsive reporter gene. The agonist activity of the compounds was examined using a four-point dose response curve at 10^{-8}, 10^{-7}, 10^{-6}, and 10^{-5} M; antagonist activity was assayed at the same four concentrations in the presence of 10^{-9} M E_2. The transcriptional activity is expressed relative to that obtained with 10^{-9} M E_2, which is set at 100%. The results are shown in Figure 2.

3.1. C-2 Monophenolic Pyrazolopyrimidines. Compounds **22a**, **24a**, and **25a** (Figure 2, panels B, E, and H, respectively) are all C-2 monophenols (i.e., 2-(4-hydroxyphenyl)-3-phenylpyrazolo[1,5-*a*]pyrimidines), and they all possess varying degrees of partial activation of ERα, with little or no activation of ER*β* (solid lines). When these same compounds are tested as antagonists (in the presence of 1 nM estradiol), they inhibited estradiol partially on ERα and fully on ER*β* (dashed lines). Thus, these ligands would be classified as partial agonists on ERα and full antagonists on ER*β*. Although compound **27a** (Figure 2, panel J) possessed the same 2-(4-hydroxyphenyl)-3-phenylpyrazolo[1,5-*a*]pyrimidine pattern, it showed very little activity as an agonist or an antagonist on either receptor. This was somewhat unexpected because it exhibited one of the highest RBA values for ERα.

3.2. C-3 Monophenolic Pyrazolopyrimidines. The only C-3 monophenolic system of interest (i.e., a 2-(phenyl)-3-(4-hydroxyphenyl)pyrazolo[1,5-*a*]pyrimidine) was **24b** (Figure 2, graph F) because it showed an RBA that was 36-fold selective for ER*β*. As expected, the low ERα binding affinity of compound **24b** (0.01%) correlated with its low potency in the ERα transfection assay. Notably, this compound showed full antagonism on ER*β*, with minimal effect on ERα. *Thus, it represents a novel pharmacological class for estrogens—ERβ potency- and efficacy-selective antagonists.*

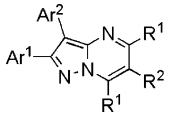
3.3. C-2 and C-3 Diphenolic Pyrazolopyrimidines. The diphenolic systems (i.e., 2,3-bis(4-hydroxyphenyl)pyrazolo[1,5-*a*]pyrimidines), **21c**, **22c**, **23c**, **24c**, **25c**, and **27c** (Figure 2, panels A, C, D, G, I, and K), were all found to act as antagonists on both ERα and ER*β*. The addition of a single hydroxyl transformed compounds that were partial agonists on ERα (**22a**, **24a**, and **25a**) into full ERα antagonists (**22c**, **24c**, and **25c**). Although at the concentrations examined compounds **22c** and **25c** did not reach full ERα antagonism, they did not show any agonism on ERα. *It is of note that compounds **22c**, **24c**, and **25c**, in particular, also represent a novel pharmacological class of for estrogens—ERβ potency-selective antagonists.*

3.4. General Discussion of Transactivation Results. The transactivation assays provided us with results that were unexpected in two respects. Although the ligands possessed only low to modest RBAs, they proved to have a very significant effect on the receptors; in addition, the ligands proved to share significant degrees of antagonism on both ERα and ER*β*. It is of particular note that several were antagonists on both ERs even though they do not contain the basic amine side chain (BSC) or additional bulky groups generally associated with imparting estrogen antagonism; this phenomenon has been termed "passive antagonism" by Shiau and co-workers.[43]

The pyrazolo[1,5-*a*]pyrimidine ER ligands illustrate multiple pharmacological classes within the same structural series; some pyrazolo[1,5-*a*]pyrimidine systems were found to be ER*β*−selective passive antagonists while showing ERα binding selectivity (**23c**, **25a**, and **25c**) or no significant subtype selectivity (**24a**, **24c**, and **27c**). This is similar to the profile exhibited by the 1,1-diarylethlene systems developed by Muthyala[44] and the tetrahydrochrysenes (THCs) developed by Meyers.[45] Additional systems represent an entirely new pharmacological classes of estrogen receptor ligands: ER*β* potency-selective antagonists (**22c**, **24c**, and **25c**) and ER*β* potency- and efficacy-selective antagonist (**24b**).

In addition to this already interesting activity, several compounds were found to act as ERα antagonists (**21c**, **22c**, **23c**, and **24c**), though with lower potency than as ER*β* antagonists. Nevertheless, these compounds represent the first ER ligands that we know of that act as ERα passive antagonists.[43] Thus, although the pyrazolo-[1,5-*a*]pyrimidines possess only modest binding affini-

Table 1. Relative Binding Affinity (RBA) of 2,3-Diaryl-5,7-dialkylpyrazolo[1,5-*a*]pyrimidines for Estrogen Receptors α and *β*, Deterimined by a Competitive Radiometric Binding Assay with [^{3}H]estradiol and Full-Length Human ERα and ER*β*, Using Methods Described in the Experimental Section[a]



		a Ar^1 = 4-HOPh Ar^2 = Ph	**b** Ar^1 = Ph Ar^2 = 4-HOPh	**c** Ar^1 = 4-HOPh Ar^2 = 4-HOPh	**d** Ar^1 = 4-HOPh Ar^2 = 3-HOPh	**e** Ar^1 = 3-HOPh Ar^2 = 4-HOPh	**f** Ar^1 = Ph Ar^2 = Ph
11							
R^1 = H	ERα						<0.01
R^2 = H	ER*β*						<0.01
	β/α						
12							
R^1 = Me	ERα						<0.01
R^2 = H	ER*β*						<0.01
	β/α						
13							
R^1 = Et	ERα						<0.01
R^2 = H	ER*β*						<0.01
	β/α						
14							
R^1 = CF$_3$	ERα						<0.01
R^2 = H	ER*β*						<0.01
	β/α						
21							
R^1 = H	ERα	<0.01	0.01 ± 0.001	<0.01	<0.01	<0.01	
R^2 = H	ER*β*	0.023 ± 0.004	0.05 ± 0.001	0.10 ± 0.002	<0.01	<0.01	
	β/α		5				
22							
R^1 = Me	ERα	0.02 ± 0.004	0.01 ± 0.002	0.04 ± 0.003	<0.01	<0.01	
R^2 = H	ER*β*	0.11 ± 0.001	0.05 ± 0.004	0.07 ± 0.01	<0.01	<0.01	
	β/α	5.5	5	1.8			
23							
R^1 = Et	ERα	0.13 ± 0.02	0.02 ± 0.003	0.16 ± 0.01	<0.01	<0.01	
R^2 = H	ER*β*	0.06 ± 0.004	0.05 ± 0.006	0.07 ± 0.01	<0.01	<0.01	
	β/α	0.5	5	0.18			
24							
R^1 = CF$_3$	ERα	0.39 ± 0.03	0.01 ± 0.003	1.9 ± 0.3	0.04 ± 0.004	0.01 ± 0.00	
R^2 = H	ER*β*	0.41 ± 0.09	0.05 ± 0.006	1.7 ± 0.06	0.08 ± 0.02	0.04 ± 0.00	
	β/α	1.1	36	0.9	2	4	
25							
R^1 = *i*-Pr	ERα	0.14 ± 0.04	0.01 ± 0.004	0.10 ± 0.02	0.01 ± 0.001	<0.01	
R^2 = H	ER*β*	0.06 ± 0.02	0.05 ± 0.002	0.07 ± 0.006	<0.01	0.01 ± 0.002	
	β/α	0.4	5	0.7			
26							
R^1 = Me	ERα	0.01 ± 0.001	<0.01	0.01 ± 0.003	<0.01	<0.01	
R^2 = Me	ER*β*	0.02 ± 0.001	0.01 ± 0.004	0.01 ± 0.00	<0.01	<0.01	
	β/α	2		1			
27							
R^1 = *t*-Bu	ERα	0.83 ± 0.07	<0.01	0.13 ± 0.003	0.02 ± 0.005	<0.01	
R^2 = Me	ER*β*	0.02 ± 0.002	0.01 ± 0.002	0.16 ± 0.04	0.01 ± 0.001	<0.01	
	β/α	0.02		1.1	0.5		
28							
R^1 = Ph	ERα	<0.01	<0.01	0.02 ± 0.06	<0.01	<0.01	
R^2 = H	ER*β*	<0.01	<0.01	0.03 ± 0.04	<0.01	<0.01	
	β/α			1.5			

[a] The RBA of estradiol is set to 100%. Where error bars are indicated, values represent the average ± range or SD of two to three independent determinations. The RBA is not reported when it was <0.01. The K_d of estradiol is 0.2 nM (ERα) and 0.5 nM (ER*β*) Because the *β*/α selectivity values are calculated from the RBA values, determined in competitive binding assays with tritiated esradiol, they favor ER*β* by 2.5-fold, which is the ratio of estradiol binding affinity for the two ER subtypes.

ties, they have provided us with new pharmacological classes of ER ligands, and they offer new insights that can be used to influence design of future ligands.

The most distinctive compound in the whole series was the C-3 monophenolic bis(trifluoromethyl)pyrazolo-[1,5-*a*]pyrazole **24b**. In binding, it was 36-fold selective for ER*β*, and it was fully effective as an ER*β* antagonist while exhibiting no significant agonism on ERα or ER*β*. Thus, as an ER*β* potency- and efficacy-selective antagonist, this ligand could be used to abrogate estrogen action through ER*β* with minimal effect on its activity through ERα. A compound with this activity could prove to be useful in evaluating the biological activity of ER*β*.

4. Molecular Modeling. The ability of the ligands to act as antagonists on ER*β* is not too surprising because it is known that the ER*β* binding pocket is approximately 100 Å^3 smaller in size than that of ERα.[10] We were surprised, however, by the ability of some members of the pyrazolo[1,5-*a*]pyrimidine system to act as antagonists on ERα without having the prototypical antagonist basic amine side chain. The larger size of the ERα pocket would suggest that the ligands should

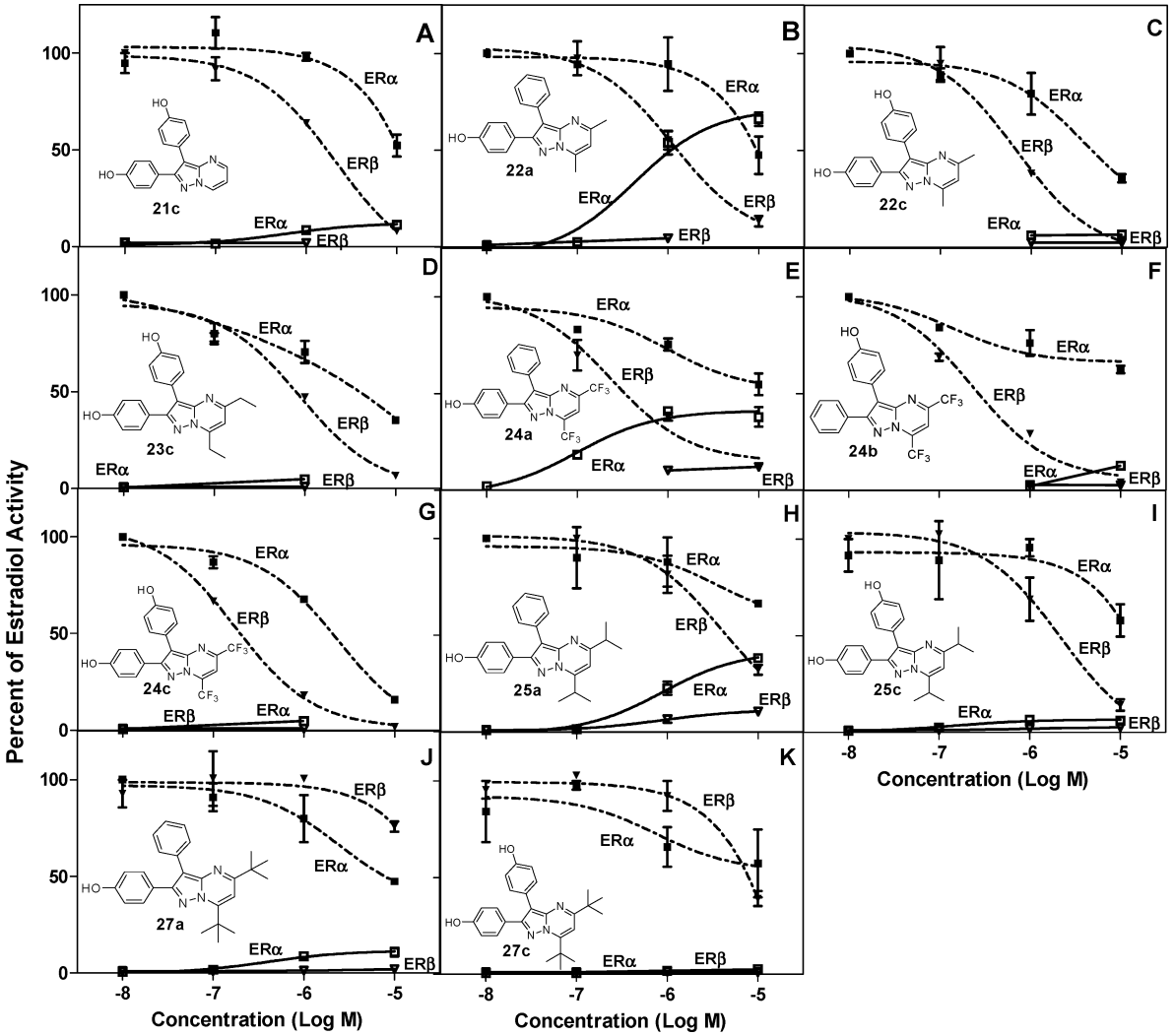


Figure 2. Transcription activation through ERα and ERβ in response to selected compounds with a pyrazolo[1,5-*a*]pyrimidine core. Human endometrial cancer cells (HEC-1) were transfected with expression vectors for ERα or ERβ and the estrogen responsive receptor gene 2ERE-pS2-Luc and were incubated with the indicated concentrations of ligands **21c**, **22a**, **23c**, **24a**−**c**, **25a**, **27a**, and **27c** (solid lines) for 24 h. Antagonistic activity was assayed in the presence of 1 nM E2 (dashed lines). The values given are the mean ± SD of two or more experiments and are expressed as a percent of the ERα or ERβ response with 10^{-9} M E2.

be able to fill the space inside the pocket without inducing antagonism. The fact that the ligands are causing partial or complete antagonism on ERα would suggest that they are binding to the receptor in a unique fashion. To gain insight into the activity of the system, we docked compound **24c** into the binding pockets of ERα and ERβ to study the potential binding orientations.

Initial molecular modeling studies of the diarylpyrazolo[1,5-*a*]pyrimidines showed that the system could function as an ER ligand and that it should be possible to place additional small substituents at the 5, 6, and 7 positions (not shown). After the RBA results for the series were obtained, ligand **24c** (which has the highest overall RBA and acts as an antagonist on both ER subtypes) was selected to be modeled into the crystal structures of ERα−E2 (1ERE) and ERβ−genistein (1QKM) using Sybyl 6.9. We hoped to understand why this ligand had the highest binding affinities for both ERα and ERβ and if there were protein−ligand interactions that might be used to rationalize the antagonistic character of **24c**. After learning that the systems are antagonistic, we also studied the antagonistic ERα−4-hydroxytamoxifen (3ERT) crystal structure and found that **24c** minimized into the same orientation as in 1ERE (not shown), thus offering no additional insight into why the ligands act as ERα antagonists.

When the ligands in the crystal structure were examined, it is important to note the key interactions of the endogenous ligand estradiol (Figure 3A). In the diarylpyrazolo[1,5-*a*]pyrimidines, there are two possible phenols that can act as the A-ring mimic of E2 and form a hydrogen bond with Glu353 and Arg394. In addition, there are two possible orientations for the remainder of the ligand structure, producing four possible binding modes to be examined by modeling (Figure 3B).

In binding modes I and II, the C-2 phenol acts as the estradiol A-ring mimic, with the second phenol being oriented either in the 11β direction relative to E2 (mode I) or in roughly the 7α direction (mode II). In either of these orientations there is potential for the fluorines on the trifluoromethyl substituents to hydrogen-bond with the His524. In modes III and IV, the C-3 phenol mimics the A-ring of estradiol. In the first of these cases (mode III), the second phenol is oriented in the 11β direction (as in mode I), but the pyrimidine portion of the core is

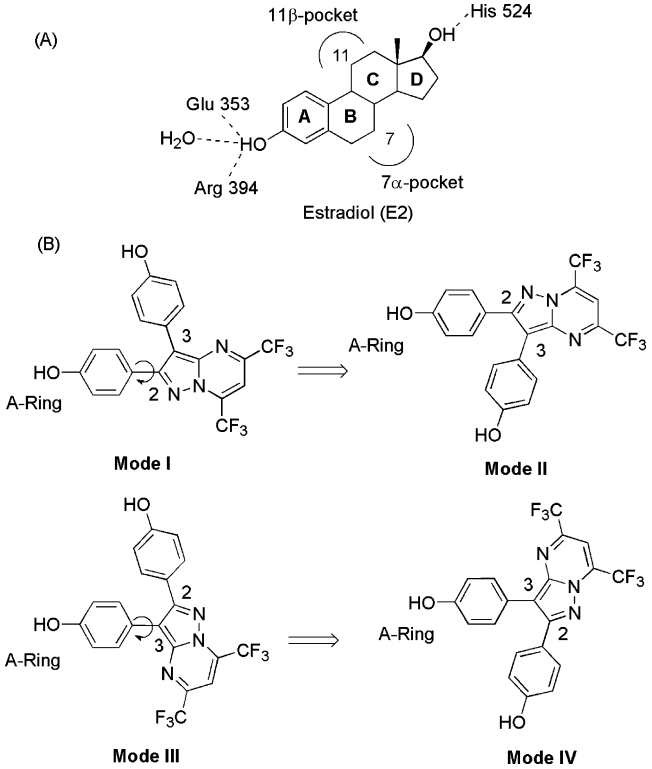


Figure 3. (A) Estradiol (E2) and its hydrogen-bonding patterns in ERα. (B) Two-dimensional illustration of the four possible binding modes for **24c**.

displaced more toward the 7α direction (instead of toward the back of the pocket, as in mode I). In this orientation it appears that greater reorganization of the receptor is required for hydrogen bonding to occur between the fluorine and the His524. Mode IV switches the orientation of the second phenol and the pyrimidine but still requires greater reorganization to achieve the proper orientation for hydrogen bonding between the fluorines and His524.

From the RBA data of the individual monophenols **24a** and **24b,** we believe that the most likely binding orientation for our pyrazolo[1,5-*a*]pyrimidines is mode I or its 180° rotation mode II, i.e., with the C-2 phenol A-ring mimic of E2. Binding modes III and IV, however, cannot be fully excluded because these orientations might account for the observed antagonistic character; thus, they were also examined during our modeling studies.

The desired binding mode was studied by modeling by first overlapping the desired phenol with the A-ring of estradiol (ERα) or the A-ring mimic in genistein (ERβ) and orienting the pyrazolo[1,5-*a*]pyrimidine core in the desired orientation. An initial minimization was performed by allowing the ligand to move while maintaining the protein in a fixed orientation. The ligand and amino acids within the binding pocket were allowed to rotate and reach a minimum energy. Finally, the ligand and the entire protein were allowed to minimize. As detailed below, good structures were obtained with compound **24c** in both modes I and II, whereas when binding modes III and IV were used to dock ligand **24c** into ERα and ERβ, the ligand was found to reorient to give binding mode I or II (ERβ and ERα, respectively) or to be ejected from the pocket.

The results from our modeling (Figure 4) showed that compound **24c** interacts differently between the two subtypes. Binding mode II (Figure 4A) appears to be the orientation of ligand **24c** in ERα, whereas in ERβ, binding mode I (Figure 4B) appears to be the preferred orientation. This is not the first instance where molecular modeling studies of multiply phenolic ER ligands indicated a preference for the same A-ring mimic but different binding modes between ERα and ERβ for the remainder of the ligand core. Nishiguchi and co-workers[46] observed similar modeling results while studying diaryldialkylpyrazoles as ER ligands, as did Wolohan[47] studying triarylalkylpyrazoles.

As shown in Figure 4A, ligand **24c** is oriented in a fashion that would allow it to hydrogen-bond with Glu353 and His524, thus maximizing the strong hydrogen-bonding interactions with the receptor. This orientation also suggests that it is the ability of the fluorines to hydrogen-bond with His524 that leads to the increased RBA values found not only for **24c** but with the whole series of trifluoromethyl-substituted compounds **24a**−**e**. Although no hydrogen-bonding interactions were found between Thr347, the only other polar residue in the ERα ligand binding pocket, the trifluoromethyl group is close enough that it is possible for this third hydrogen-bonding pair to exist.

The orientation of **24c** in the binding pocket of ERα (Figure 4A) offers no clear insight of why the compounds act as antagonists or partial antagonists on this ER subtype. The orientation of **24c** in ERβ (Figure 4B), however, does suggest why most of these ligands are antagonistic on this ER subtype. The aromatic ring at the C-3 position is oriented in the direction that a basic amine side chain would align to form the salt bridge with Asp303 and induce antagonism because ERβ has a smaller ligand binding pocket;[10] the basic side chain may not be required to disrupt the ERβ structure sufficiently to engender antagonist character, as has been noted with the ERβ-selective passive antagonist *R*,*R*-diethyltetrahydrochrysene.[45] In Figure 4B, ligand **24c** was found to have fewer hydrogen-bonding pairs; the hydrogen bond distance to His475 is 4.8 Å and the distance to Thr299 was >5 Å, both distances where hydrogen bonding would not occur. Since the RBA is comparable between ERα and ERβ, it is possible that in solution His475 (which corresponds to His524 in ERα) moves closer, enabling an additional hydrogen-bonding interaction.

The modeling has shown that it is the ability of **24c** to form additional hydrogen-bonding pairs through the trifluoromethyl groups that has led to the ligands within this series having RBA values higher than compounds having just hydrophobic groups of similar size. The difference between the receptor subtypes has also been emphasized, showing not only that the same ligand is able to have multiple binding modes but that the ER subtypes may prefer different binding orientations of the same ligand.

Conclusion

Estrogen receptor ligands built on the pyrazolo[1,5-*a*]pyrimidine core have been shown to exhibit unique profiles when binding to the ER. While having only modest binding affinities that typically exhibited affinity

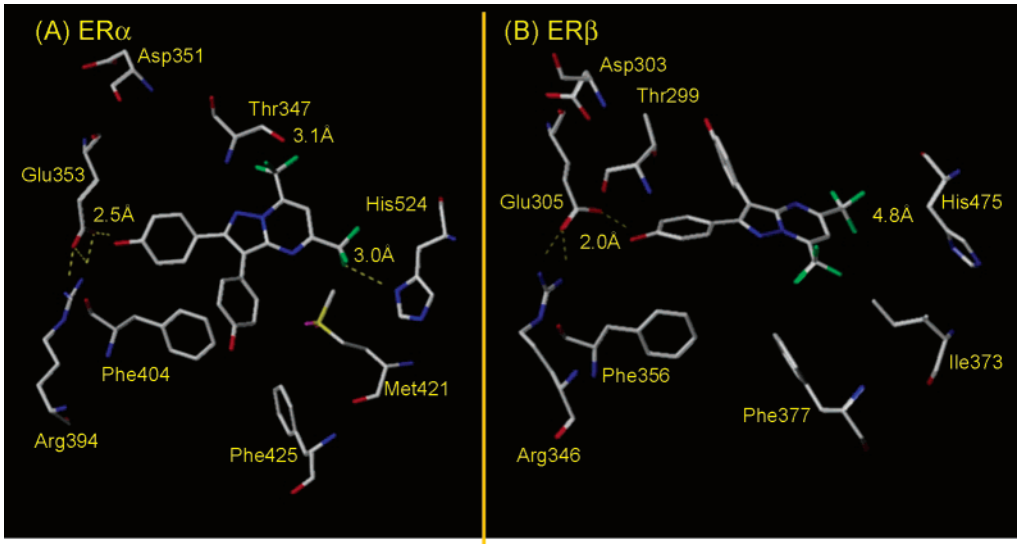


Figure 4. (A) Minimized docking structure of **24c** into the binding pocket of ERα showing hydrogen-bonding interactions and distances. (B) Minimized docking structure of **24c** into the binding pocket of ER*β* showing hydrogen-bonding interactions and distances. Selected binding pocket residues are shown and are in homologous positions in ERα and ER*β*.

selectivity for ER*β*, they had a significant effect in the receptor transactivation assays. The ligands were found to act as passive antagonists on both ERα and ER*β*, with some showing pronounced selective antagonism on ER*β*. While multiple examples of ER*β* passive antagonists are reported,[44,45] these are the first systems that have been found to act as passive antagonists on ERα. Thus, the pyrazolo[1,5-*a*]pyrimidine core has provided us with new pharmacological profiles of ER*β*-selective antagonists and ERα passive antagonists. Although the modeling studies provide no definitive answer to the mechanism of antagonism, we were able to learn from them that the ligands are likely presenting themselves differently to each receptor subtype and that this may have some influence on the antagonistic character. The pyrazolo-[1,5-*a*]pyrimidine core has offered new insights into the interaction between the estrogen receptor and novel ligand systems. Furthermore, it has furnished a compound that effectively antagonizes ER*β* with minimal effect on ERα. This compound (2-phenyl-3-(4-hydroxyphenyl)-5,7-bis(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidine, **24b**) could prove to be useful in evaluating the biological activity of ER*β*.

Experimental Section

Materials and Methods. All reagents and solvents were purchased from Aldrich, Acros, or Fisher. Methylene chloride and tetrahydrofuran were obtained immediately prior to use from a solvent-dispensing system (SDS) built by J. C. Meyer on the basis of a design developed by Pangborn et al.[48] The reaction samples were kept under a nitrogen atmosphere unless otherwise noted. Reactions were monitored by thin-layer chromatography (TLC) with 0.25 mm silica gel plastic plates containing F_{254} indicator. Visualization was obtained using a UV lamp. Column chromatography was performed using Woelm 32−63 μm silica gel packing. Melting points were obtained on a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra were obtained on Varian Unity 500 MHz spectrometer. ^{13}C NMR spectra were obtained at 125 MHz. Chemical shifts are reported downfield in parts per million from TMS utilizing the solvent peaks as the reference. Mass spectra were recorded under electron impact (EI) conditions at 70 eV by the Mass Spectrometry Laboratory at the University of Illinois. Elemental analysis of carbon, hydrogen, and nitrogen was performed by the Microanalytical Service Laboratory at the University of Illinois on an Exter Analytical CE440 analyzer.

General Procedure A for the Synthesis of 2,3-Diaryl-3-oxopropionitriles. To a suspension of 60% sodium hydride (33.6 mmol) in THF was added the benzyl cyanide (15.5 mmol) and methyl benzoate (17.1 mmol). The mixture was stirred at 60 °C for 48 h. Water (10 mL) was added, and the mixture was concentrated by rotary evaporation. An additional 20 mL of water was added and extracted (3 × 50 mL) with CH_2Cl_2. The organic phases were combined and discarded, and the aqueous portion was acidified with 3 M HCl until no more precipitate formed. The aqueous solution was then extracted (3 × 50 mL) with CH_2Cl_2, and the organic phases were combined. The combined organic phase was washed (2 × 25 mL) with a saturated NaCl solution and dried with Na_2SO_4. The dichloromethane was then removed by rotary evaporation. The resulting 2,3-diaryl-3-oxopropionitriles were carried on to the next step without further purification.

2-(4-Methoxyphenyl)-3-oxo-3-phenylpropionitrile (8a). Following general procedure A, methyl benzoate **6c** and benzyl cyanide **7a** were coupled to yield propionitrile **8a**. Yield 60%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.78 (s, 3H, Ar−OC*H*$_3$), 5.57 (s, 1H, C=OC*H*CN), 6.90 (AA′XX′, 2H, Ar−H), 7.35 (AA′XX′, 2H, Ar−H), 7.45 (m, 2H, Ar−H), 7.58 (m, 1H, Ar−H), 7.94 (m, 2H, Ar−H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 46.09 (C=O*C*HCN), 55.50 (Ar−O*C*H$_3$), 115.23 (2C, Ar−C), 116.98 (C=OCH*C*N), 122.28 (Ar−C), 129.16 (Ar−C), 129.41 (2C, Ar−C), 129.67 (2C, Ar−C), 133.77 (Ar−C), 134.51 (Ar−C), 160.26 (Ar−*C*OCH$_3$), 189.27 (C=O); LRMS *m/z* 251.1; HRMS ($C_{16}H_{13}NO_2$) calcd 251.0954, found 251.0946.

3-(4-Methoxyphenyl)-3-oxo-2-phenylpropionitrile (8b). Following general procedure A, methyl benzoate **6a** and benzyl cyanide **7c** were coupled to yield propionitrile **8b**. Yield 68%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.84 (s, 3H, Ar−OC*H*$_3$), 5.56 (s, 1H, C=OC*H*CN), 6.92 (AA′XX′, 2H, Ar−H), 7.37 (m, 3H Ar−H), 7.44 (m, 2H, Ar−H), 7.94 (AA′XX′, 2H, Ar−H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 46.54 (C=O*C*HCN), 55.77 (Ar−O*C*H$_3$), 114.42 (2C, Ar−C), 117.01 (C=OCH*C*N), 126.51 (Ar−C), 128.31 (2C, Ar−C), 129.17 (Ar−C), 129.76 (2C, Ar−C), 130.94 (Ar−C), 131.95 (2C, Ar−C), 164.66 (Ar−*C*OCH$_3$), 187.45 (C=O); LRMS *m/z* 251.1; HRMS ($C_{16}H_{13}NO_2$) calcd 251.0944, found 251.0946.

2,3-Bis(4-methoxyphenyl)-3-oxopropionitrile (8c). Following general procedure A, methyl benzoate **6a** and benzyl cyanide **7a** were coupled to yield propionitrile **8c**. Yield 79%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.77 (3H, s, OC*H*$_3$), 3.84 (3H, s, OC*H*$_3$), 5.53 (1H, s, C=OC*H*CN), 6.90 (4H, m, ArH), 7.34 (2H, AA′XX′, ArH), 7.92 (2H, AA′XX′, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 45.76 (C=O*C*HCN), 55.44 (Ar−O*C*H$_3$), 55.72 (Ar−

OCH_3), 114.36 (2Ar−C), 115.11 (2Ar−C), 117.27 (*C*N), 122.78 (Ar−C), 126.50 (Ar−C), 129.53 (2Ar−C), 131.85 (2Ar−C), 160.12 (Ar−*C*OCH_3), 164.55 (Ar−*C*OCH_3), 187.72 (C=O); LRMS *m/z* 281.1; HRMS ($C_{17}H_{15}NO_3$) calcd 281.1054, found 281.1051.

2-(4-Methoxyphenyl)-3-(3-methoxyphenyl)-3-oxopropionitrile (8d). Following general procedure A, methyl benzoate **6b** and benzyl cyanide **7a** were coupled to yield propionitrile **8d**. Yield 53%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.77 (s, 3H, Ar−OCH_3), 3.81 (s, 3H, Ar−OCH_3), 5.55 (s, 1H, C=OC*H*CN), 6.99 (AA′XX′, 2H, Ar−H), 7.11 (ddd, 1H, J = 8.4, 2.8, 0.9 Hz, Ar−H), 7.34 (m, 3H, Ar−H), 7.44 (dd, 1H, J = 2.4, 1.7 Hz, Ar−H), 7.49 (ddd, 1H, J = 7.7, 1.5, 0.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 46.16 (C=O*C*HCN), 55.48 (Ar−O*C*H$_3$), 55.62 (Ar−O*C*H$_3$), 113.68 (Ar−C), 115.22 (2C, Ar−C), 116.97 (C=OCH*C*N), 121.00 (Ar−C), 121.82 (Ar−C), 122.37 (Ar−C), 129.64 (2C, Ar−C), 130.07 (Ar−C), 135.08 (Ar−C), 160.26 (2C, Ar−*C*OCH$_3$), 189.16 (*C*=OCHCN); LRMS *m/z* 281.1.

2-(3-Methoxyphenyl)-3-(4-methoxyphenyl)-3-oxopropionitrile (8e). Following general procedure A, methyl benzoate **6a** and benzyl cyanide **7b** were coupled to yield propionitrile **8e**. Yield 58%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.77 (s, 3H, Ar−OCH_3), 3.84 (s, 3H, Ar−OCH_3), 5.54 (s, 1H, C=OC*H*CN), 6.86 (dd, 1H, J = 8.4, 2.6 Hz, Ar−H), 6.90 (AA′XX′, 2H, Ar−H), 6.97 (dd, 1H, J = 2.4, 1.7 Hz, Ar−H), 7.00 (dd, 1H, J = 7.7, 0.9 Hz, Ar−H), 7.29 (t, 1H, J = 7.9 Hz, Ar−H), 7.93 (AA′XX′, 2H, Ar−H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 46.53 (C=O*C*HCN), 55.48 (Ar−O*C*H$_3$), 55.73 (Ar−O*C*H$_3$), 113.87 (Ar−C), 114.39 (2C, Ar−C), 114.65 (Ar−C), 116.95 (C=OCH*C*N), 120.52 (Ar−C), 126.52 (Ar−C), 130.75 (Ar−C), 131.90 (2C, Ar−C), 132.48 (Ar−C), 160.49 (Ar−*C*OCH$_3$), 164.64 (Ar−*C*OCH$_3$), 187.39 (*C*=OCHCN); LRMS *m/z* 281.1

2,3-Diphenyl-3-oxopropionitrile (8f). Following general procedure A, methyl benzoate **6c** and benzyl cyanide **7c** were coupled to yield propionitrile **8f**. Yield 63%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.65 (s, 1H, C=OC*H*CN), 7.42 (m, 7H, Ar−H), 7.59 (m, 1H, Ar−H), 7.96 (m, 2H, Ar−H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 46.76 (C=O*C*HCN), 116.78 (*C*N), 128.41 (2C, Ar−C), 129.16 (2C, Ar−C), 129.28 (Ar−C), 129.41 (2C, Ar−C), 129.80 (2C, Ar−C), 130.49 (Ar−C), 133.70 (Ar−C), 134.60 (Ar−C), 189.12 (C=O); LRMS *m/z* 221.1.

General Procedure B for the Synthesis of 3-Amino-4,5-diarylpyrazoles. The 2,3-diaryl-3-ketopropionitriles were dissolved in 60 mL of absolute EtOH, and 3 mL of concentrated HCl was added. The mixture was brought to reflux, at which time a 5- to 7-fold excess of a solution of hydrazine hydrate **5** was added slowly over several minutes. The reaction mixture was stirred at reflux for an additional 9 h. The solution was condensed to approximately 15 mL by rotary evaporation, and 10 mL of water was added. A solution of saturated $NaHCO_3$ was added until a slightly basic pH was obtained. The solution was then extracted (3 × 50 mL) with ethyl acetate, and the organic layers were combined. The combined organic layers were washed (2 × 25 mL) with a saturated NaCl solution and dried with Na_2SO_4. The ethyl acetate was removed by rotary evaporation. The remaining material was purified by flash chromatography on silica gel using a 10% MeOH/90% $CHCl_3$ as the solvent.

3-Amino-4-(4-methoxyphenyl)-5-phenylpyrazole (9a). Following general procedure B, **8a** was reacted with **5** to yield **9a**. Isolated yield 78%; white solid; mp 87−89 °C; ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 3.78 (s, 3H, Ar−OCH_3), 4.30 (bs, 2H, NH_2), 6.90 (AA′XX′, 2H, Ar−H), 7.17 (AA′XX′, 2H, Ar−H), 7.26 (m, 3H, Ar−H), 7.40 (m, 2H, Ar−H); ^{13}C NMR (125 MHz, $(CD_3)_2CO$) δ 55.37 (Ar−O*C*H$_3$), 114.88, 126.67, 128.06, 128.30, 129.16, 131.55, 159.05 (Ar−*C*OCH$_3$); LRMS *m/z* 265.1; HRMS ($C_{16}H_{15}N_3O$) calcd 265.1211, found 265.1215.

3-Amino-5-(4-methoxyphenyl)-4-phenylpyrazole (9b). Following general procedure B, **8b** was reacted with **5** to yield **9b**. Isolated yield 76%; white solid; mp 101−103 °C; ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 3.76 (s, 3H, OCH_3), 4.31 (bs, 2H, NH_2), 6.83 (AA′XX′, 2H, Ar−H), 7.21 (m, 1H, Ar−H) 7.28 (m, 6H, Ar−H); ^{13}C NMR (125 MHz, $(CD_3)_2CO$) δ 55.46 (Ar−O*C*H$_3$), 114.59, 126.66, 129.38, 129.54, 130.26, 134.29, 160.23 (Ar−*C*OCH$_3$); LRMS *m/z* 265.1; HRMS ($C_{16}H_{15}N_3O$) 265.1215, found 265.1215.

3-Amino-4,5-bis(4-methoxyphenyl)pyrazole (9c). Following general procedure B, **8c** was reacted with **5** to yield **9c**. Isolated yield 80%; white solid; mp 169−172 °C; ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 3.74 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 4.27 (bs, 2H, NH_2), 6.83 (AA′XX′, 2H Ar−H), 6.90 (AA′XX′, 2H, Ar−H), 7.18 (AA′XX′, 2H, Ar−H), 7.31 (AA′XX′, 2H, Ar−H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 55.34 (Ar−O*C*H$_3$), 55.40 (Ar−O*C*H$_3$), 114.52, 126.73, 129.32, 131.47, 158.89 (Ar−*C*OCH$_3$), 160.05 (Ar−*C*OCH$_3$); LRMS *m/z* 295.1; HRMS ($C_{17}H_{17}N_3O_2$) calcd 295.1318, found 295.1321.

3-Amino-4-(4-methoxyphenyl)-5-(3-methoxyphenyl)-pyrazole (9d). Following general procedure B, **8d** was reacted with **5** to yield **9d**. Isolated yield 86%; white solid; mp 51−55 °C; ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 3.66 (s, 3H, Ar−OCH_3), 3.79 (s, 3H, Ar−OCH_3), 4.19 (bs, 2H, −NH_2), 6.81 (dd, 1H, J = 7.7, 2.4 Hz, Ar−H), 6.92 (AA′XX′, 2H, Ar−H), 6.96 (m, 2H, Ar−H), 7.18 (m, 3H, Ar−H); ^{13}C NMR (125 MHz, $(CD_3)_2CO$) δ 55.25 (Ar−O*C*H$_3$), 55.43 (Ar−O*C*H$_3$), 113.28, 114.06, 114.91, 120.23, 126.80, 130.20, 131.72, 159.18 (Ar−*C*OCH$_3$), 160.55 (Ar−*C*OCH$_3$); LRMS *m/z* 295.2; HRMS ($C_{17}H_{17}N_3O_2$) calcd 295.1320, found 295.1321.

3-Amino-4-(3-methoxyphenyl)-5-(4-methoxyphenyl)-pyrazole (9e). Following general procedure B, **8e** was reacted with **5** to yield **9e**. Isolated yield 55%; white solid; mp 58−62 °C; ^{1}H NMR (500 MHz, CD_3CO_2D) δ 3.72 (s, 3H, Ar−OCH_3), 3.77 (s, 3H, Ar−OCH_3), 6.87 (m, 5H, Ar−H), 7.28 (dd, 1H, J = 8.2, 7.9 Hz, Ar−H), 7.35 (AA′XX′, 2H, Ar−H); ^{13}C NMR (125 MHz, CD_3CO_2D) δ 55.49 (Ar−O*C*H$_3$), 55.68 (Ar−O*C*H$_3$), 105.26 (pyrazole−C), 113.96 (Ar−C), 115.11 (2C, Ar−C), 116.32 (Ar−C), 121.62 (Ar−C), 123.10 (Ar−C), 130.89 (2C, Ar−C), 131.08 (Ar−C), 133.14 (Ar−C), 144.17 (pyrazole−C), 150.95 (pyrazole−C), 161.17 (Ar−*C*OCH$_3$), 161.77 (Ar−*C*OCH$_3$); LRMS *m/z* 295.1; HRMS ($C_{17}H_{17}N_3O_2$) calcd 295.1323, found 295.1321.

3-Amino-4,5-diphenylpyrazole (9f). Following general procedure B, **8f** was reacted with **5** to yield **9f**. Isolated yield 88%; white solid; mp 143−146 °C; ^{1}H NMR (500 MHz, $(CD_3)_2$-CO) δ 4.32 (bs, 2H, NH_2), 7.21 (m, 1H, Ar−H), 7.29 (m, 7H, Ar−H), 7.38 (m, 2H, Ar−H), 11.36 (bs, 1H, N*H*); ^{13}C NMR (125 MHz, $(CD_3)_2CO$) δ 126.77, 128.26, 128.40, 129.17, 129.41, 130.31, 134.81; LRMS *m/z* 235.1; HRMS ($C_{15}H_{13}N_3$) calcd 235.1112, found 235.1109.

General Procedure C for the Synthesis of Pyrazolo-[1,5-*a*]pyrimidines Using Acetic Acid. The desired 3-amino-4,5-diarylpyrazoles (0.5 mmol) were dissolved in 10 mL of acetic acid. To this solution 0.75 mmol of the dicarbonyl compound was added, and the mixture was heated to 110 °C for 1.5 h. The acetic acid was then removed by rotary evaporation. The pyrazolo[1,5-*a*]pyrimidine was obtained by dissolving the solid mixture in hot ethanol and allowing it to cool. The resulting solid was filtered, and the mother liquor was discarded.

2-(4-Methoxyphenyl)-3-phenylpyrazolo[1,5-*a*]pyrimidine (11a). Following general procedure C, **9a** was reacted with 1,1,3,3-tetramethoxypropane **10a** to yield **11a**. Isolated yield 70%; white solid; mp 138−140 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.83 (s, 3H, OCH_3), 6.81 (dd, 1H, J = 6.9, 4.1, pyrimidine−H), 6.90 (AA′XX′, 2H, Ar−H), 7.31 m, 1H, Ar−H), 7.40 (m, 2H, Ar−H), 7.54 (m, 2H, Ar−H), 7.60 (AA′XX′, 2H, Ar−H), 8.48 (dd, 1H, J = 3.9, 1.7 Hz, pyrimidine−H), 8.68 (dd, 1H, J = 6.9, 1.7 Hz, pyrimidine−H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.40 (Ar−C), 108.21 (pyrimidine−C), 108.89 (pyrazole−C), 114.10 (2C, Ar−C), 125.46 (Ar−C), 126.96 (Ar−C), 128.71 (2C, Ar−C), 130.08 (2C, Ar−C), 130.37 (2C, Ar−C), 132.04 (Ar−C), 134.79 (pyrimidine−C), 147.03 (pyrazole−C), 149.41 (pyrimidine−C), 154.09 (pyrazole−C), 160.17 (Ar−*C*OCH$_3$); LRMS *m/z* 301.1; HRMS ($C_{19}H_{15}N_3O$) calcd 301.1213, found 301.1215.

3-(4-Methoxyphenyl)-2-phenylpyrazolo[1,5-*a*]pyrimidine (11b). Following general procedure C, **9b** was reacted with 1,1,3,3-tetramethoxypropane **10a** to yield **11b**. Isolated yield 66%; yellow solid; mp 171−172 °C; ^{1}H NMR (500 MHz,

$CDCl_3$) δ 3.83 (s, 3H, OCH_3), 6.80 (dd, 1H, J = 6.9, 4.1 Hz, pyrimidine−H), 6.95 (AA′XX′, 2H, Ar−H), 738 (m, 3H, Ar−H), 7.47 (AA′XX′, 2H, Ar−H), 7.68 (m, 2H, Ar−H), 8.48 (dd, 1H, J = 4.1, 1.7 Hz, pyrimidine−H), 8.68 (dd, 1H, J = 6.9, 1.5 Hz pyrimidine−H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.38 (Ar−OCH_3), 108.28 (pyrimidine−C), 109.09 (pyrazole−C), 114.24 (2C, Ar−C), 124.08 (Ar−C), 128.71 (2C, Ar−C), 129.01 (2C, Ar−C), 131.16 (2C, Ar−C), 133.14 (2C, Ar−C), 134.80 (pyrimidine−C), 146.88 (pyrazole−C), 149.25 (pyrimidine−C), 153.91 (pyrazole−C); LRMS (EI, 70 eV) *m/z* 301.1; HRMS ($C_{19}H_{15}N_3O$) 301.1216, found 301.1215.

2,3-Bis(4-methoxyphenyl)pyrazolo[1,5-*a*]pyrimidine (11c). Following general procedure C, **9c** was reacted with 1,1,3,3-tetramethoxypropane **10a** to yield **11c**. Isolated yield 79%; yellow solid; mp 175−177 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.83 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 6.80 (dd, 1H, J = 7.1, 4.1 Hz, pyrimidine−H), 6.90 (AA′XX′, 2H, Ar−H), 6.96 (AA′XX′, 2H, Ar−H), 7.46 (AA′XX′, 2H, Ar−H), 7.61 (AA′XX′, 2H, Ar−H), 8.46 (dd,1H, J = 4.1, 1.7 Hz, pyrimidine−H), 8.67 (dd, 1H, J = 4.1, 1.7 Hz, pyrimidine−H); ^{13}C NMR δ (125 MHz, $CDCl_3$) δ 55.49 (Ar−OCH_3), 55.50 (Ar−OCH_3), 108.15 (pyrimidine−C), 108.64 (pyrazole−C), 114.18 (2C, Ar−C), 114.37 (2C, Ar−C), 124.38 (Ar−C), 125.65 (Ar−C), 130.35 (2C, Ar−C), 131.29 (2C, Ar−C), 134.82 (pyrimidine−C), 147.07 (pyrazole−C), 149.27 (pyrimidine−C), 153.91 (pyrazole−C), 158.79 (Ar−*C*OCH$_3$), 160.19 (Ar−*C*OCH$_3$); LRMS *m/z* 331.2; HRMS ($C_{20}H_{17}N_3O_2$) 331.1319, found 331.1321.

2-(4-Methoxyphenyl)-3-(3-methoxyphenyl)pyrazolo-[1,5-*a*]pyrimidine (11d). Following general procedure C, **9d** was reacted with 1,1,3,3-tetramethoxypropane **10a** to yield **11d**. Isolated yield 68%; off-white solid; mp 120−122 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.74 (s, 3H, Ar−OCH_3), 3.81 (s, 3H, Ar−OCH_3), 6.77 (dd, 1H, J = 6.9, 3.9 Hz, pyrimidine−H), 6.85 (ddd, 1H, J = 8.4, 2.6, 0.9 Hz, Ar−H), 6.90 (AA′XX′, 2H, Ar−H), 7.11 (dd, 1H, J = 2.4, 1,5 Hz, Ar−H), 7.14 (dt, 1H, J = 7.5, 1.1 Hz, Ar−H), 7.31 (t, 1H, J = 7.9 Hz, Ar−H), 7.61 (AA′XX′, 2H, Ar−H), 8.46 (dd, 1H, J = 4.1, 1.9 Hz, pyrimidine−H), 8.66 (dd, 1H, J = 7.1, 1.9 Hz, pyrimidine−H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.22 (Ar−OCH_3), 55.34 (Ar−OCH_3), 108.15 (pyrimidine−C), 108.64 (pyrazole−C), 112.69 (Ar−C), 14.01 (2C, Ar−C), 115.47 (2C, Ar−C), 122.50 (Ar−C), 125.38 (Ar−C), 129.60 (Ar−C), 130.34 (2C, Ar−C), 133.29 (Ar−C), 134.70 (pyrimidine−C), 146.95 (pyrazole−C), 149.35 (pyrimidine−C), 154.02 (pyrazole−C), 159.70 (Ar−*C*OCH$_3$), 160.12 (Ar−*C*OCH$_3$); LRMS *m/z* 331.1; HRMS ($C_{20}H_{17}N_3O_2$) calcd 331.1321, found 331.1321.

2-(3-Methoxyphenyl)-3-(4-methoxyphenyl)pyrazolo-[1,5-*a*]pyrimidine (11e). Following general procedure C, **9e** was reacted with 1,1,3,3-tetramethoxypropane **10a** to yield **11e**. Isolated yield 85%; orange solid; mp 159−161 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.71 (s, 3H, Ar−OCH_3), 3.81 (s, 3H, Ar−OCH_3), 6.77 (dd, 1H, J = 6.9, 3.9 Hz, pyrimidine−H), 6.88 (dt, 1H, J = 7.3, 2.4 Hz, Ar−H), 6.93 (AA′XX′, 2H, Ar−H), 7.23 (m, 3H, Ar−H), 7.43 (AA′XX′, 2H, Ar−H), 8.44 (dd, 1H, J = 4.1, 1.7 Hz, pyrimidine−H), 8.65 (dd, 1H, J = 7.1, 1.7 Hz, pyrimidine−H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.30 (Ar−OCH_3), 55.40 (Ar−OCH_3), 108.31 (pyrimidine−C), 109.24 (pyrazole−C), 113.82 (Ar−C), 114.23 (2C, Ar−C), 115.06 (Ar−C), 121.48 (Ar−C), 124.07 (Ar−C), 129.65 (Ar−C), 131.27 (2C, Ar−C), 134.41 (Ar−C), 134.79 (pyrimidine−C), 146.91 (pyrazole−C), 149.26 (pyrimidine−C), 153.72 (pyrazole−C), 158.78 (Ar−*C*OCH$_3$), 159.71 (Ar−*C*OCH$_3$); LRMS *m/z* 331.2; HRMS ($C_{20}H_{17}N_3O_2$) calcd 331.1324, found 331.1321.

2,3-Diphenylpyrazolo[1,5-*a*]pyrimidine (11f). Following general procedure C, **9f** was reacted with 1,1,3,3-tetramethoxypropane **10a** to yield **11f**. Isolated yield 90%; yellow solid; mp 127−129 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.76 (dd, 1H, J = 6.9, 3.9 Hz, Ar−H), 7.31 (m, 1H, pyrimidine−H), 7.39 (m, 5H, Ar−H), 7.57 (m, 2H, Ar−H), 7.68 (m, 2H, Ar−H), 8.47 (dd, 1H, J = 3.9, 1.7 Hz, pyrimidine−H), 8.68 (dd, 1H, J = 6.9, 1.7 Hz, pyrimidine−H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 108.31 (pyrimidine−C), 109.21 (pyrazole−C), 126.88 (Ar−C), 128.53 (2C, Ar−C), 128.57 (2C, Ar−C), 128.69 (Ar−C), 129.02 (2C, Ar−C), 129.95 (2C, Ar−C), 131.72 (Ar−C), 132.97 (Ar−C), 134.75 (pyrimidine−C), 146.80 (pyrazole−C), 149.37 (pyrimidine−C), 154.06 (pyrazole−C); LRMS *m/z* 271.1; HRMS ($C_{18}H_{13}N_3$) calcd 271.1111, found 271.1109. Anal. ($C_{18}H_{13}N_3$) C, H, N calcd: 79.68% C, 4.83% H, 15.49% N. Found: 79.53% C, 4.90% H, 15.32% N.

2-(4-Methoxyphenyl)-5,7-dimethyl-3-phenylpyrazolo-[1,5-*a*]pyrimidine (12a). Following general procedure C, **9a** was reacted with 2,4-pentandione **10b** to yield **12a**. Isolated yield 64%; white solid; mp 139−140 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.56 (s, 3H, pyrimidine−CH_3), 2.78 (s, 3H, pyrimidine−CH_3), 3.83 (s, 3H, Ar−OCH_3), 6.55 (s, 1H, pyrimidine−H), 6.91 (AA′XX′, 2H, Ar−H), 7.28 (m, 1H, Ar−H), 7.38 (m, 2H, Ar−H), 7.60 (m, 4H, Ar−H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.12 (pyrimidine−*C*H$_3$), 24.93 (pyrimidine−*C*H$_3$), 55.35 (Ar−O*C*H$_3$) 107.70 (pyrazole−C), 108.82 (pyrimidine−C), 113.96 (2C, Ar−C), 126.20 (Ar−C), 126.45 (Ar−C), 128.42 (2C, Ar−C), 130.14 (2C, Ar−C), 130.45 (2C, Ar−C), 132.64 (Ar−C), 144.92 (pyrimidine−*C*CH$_3$), 146.83 (pyrazole−C), 153.43 (pyrazole−C), 158.74 (pyrimidine−*C*CH$_3$), 159.90 (Ar−*C*OCH$_3$); LRMS *m/z* 329.1; HRMS ($C_{21}H_{19}N_3O$) calcd 329.1524, found 329.1528.

3-(4-Methoxyphenyl)-5,7-dimethyl-2-phenylpyrazolo-[1,5-*a*]pyrimidine (12b). Following general procedure C, **9b** was reacted with 2,4-pentandione **10b** to yield **12b**. Isolated yield 72%; white solid; mp 182−183 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.57 (s, 3H, pyrimidine−CH_3), 2.79 (d, 3H, J = 0.4 Hz, pyrimidine−CH_3), 3.84 (s, 3H, Ar−OCH_3), 6.57 (q, 1H, J = 0.9 Hz, pyrimidine−H), 6.93 (AA′XX′, 2H, Ar−H), 7.37 (m, 3H, Ar−H), 7.47 (AA′XX′, 2H, Ar−H), 7.67 (m, 2H, Ar−H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.18 (pyrimidine−*C*H$_3$), 25.04 (pyrimidine−*C*H$_3$), 55.40 (Ar−O*C*H$_3$), 107.94 (pyrazole−C), 108.94 (pyrimidine−C), 114.09 (2C, Ar−C), 124.86 (Ar−C), 128.41 (Ar−C), 128.56 (2C, Ar−C), 129.22 (2C, Ar−C), 131.27 (2C, Ar−C), 133.93 (Ar−C), 144.99 (pyrimidine−*C*CH$_3$), 146.80 (pyrazole−C), 153.41 (pyrazole−C), 158.47 (Ar−*C*OCH$_3$), 158.64 (pyrimidine−*C*CH$_3$); LRMS *m/z* 329.1; HRMS ($C_{21}H_{19}N_3O$) calcd 329.1530, found 329.1528.

2,3-Bis(4-methoxyphenyl)-5,7-dimethylpyrazolo[1,5-*a*]-pyrimidine (12c). Following general procedure C, **9c** was reacted with 2,4-pentandione **10b** to yield **12c**. Isolated yield 74%; light-yellow solid; mp 171−172 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.55 (s, 3H, pyrimidine−CH_3), 2.77 (d, 3H, J = 0.9 Hz, pyrimidine−CH_3), 3.82 (s, 3H, Ar−OCH_3), 3.83 (s, 3H, Ar−OCH_3), 6.53 (q, 1H, J = 0.9 Hz, pyrimidine−H), 6.90 (AA′XX′, 2H, Ar−H), 6.93 (AA′XX′, 2H, Ar−H), 7.47 (AA′XX′, 2H, Ar−H), 7.61 (AA′XX′, 2H, Ar−H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.11 (pyrimidine−*C*H$_3$), 24.89 (pyrimidine−*C*H$_3$), 55.35 (2C, Ar−O*C*H$_3$), 107.45 (pyrazole−C), 108.70 (pyrimidine−C), 113.96 (2C, Ar−C), 114.04 (2C, Ar−C), 124.97 (Ar−C), 126.28 (Ar−C), 130.37 (2C, Ar−C), 131.29 (2C, Ar−C), 144.90 (pyrimidine−*C*CH$_3$), 146.76 (pyrazole−C), 153.91 (pyrazole−C), 158.40 (Ar−*C*OCH$_3$), 158.50 (pyrimidine−*C*CH$_3$), 159.85 (Ar−*C*OCH$_3$); LRMS *m/z* 359.2; HRMS ($C_2 2H_{21}N_3O_2$) calcd 359.1640, found 359.1631.

2-(4-Methoxyphenyl)-3-(3-methoxyphenyl)-5,7-dimethylpyrazolo[1,5-*a*]pyrimidine (12d). Following general procedure C, **9d** was reacted with 2,4-pentandione **10b** to yield **12d**. Isolated yield 87%; white solid; mp 142−143 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.57 (s, 3H, pyrimidine−CH_3), 2.78 (d, 3H, J = 0.64 Hz, pyrimidine−CH_3), 3.75 (s, 3H, Ar−OCH_3), 3.83 (s, 3H, Ar−OCH_3), 6.57 (q, 1H, J = 0.9 Hz, pyrimidine−H), 6.82 (ddd, 1H, J = 8.2, 2.6, 0.9 Hz, Ar−H), 6.91 (AA′XX′, 2H, Ar−H), 7.15 (dt, 1H, J = 7.5, 1.2 Hz, Ar−H), 7.18 (dd, 1H J = 2.4, 1.3 Hz, Ar−H), 7.27 (t, 1H, J = 7.9 Hz, Ar−H), 7.60 (AA′XX′, 2H, Ar−H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.19 (pyrimidine−*C*H$_3$), 25.04 (pyrimidine−*C*H$_3$), 55.29 (Ar−O*C*H$_3$), 55.43 (Ar−O*C*H$_3$), 107.57 (pyrazole−C), 108.87 (pyrimidine−C), 112.42 (Ar−C), 114.01 (2C, Ar−C), 115.44 (Ar−C), 122.67 (Ar−C), 126.26 (Ar−C), 129.40 (Ar−C), 130.56 (2C, Ar−C), 133.98 (Ar−C), 145.00 (pyrimidine−*C*CH$_3$), 146.87 (pyrazole−C), 153.58 (pyrazole−C), 158.82 (Ar−*C*OCH$_3$), 159.64 (Ar−*C*OCH$_3$), 159.99 (pyrimidine−*C*CH$_3$); LRMS *m/z* 359.2; HRMS ($C_{22}H_{21}N_3O_2$) calcd 359.1627, found 359.1634.

2-(3-Methoxyphenyl)-3-(4-methoxyphenyl)-5,7-dimethylpyrazolo[1,5-*a*]pyrimidine (12e). Following general pro-

cedure C, **9e** was reacted with 2,4-pentandione **10b** to yield **12e**. Isolated yield 72%; off-white solid; mp 128−131 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.56 (s, 3H, pyrimidine−CH_3), 2.79 (s, 3H, pyrimidine−CH_3), 3.74 (Ar−OCH_3), 3.83 (Ar−OCH_3), 6.56 (s, 1H, pyrimidine−H), 6.92 (m, 3H, Ar−H), 7.26 (m, 3H, Ar−H), 7.49 (AA′XX′, 2H, Ar−H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.12 (pyrimidine−CH$_3$), 25.00 (pyrimidine−CH$_3$), 55.29 (Ar−OCH$_3$), 55.38 (Ar−OCH$_3$), 108.01 (pyrazole−C), 108.95 (pyrimidine−C), 114.04 (2C, Ar−C), 114.12 (Ar−C), 114.61 (Ar−C), 121.68 (Ar−C), 124.81 (Ar−C), 129.55 (Ar−C), 131.33 (2C, Ar−C), 135.16 (Ar−C), 144.96 (pyrimidine−CCH$_3$), 146.77 (pyrazole−C), 153.14 (pyrazole−C), 158.49 (Ar−COCH$_3$), 158.63 (Ar−COCH$_3$), 159.66 (pyrimidine−CCH$_3$); LRMS *m/z* 359.3; HRMS ($C_{22}H_{21}N_3O$) calcd 359.1637, found 359.1634.

5,7-Dimethyl-2,3-diphenylpyrazolo[1,5-*a*]pyrimidine (12f). Following general procedure C, **9f** was reacted with 2,4-pentandione **10b** to yield **12f**. Isolated yield 86%; peach solid; mp 170−171 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.58 (s, 3H, pyrimidine−CH_3), 2.81 (d, 3H, J = 0.9 Hz, pyrimidine−CH_3), 6.59 (q, 1H, J = 0.9 Hz, pyrimidine−H), 7.28 (m, 1H, Ar−H), 7.37 (m, 5H, Ar−H), 7.57 (m, 2H, Ar−H), 7.67 (m, 2H, Ar−H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.19 (pyrimidine−CH$_3$), 25.05 (pyrimidine−CH$_3$), 108.20 (pyrazole−C), 126.53 (Ar−C), 128.48 (3C, Ar−C), 128.56 (2C, Ar−C), 129.30 (2C, Ar−C), 130.16 (2C, Ar−C), 132.50 (Ar−C), 133.84 (Ar−C), 145.07 (pyrimidine−CCH$_3$), 146.86 (pyrazole−C), 153.70 (pyrazole−C), 158.90 (pyrimidine−CCH$_3$); LRMS *m/z* 299.2; HRMS ($C_{20}H_{17}N_3$) calcd 299.1423, found 299.1422. Anal. ($C_{20}H_{17}N_3$) C, H, N calcd: 80.24% C, 5.72% H, 14.04% N. Found: 79.93% C, 5.64% H, 13.94% N.

5,7-Diethyl-2-(4-methoxyphenyl)-3-phenylpyrazolo[1,5-*a*]pyrimidine (13a). Following general procedure C, **9a** was reacted with 3,5-heptanedione **10c** to yield **13a**. Isolated yield 81%; white solid; mp 123−125 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.38 (t, 3H, J = 7.5 Hz, −CH$_2$CH_3), 1.49 (t, 3H, J = 7.5 Hz, −CH$_2$CH_3), 2.87 (q, 2H, J = 7.6 Hz, pyrimidine−CH_2CH$_3$), 3.26 (q, 2H, J = 7.5 Hz, pyrimidine−CH_2CH$_3$), 3.84 (s, 3H, Ar−OCH_3), 6.59 (s, 1H, pyrimidine−H), 6.93 (AA′XX′, 2H, Ar−H), 7.28 (m, 1H, Ar−H), 7.39 (m, 2H, Ar−H), 7.63 (m, 4H, Ar−H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.41 (−CH$_2$$CH_3$), 13.10 (−CH$_2$$CH_3$), 23.54 (pyrimidine−$CH_2CH_3$), 31.69 (pyrimidine−$CH_2CH_3$), 55.35 (Ar−O$CH_3$), 105.48 (pyrimidine−H), 107.54 (pyrazole−C), 113.96 (2C, Ar−C), 126.26 (Ar−C), 126.45 (Ar−C), 128.34 (2C, Ar−C), 130.06 (2C, Ar−C), 130.50 (2C, Ar−C), 132.81 (Ar−C), 146.87 (pyrazole−C), 149.97 (pyrimdine-CCH$_2$CH$_3$), 153.29 (pyrazole−C), 159.88 (Ar−COCH$_3$), 163.57 (pyrimidine−CCH$_2$CH$_3$); LRMS *m/z* 357.2; HRMS ($C_{23}H_{23}N_3O$) calcd 357.1834, found 357.1841.

5,7-Diethyl-3-(4-methoxyphenyl)-2-phenylpyrazolo[1,5-*a*]pyrimidine (13b). Following general procedure C, **9b** was reacted with 3,5-heptanedione **10c** to yield **13b**. Isolated yield 82%; light-yellow solid; mp 111−113 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.38 (t, 3H, J = 7.5 Hz, −CH$_2$CH_3), 1.50 (t, 3H, J = 7.5 Hz, −CH$_2$CH$_3$), 2.87 (q, 2H, J = 7.6 Hz, pyrimidine−CH_2-CH$_3$), 3.26 (q, 2H, J = 7.43 Hz, pyrimidine−CH_2CH$_3$), 3.85 (s, 3H, Ar−OCH_3), 6.60 (s, 1H, pyrimidine−H), 6.96 (AA′XX′, 2H, Ar−H), 7.38 (m, 3H, Ar−H), 7.54 (AA′XX′, 2H, Ar−H), 7.71 (m, 2H, Ar−H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.41 (−CH$_2$$CH_3$), 13.13 (−CH$_2$$CH_3$), 23.51 (pyrimidine−$CH_2CH_3$), 31.70 (pyrimidine−$CH_2CH_3$), 55.31 (Ar−O$CH_3$), 105.52 (pyrimidine−H), 107.71 (pyrazole−C), 113.93 (2C, Ar−C), 124.96 (Ar−C), 128.28 (Ar−C), 128.48 (2C, Ar−C), 129.23 (2C, Ar−C), 131.15 (2C, Ar−C), 134.10 (Ar−C), 146.72 (pyrazole−C), 149.98 (pyrimidine−CCH$_2$CH$_3$), 153.16 (pyrazole−C), 158.29 (Ar−COCH$_3$), 163.41 (pyrimidine−CCH$_2$CH$_3$); LRMS *m/z* 357.2; HRMS ($C_{23}H_{24}N_3O$) calcd 357.1843, found 357.1841.

5,7-Diethyl-2,3-bis(4-methoxyphenyl)pyrazolo[1,5-*a*]-pyrimidine (13c). Following general procedure C, **9c** was reacted with 3,5-heptanedione **10c** to yield **13c**. Isolated yield 88%; light-yellow solid; mp 129−131 °C; ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 1.29 (t, 3H, J = 7.6 Hz, −CH$_2$CH_3), 1.43 (t, 3H, J = 7.5 Hz, −CH$_2$CH_3), 2.79 (q, 2H, J = 7.6 Hz, pyrimidine−CH_2CH$_3$), 3.18 (qd, 2H, J = 7.5, 0.6 Hz, pyrimidine−CH_2CH$_3$), 3.81 (s, 6H, Ar−OCH_3), 6.78 (t, 1H, J = 0.64 Hz, pyrimidine−H), 6.92 (m, 4H, Ar−H), 7.45 (AA′XX′, 2H, Ar−H), 7.58 (AA′XX′, 2H, Ar−H); ^{13}C NMR (125 MHz, $(CD_3)_2CO$) δ 10.66 (−CH$_2$$CH_3$), 13.07 (−CH$_2$$CH_3$), 23.99 (pyrimidine−$CH_2CH_3$), 31.88 (pyrimidine−$CH_2CH_3$), 55.41 (Ar−O$CH_3$), 55.52 (Ar−O$CH_3$), 106.45 (pyrimidine−H), 107.65 (pyrazole−C), 114.39 (2C, Ar−C), 114.47 (2C, Ar−C), 126.04 (Ar−C), 127.33 (Ar−C), 130.88 (2C, Ar−C), 131.93 (2C, Ar−C), 147.48 (pyrazole−C), 150.67 (pyrimidine−CCH$_2$CH$_3$), 153.19 (pyrazole−C), 159.22 (Ar−COCH$_3$), 160.77 (Ar−COCH$_3$), 163.98 (pyrimidine−CCH$_2$-CH$_3$); LRMS *m/z* 387.3; HRMS ($C_{24}H_{25}N_3O_2$) calcd 387.1945, found 387.1947.

5,7-Diethyl-2-(4-methoxyphenyl)-3-(3-methoxyphenyl)-pyrazolo[1,5-*a*]pyrimidine (13d). Following general procedure C, **9d** was reacted with 3,5-heptanedione **10c** to yield **13d**. Isolated yield 79%; white solid; mp 85−88 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.36 (t, 3H, J = 7.6 Hz −CH$_2$CH_3), 1.47 (t, 3H, J = 7.5 Hz, −CH$_2$CH_3), 2.86 (q, 2H, J = 7.6 Hz, pyrimidine−CH_2CH$_3$), 3.23 (q, 2H, J = 7.5 Hz, pyrimidine−CH_2CH$_3$), 3.76 (s, 3H, Ar−OCH_3), 3.83 (s, 3H, Ar−OCH_3), 6.58 (s, 1H, pyrimidine−H), 6.82 (ddd, 1H, J = 8.2, 2.6, 1.1 Hz, Ar−H), 6.91 (AA′XX′, 2H, Ar−H), 7.17 (dd, 1H, J = 7.5, 0.9 Hz, Ar−H), 7.25 (m, 2H, Ar−H), 7.61 (AA′XX′, 2H. Ar−H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.45 (−CH$_2$$CH_3$), 13.02 (−CH$_2$$CH_3$), 23.57 (pyrimidine−$CH_2CH_3$), 31.68 (pyrimidine−$CH_2CH_3$), 55.24 (Ar−O$CH_3$), 55.42 (Ar−O$CH_3$), 105.57 (pyrimidine−C), 107.36 (pyrazole−C), 112.43 (Ar−C), 113.98 (2C, Ar−C), 115.11 (Ar−C), 122.50 (Ar−C), 126.47 (Ar−C), 129.25 (2C, Ar−C), 130.61 (2C, Ar−C), 134.11 (Ar−C), 146.86 (pyrazole−C), 150.02 (pyrimidine−CCH$_2$CH$_3$), 153.42 (pyrazole−C), 159.56 (Ar−COCH$_3$), 159.94 (Ar−COCH$_3$), 163.60 (pyrimidine−CCH$_2$CH$_3$); LRMS *m/z* 387.3; HRMS ($C_{24}H_{25}N_3O_2$) calcd 387.1944, found 387.1947.

5,7-Diethyl-2-(3-methoxyphenyl)-3-(4-methoxyphenyl)-pyrazolo[1,5-*a*]pyrimidine (13e). Following general procedure C, **9e** was reacted with 3,5-heptanedione **10c** to yield **13e**. Isolated yield 91%; yellow solid; mp 100−101 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.34 (t, 3H, J = 7.6 Hz, −CH$_2$CH_3), 1.46 (t, 3H, J = 7.5 Hz, −CH$_2$CH_3), 2.84 (q, 2H, J = 7.6 Hz, pyrimidine−CH_2CH$_3$), 3.23 (q, 2H, J = 7.4 Hz, pyrimidine−CH_2CH$_3$), 3.73 (s, 3H, Ar−OCH_3), 3.82 (s, 3H, Ar−OCH_3), 6.57 (s, 1H, pyrimidine−H), 6.90 (m, 3H, Ar−H), 7.25 (m, 3H, Ar−H), 7.50 (AA′XX′, 2H, Ar−H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.44 (−CH$_2$$CH_3$), 13.17 (−CH$_2$$CH_3$), 23.53 (pyrimidine−$CH_2$-CH$_3$), 31.73 (pyrimidine−$CH_2CH_3$), 55.30 (Ar−O$CH_3$), 55.37 (Ar−O$CH_3$), 105.59 (pyrimidine−H), 107.87 (pyrazole−C), 113.95 (2C, Ar−C), 114.28 (Ar−C), 114.48 (Ar−C), 121.76 (Ar−C), 124.95 (Ar−C), 129.54 (Ar−C), 131.26 (2C, Ar−C), 135.59 (Ar−C), 146.75 (pyrazole−C), 150.04 (pyrimidine−CCH$_2$CH$_3$), 152.98 (pyrimidine−CCH$_2$CH$_3$), 158.36 (Ar−COCH$_3$), 159.66 (Ar−COCH$_3$), 163.49 (pyrimidine−CCH$_2$CH$_3$); LRMS *m/z* 387.3; HRMS ($C_{24}H_{25}N_3O_2$) calcd 387.1942, found 387.1947.

5,7-Diethyl-2,3-diphenylpyrazolo[1,5-*a*]pyrimidine (13f). Following general procedure C, **9f** was reacted with 3,5-heptanedione **10c** to yield **13f**. Isolated yield 79%; off-white solid; mp 143−144 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.39 (t, 3H, J = 7.6 Hz, −CH$_2$CH_3), 1.51 (t, 3H, J = 7.50 Hz, −CH$_2$CH_3), 2.88 (q, 2H, J = 7.6 Hz, −CH_2CH$_3$), 3.27 (qd 2H, J = 7.5, 0.6 Hz, −CH_2CH$_3$), 6.62 (t, 1H, J = 0.6 Hz, pyrimidine−H), 7.28 (m, 1H, Ar−H), 7.38 (m, 5H, Ar−H), 7.63 (m, 2H, Ar−H), 7.69 (m, 2H, Ar−H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.43 (−CH$_2$$CH_3$), 13.10 (−CH$_2$$CH_3$), 23.57 (pyrimidine−$CH_2$-CH$_3$), 31.73 (pyrimidine−$CH_2CH_3$), 105.71 (pyrimidine−C), 108.01 (pyrazole−C), 126.33 (Ar−C), 128.35 (2C, Ar−C), 128.39 (Ar−C), 128.51 (2C, Ar−C), 129.33 (2C, Ar−C), 130.08 (2C, Ar−C), 132.61 (Ar−C), 134.02 (Ar−C), 146.84 (pyrazole−C), 150.09 (pyrimidine−CCH$_2$CH$_3$), 153.51 (pyrazole−C), 163.71 (pyrimidine−CCH$_2$CH$_3$); LRMS *m/z* 327.2; HRMS ($C_{22}H_{21}N_3$) calcd 327.1729, found 327.1735. Anal. ($C_{22}H_{21}N_3$) C, H, N calcd: 80.70% C, 6.46% H, 12.83% N. Found: 80.38% C, 6.42% H, 12.77% N.

2-(4-Methoxyphenyl)-3-phenyl-5,7-bis(trifluoromethyl)-pyrazolo[1,5-*a*]pyrimidine (14a). Following general procedure C, **9a** was reacted with 1,1,1,5,5,5-hexfluoro-2,4-pentadione **10d** to yield **14a**. Isolated yield 60%; yellow solid; mp

159−161 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.85 (s, 3H, Ar−OC*H*$_3$), 6.93 (AA′XX′, 2H, Ar−H), 7.41 (m, 1H, Ar−H), 7.47 (m, 3H, Ar−H, pyrimidine−H), 7.59 (m, 2H, Ar−H), 7.69 (AA′XX′, 2H, Ar−H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.40 (Ar−O*C*H$_3$), 102.28 (m, pyrimidine−C), 112.31 (pyrazole−C), 114.25 (2C, Ar−C), 119.32 (q, J = 275.3 Hz, −*C*F$_3$), 120.46 (q, J = 275.3 Hz, −*C*F$_3$), 124.17 (Ar−C), 127.97 (Ar−C), 128.82 (Ar−C), 130.25 (2C, Ar−C), 130.28 (2C, Ar−C), 134.90 (2C, Ar−C), 135.06 (q, J = 37.8 Hz, pyrimidine−*C*CF$_3$), 145.46 (q, J = 37.8 Hz, pyrimidine−*C*CF$_3$), 146.73 (pyrazole−C), 156.77 (pyrazole−C), 160.87 (Ar−*C*OCH$_3$); LRMS *m/z* 437.2; HRMS ($C_{21}F_{13}F_6N_3O$) calcd 437.0963, found 437.0963;

3-(4-Methoxyphenyl)-2-phenyl-5,7-bis(trifluoromethyl)-pyrazolo[1,5-*a*]pyrimidine (14b). Following general procedure C, **9b** was reacted with 1,1,1,5,5,5-hexfluoro-2,4-pentadione **10d** to yield **14b**. Isolated yield 76%; yellow solid; mp 149−151 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.87 (s, 3H, Ar−OC*H*$_3$), 6.99 (AA′XX′, 2H, Ar−H), 7.41 (m, 3H, Ar−H), 7.47 (s, 1H, pyrimidine−H), 7.50 (AA′XX′, 2H, Ar−H), 7.75 (m, 2H, Ar−H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.47 (Ar−O*C*H$_3$), 102.51 (m, pyrimidine−C), 112.85 (pyrazole−C), 114.44 (2C, Ar−C), 119.37 (q, J = 275.3 Hz, −*C*F$_3$), 120.53 (q, J = 275.3 Hz, −*C*F$_3$), 122.24 (Ar−C), 128.88 (2C, Ar−C), 129.46 (2C, Ar−C), 129.64 (Ar−C), 131.47 (2C, Ar−C), 132.95 (Ar−C), 135.31 (q, J = 37.8 Hz, pyrimidine−*C*CF$_3$), 145.37 (q, J = 37.8 Hz, pyrimidine−*C*CF$_3$), 146.54 (pyrazole−C), 156.75 (pyrazole−C), 159.61 (Ar−*C*OCH$_3$); LRMS *m/z* 437.3; HRMS ($C_{22}H_{15}F_6N_3O$) calcd 437.0957, found 437.0959.

2,3-Bis(4-methoxyphenyl)-5,7-bis(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidine (14c). Following general procedure C, **9c** was reacted with 1,1,1,5,5,5-hexfluoro-2,4-pentadione **10d** to yield **14c**. Isolated yield 84%; orange solid; mp 160−161 °C; ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 3.83 (s, 3H, Ar−OC*H*$_3$), 3.85 (s, 3H, Ar−OC*H*$_3$), 6.96 (AA′XX′, 2H, Ar−H), 7.02 (AA′XX′, 2H, Ar−H), 7.45 (AA′XX′, 2H, Ar−H), 7.64 (AA′XX′, 2H, Ar−H), 7.85 (s, 1H, pyrimidine−H); ^{13}C NMR (125 MHz, $(CD_3)_2CO$) δ 55.56 (Ar−O*C*H$_3$), 55.64 (Ar−O*C*H$_3$), 103.98 (m, pyrimidine−C), 112.37 (pyrazole−C), 114.89 (2C, Ar−C), 114.97 (2C, Ar−C), 120.40 (q, J = 274.3, *C*F$_3$), 121.52 (q, J = 274.3, *C*F$_3$), 123.30 (Ar−C), 125.11 (Ar−C), 131.09 (2C, Ar−C), 132.15 (2C, Ar−C), 135.35 (q, J = 37.8, pyrimidine−*C*CF$_3$), 145.86 (q, J = 37.8, pyrimidine−*C*CF$_3$), 147.55 (pyrazole−C), 156.53 (pyrazole−C), 160.41 (Ar−*C*OCH$_3$), 161.68 (Ar−*C*OCH$_3$); LRMS *m/z* 467.3; HRMS ($C_{22}H_{15}F_6N_3O_2$) calcd 467.1063, found 467.1068.

3-(3-Methoxyphenyl)-2-(4-methoxyphenyl)-5,7-bis(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidine (14d). Following general procedure C, **9d** was reacted with 1,1,1,5,5,5-hexfluoro-2,4-pentadione **10d** to yield **14d**. Isolated yield 87%; yellow solid; mp 137−140 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.79 (s, 3H, Ar−OC*H*$_3$), 3.85 (s, 3H, Ar−OC*H*$_3$), 6.93 (m, 3H, Ar−H), 7.12 (dt, 1H, J = 7.7, 1.1 Hz, Ar−H), 7.15 (dd, 1H, J = 2.6, 1.5 Hz, Ar−H), 7.34 (dd, 1H, J = 8.2, 7.7 Hz, Ar−H), 7.44 (s, 1H, pyrimidine−H), 7.68 (AA′XX′, 2H, Ar−H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.42 (Ar−O*C*H$_3$), 55.52 (Ar−O*C*H$_3$), 102.30 (m, pyrimidine−C), 112.19 (pyrazole−C), 114.01 (2C, Ar−C), 114.31 (2C, Ar−C), 115.55 (Ar−C), 119.32 (q, J = 275.3 Hz, −*C*F$_3$), 120.46 (q, J = 275.3 Hz, −*C*F$_3$), 122.65 (Ar−C), 124.20 (Ar−C), 129.86 (Ar−C), 130.87 (2C, Ar−C), 135.12 (q, J = 38.7 Hz, pyrimidine−*C*CF$_3$), 145.52 (q, J = 37.8 Hz, pyrimidine−*C*CF$_3$), 146.74 (pyrazole−C), 156.88 (pyrazole−C), 159.91 (Ar−*C*OCH$_3$), 160.96 (Ar-*C*OCH$_3$); LRMS *m/z* 467.2; HRMS ($C_{22}H_{15}N_3O_2$) calcd 467.1063, found 467.1068.

2-(3-Methoxyphenyl)-3-(4-methoxyphenyl)-5,7-bis(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidine (14e). Following general procedure C, **9e** was reacted with 1,1,1,5,5,5-hexfluoro-2,4-pentadione **10d** to yield **14e**. Isolated yield 93%; light-orange solid; mp 142−143 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.76 (s, 3H, Ar−OC*H*$_3$), 3.86 (s, 3H, Ar−OC*H*$_3$), 6.98 (m, 3H, Ar−H), 7.31 (m, 3H, Ar−H), 7.47 (s, 1H, pyrimidine−H), 7.50 (AA′XX′, 2H, Ar−H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.35 (Ar−O*C*H$_3$), 55.40 (Ar−O*C*H$_3$), 102.47 (m, pyrimidine−C), 112.88 (pyrazole−C), 114.34 (2C, Ar−C), 114.50 (Ar−C), 115.53 (Ar−C), 119.28 (q, J = 275.3 Hz, −*C*F$_3$) 120.45 (q, J = 275.3, −*C*F$_3$), 121.81 (Ar−C), 122.14 (Ar−C), 129.85 (Ar−C), 131.46 (2C, Ar−C), 135.13 (q, J = 37.8 Hz, pyrimidine−*C*CF$_3$), 145.25 (q, J = 37.8 Hz, pyrimidine−*C*CF$_3$), 146.48 (pyrazole−C), 156.45 (pyrazole−C), 159.56 (Ar−*C*OCH$_3$), 159.84 (Ar−*C*OCH$_3$); LRMS *m/z* 467.2; HRMS ($C_{22}H_{15}F_6N_3O_2$) calcd 467.1064, found 467.1068.

2,3-Diphenyl-5,7-bis(trifluoromethyl)pyrazolo[1,5-*a*]-pyrimidine (14f). Following general procedure C, **9f** was reacted with 1,1,1,5,5,5-hexfluoro-2,4-pentadione **10d** to yield **14f**. Isolated yield 73%; yellow solid; mp 177−179 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (m, 6H, Ar−H), 7.50 (s, 1H, Ar−H), 7.59 (m, 2H, Ar−H), 7.75 (m, 2H, Ar−H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 102.59 (m, pyrimidine−C), 112.99 (pyrazole−C), 119.27 (q, J = 275.3 Hz, −*C*F$_3$), 120.42 (q, J = 275.3 Hz, −*C*F$_3$), 128.06 (Ar−C), 128.83 (2C, Ar−C), 128.85 (Ar−C), 129.47 (2C, Ar−C), 129.67 (2C, Ar−C), 130.03 (2C, Ar−C), 131.82 (Ar−C), 135.27 (q, J = 37.8 Hz, pyrimidine−*C*CF$_3$), 145.60 (q, J = 37.8 Hz, pyrimidine−*C*CF$_3$), 146.61 (pyrazole−C), 156.98 (pyrazole−C); LRMS *m/z* 407.2; HRMS ($C_{20}H_{11}F_6N_3$) calcd 407.0853, found 407.0853. Anal. ($C_{20}H_{11}F_6N_3$·0.1H_2O) C, H, N calcd: 58.72% C, 2.76% H, 10.27% N. Found: 58.44% C, 2.68% H, 10.00% N.

2-(4-Methoxyphenyl)-3-phenyl-5,7-diisopropylpyrazolo-[1,5-*a*]pyrimidine (15a). Following general procedure C, **9a** was reacted with 2,6-dimethyl-3,5-heptanedione **10e** to yield **15a**. Isolated yield 73%; white solid; mp 118−120 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.37 (d, 6H, J = 6.9 Hz, −CH(C*H*$_3$)$_2$), 1.51 (d, 6H, J = 6.9 Hz, −CH(C*H*$_3$)$_2$), 3.12 (sept, 1H, J = 6.9 Hz, pyrimidine−*C*H(CH$_3$)$_2$), 3.99 (sept, 1H, J = 6.9 Hz, pyrimidine−*C*H(CH$_3$)$_2$), 3.85 (s, 3H, Ar−OC*H*$_3$), 6.61 (s, 1H, pyrimidine−H), 6.93 (AA′XX′, 2H, Ar−H), 7.28 (m, 1H, Ar−H), 7.38 (m, 2H, Ar−H), 7.66 (m, 4H, Ar−H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.12 (2C, −CH(*C*H$_3$)$_2$), 22.12 (2C, −CH(*C*H$_3$)$_2$), 28.48 (pyrimidine−*C*H(CH$_3$)$_2$), 36.85 (pyrimidine−*C*H(CH$_3$)$_2$), 55.40 (Ar−O*C*H$_3$), 102.24 (pyrimidine−C), 107.38 (pyrazole−C), 113.98 (2C, Ar−C), 126.10 (Ar−C), 126.68 (Ar−C), 128.26 (2C, Ar−C), 130.02 (2C, Ar−C), 130.59 (2C, Ar−C), 132.96 (Ar−C), 146.90 (pyrazole−C), 153.20 (pyrazole−C), 154.45 (pyrimidine−*C*CH(CH$_3$)$_2$), 159.88 (Ar−*C*OCH$_3$), 167.34 (pyrimidine−*C*CH(CH$_3$)$_2$); LRMS *m/z* 385.3; HRMS ($C_{25}H_{27}N_3O$) calcd 385.2155, found 385.2154.

3-(4-Methoxyphenyl)-3-phenyl-5,7-diisopropylpyrazolo-[1,5-*a*]pyrimidine (15b). Following general procedure C, **9b** was reacted with 2,6-dimethyl-3,5-heptanedione **10e** to yield **15b**. Isolated yield 83%; off-white solid; mp 147−148 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.36 (d, 6H, J = 7.1 Hz, −CH(C*H*$_3$)$_2$), 1.51 (d, 6H, J = 6.9 Hz, −CH(C*H*$_3$)$_2$), 3.11 (sept, 1H, J = 6.9 Hz, pyrimidine−*C*H(CH$_3$)$_2$), 3.98 (sept, 1H, J = 6.9 Hz, pyrimidine−*C*H(CH$_3$)$_2$), 6.93 (s, 1H, pyrimidine−H), 7.39 (AA′XX′, 2H, Ar−H), 7.39 (m, 3H, Ar−H), 7.55 (AA′XX′, 2H, Ar−H), 7.69 (m, 2H, Ar−H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.33 (2C, −CH(*C*H$_3$)$_2$), 22.14 (2C, −CH(*C*H$_3$)$_2$), 28.48 (pyrimidine−*C*H(CH$_3$)$_2$), 36.86 (pyrimidine−*C*H(CH$_3$)$_2$), 55.35 (Ar−O*C*H$_3$), 102.26 (pyrimidine−C), 107.57 (pyrazole−C), 113.85 (2C, Ar−C), 125.14 (Ar−C), 128.29 (Ar−C), 128.51 (2C, Ar−C), 129.35 (2C, Ar−C), 131.13 (2C, Ar−C), 134.34 (Ar−C), 146.72 (pyrazole−C), 153.09 (pyrazole−C), 154.51 (pyrimidine−*C*CH(CH$_3$)$_2$), 158.19 (Ar−*C*OCH$_3$), 167.19 (pyrimidine−*C*CH(CH$_3$)$_2$); LRMS *m/z* 385.2; HRMS ($C_{25}H_{27}N_3O$) calcd 385.2153, found 385.2154.

2,3-Bis(4-methoxyphenyl)-5,7-diisopropylpyrazolo[1,5-*a*]pyrimidine (15c). Following general procedure C, **9c** was reacted with 2,6-dimethyl-3,5-heptanedione **10e** to yield **15c**. Isolated yield 89%; off-white solid; 108−110 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.34 (d, 6H, J = 6.9 Hz, −CH(C*H*$_3$)$_2$), 1.48 (d, 6H, J = 6.9 Hz, −CH(C*H*$_3$)$_2$), 3.09 (sept, 1H, J = 6.9 Hz, −C*H*(CH$_3$)$_2$), 3.95 (sept, 1H, J = 6.9 Hz, −C*H*(CH$_3$)$_2$), 3.84 (s, 3H, Ar−OC*H*$_3$), 3.85 (s, 3H, Ar−OC*H*$_3$), 6.57 (s, 1H, pyrimidine−H), 6.92 (m, 4H, Ar−H), 7.54 (AA′XX′, 2H, Ar−H), 7.61 (AA′XX′, 2H, Ar−H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.23 (2C, −CH(*C*H$_3$)$_2$), 22.15 (2C, −CH(*C*H$_3$)$_2$), 28.46 (pyrimidine−*C*H-(CH$_3$)$_2$), 36.86 (pyrimidine−*C*H(CH$_3$)$_2$), 55.35 (Ar−O*C*H$_3$), 55.42 (Ar−O*C*H$_3$), 102.02 (pyrimidine−C), 107.11 (pyrazole−C), 113.85 (2C, Ar−C), 113.98 (2C, Ar−C), 125.33 (Ar−C), 126.80 (2C, Ar−C), 130.53 (2C, Ar−C), 131.11 (2C, Ar−C),

146.76 (pyrazole−C), 152.89 (pyrazole−C), 154.39 (pyrimidine−*C*CH(CH$_3$)$_2$), 158.13 (Ar−*C*OCH$_3$), 159.82 (Ar−*C*OCH$_3$), 167.08 (pyrimidine−*C*CH(CH$_3$)$_2$); LRMS *m/z* 415.3; HRMS ($C_{26}H_{29}N_3O_2$) calcd 415.2260, found 415.2260.

3-(3-Methoxyphenyl)-2-(4-methoxyphenyl)-5,7-diisopropylpyrazolo[1,5-*a*]pyrimidine (15d). Following general procedure C, **9d** was reacted with 2,6-dimethyl-3,5-heptanedione **10e** to yield **15d**. Isolated yield 82%; off-white solid; mp 125−126 °C; ^{1}H NMR (500 MHz, CDCl$_3$) δ 1.39 (d, 6H, J = 6.9 Hz, −CH(C*H*$_3$)$_2$), 1.51 (d, 6H, J = 6.9 Hz, −CH(C*H*$_3$)$_2$), 3.13 (sept, 1H, pyrimidine−C*H*(CH$_3$)$_2$), 3.80 (s, 3H, Ar−OC*H*$_3$), 3.86 (s, 3H, Ar−OC*H*$_3$), 3.98 (sept, 1H, pyrimidine−C*H*(CH$_3$)$_2$), 6.62 (s, 1H, pyrimidine−H), 6.84 (ddd, 1H, J = 8.2, 2.6, 0.9 Hz, Ar−H), 6.96 (AA′XX′, 2H, Ar−H), 7.12 (dt, 1H, J = 7.7, 1.2 Hz, Ar−H), 7.28 (dd, 1H, J = 8.2, 7.5 Hz, Ar−H), 7.37 (dd, 1H, J = 2.6, 1.5 Hz, Ar−H), 7.66 (AA′XX′, 2H, Ar−H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 20.21 (2C, −CH(*C*H$_3$)$_2$), 22.09 (2C, −CH(*C*H$_3$)$_2$), 28.47 (pyrimidine−*C*H(CH$_3$)$_2$), 36.77 (pyrimidine−*C*H(CH$_3$)$_2$), 55.21 (Ar−O*C*H$_3$), 55.41 (Ar−O*C*H$_3$), 102.39 (pyrimidine−C), 107.14 (pyrazole−C), 112.43 (Ar−C), 113.97 (2C, Ar−C), 114.83 (Ar−C), 122.36 (Ar−C), 126.67 (Ar−C), 129.11 (Ar−C), 130.67 (2C, Ar−C), 134.23 (Ar−C), 146.86 (pyrazole−C), 153.33 (pyrazole−C), 154.47 (pyrimidine−*C*CH(CH$_3$)$_2$), 159.49 (Ar−*C*OCH$_3$), 159.92 (Ar−*C*OCH$_3$), 167.34 (pyrimidine−*C*CH(CH$_3$)$_2$); LRMS *m/z* 415.2; HRMS ($C_{26}H_{29}N_3O_2$) calcd 415.2261, found 415.2260.

2-(3-Methoxyphenyl)-3-(4-methoxyphenyl)-5,7-diisopropylpyrazolo[1,5-*a*]pyrimidine (15e). Following general procedure C, **9e** was reacted with 2,6-dimethyl-3,5-heptanedione **10e** to yield **15e**. Isolated yield 89%; white solid; mp 118−120 °C; ^{1}H NMR (500 MHz, CDCl$_3$) δ 1.35 (d, 6H, J = 6.9 Hz, −CH(C*H*$_3$)$_2$), 1.48 (d, 6H, J = 7.1 Hz, −CH(C*H*$_3$)$_2$), 3.10 (sept, 1H, J = 6.9 Hz, pyrimidine−C*H*(CH$_3$)$_2$), 3.76 (s, 3H, Ar−OC*H*$_3$), 3.84 (s, 3H, Ar−OC*H*$_3$), 3.96 (sept, 1H, J = 6.9 Hz, pyrimidine−C*H*(CH$_3$)$_2$), 6.59 (s, 1H, pyrimidine−H), 6.92 (m, 3H, Ar−H), 7.27 (m, 3H, Ar−H), 7.55 (AA′XX′, 2H, Ar−H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 20.24 (2C, −CH(*C*H$_3$)$_2$), 22.13 (2C, −CH(*C*H$_3$)$_2$), 28.45 (pyrimidine−*C*H(CH$_3$)$_2$), 36.86 (pyrimidine−*C*H(CH$_3$)$_2$), 55.32 (Ar−O*C*H$_3$), 55.36 (Ar−O*C*H$_3$), 102.30 (pyrimidine−C), 107.67 (pyrazole−C), 113.83 (2C, Ar−C), 114.32 (Ar−C), 114.45 (Ar−C), 121.84 (Ar−C), 125.09 (Ar−C), 129.53 (Ar−C), 131.19 (2C, Ar−C), 135.62 (Ar−C), 146.71 (pyrazole−C), 152.85 (pyrazole−C), 154.50 (pyrimidine−*C*CH(CH$_3$)$_2$), 158.22 (Ar−*C*OCH$_3$), 159.66 (Ar−*C*OCH$_3$), 167.21 (pyrimidine−*C*CH(CH$_3$)$_2$); LRMS *m/z* 415.3; HRMS ($C_{26}H_{29}N_3O_2$) calcd 415.2261, found 415.2260.

2-(4-Methoxyphenyl)-5,6,7-trimethyl-3-phenylpyrazolo-[1,5-*a*]pyrimidine (17a). Following general procedure C, **9a** was reacted with 3-methyl-2,4-pentanedione **16** to yield **17a**. Isolated yield 87%; white solid; mp 189−190 °C; ^{1}H NMR (500 MHz, CDCl$_3$) δ 2.31 (s, 3H, pyrimidine−C*H*$_3$), 2.57 (s, 3H, pyrimidine−C*H*$_3$), 2.83 (s, 3H, pyrimidine−C*H*$_3$), 3.83 (s, 3H, Ar−OC*H*$_3$), 6.90 (AA′XX′, 2H, Ar−H), 7.26 (m. 1H, ArH), 7.37 (m, 2H, Ar−H), 7.60 (m, 4H, Ar−H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 13.71 (pyrimidine−*C*H$_3$), 14.14 (pyrimidine−*C*H$_3$), 24.50 (pyrimidine−*C*H$_3$), 55.40 (Ar−O*C*H$_3$), 107.31 (pyrazole−C), 113.98 (2C, Ar−C), 114.72 (pyrimidine−*C*CH$_3$), 126.28 (Ar−C), 126.55 (Ar−C), 128.42 (2C, Ar−C), 130.09 (2C, Ar−C), 130.46 (2C, Ar−C), 132.88 (Ar−C), 141.99 (pyrimidine−*C*CH$_3$), 145.33 (pyrazole−C), 152.36 (pyrazole−C), 158.72 (pyrimidine−*C*CH$_3$), 159.84 (Ar−*C*OCH$_3$); LRMS *m/z* 343.2; HRMS ($C_{22}H_{21}N_2O$) calcd 343.1682, found 343.1685.

3-(4-Methoxyphenyl)-5,6,7-trimethyl-2-phenylpyrazolo-[1,5-*a*]pyrimidine (17b). Following general procedure C, **9b** was reacted with 3-methyl-2,4-pentanedione **16** to yield **17b**. Isolated yield 81%; white solid; mp 182−184 °C; ^{1}H NMR (500 MHz, CDCl$_3$) δ 2.32 (s, 3H, pyrimidine−C*H*$_3$), 2.52 (s, 3H, pyrimidine−C*H*$_3$), 2.84 (s, 3H, pyrimidine−C*H*$_3$), 3.83 (s, 3H, Ar−OC*H*$_3$), 6.92 (AA′XX′, 2H, Ar−H), 7.35 (m, 3H, Ar−H), 7.48 (AA′XX′, 2H, Ar−H), 7.67 (m, 2H, Ar−H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 13.76 (pyrimidine−*C*H$_3$), 14.21 (pyrimidine−*C*H$_3$), 24.51 (pyrimidine−*C*H$_3$), 55.43 (Ar−O*C*H$_3$), 107.56 (pyrazole−C), 114.07 (2C, Ar−C), 114.82 (pyrimidine−*C*CH$_3$), 125.05 (Ar−C), 128.26 (2C, Ar−C), 129.22 (2C, Ar−C), 131.24 (2C, Ar−C), 134.316 (pyrimidine−*C*CH$_3$), 142.09 (pyrimidine−*C*CH$_3$), 145.10 (pyrazole−C), 152.30 (pyrazole−C), 158.39 (Ar−*C*OCH$_3$); LRMS *m/z* 343.2; HRMS ($C_{22}H_{21}N_3O$) calcd 343.1679, found 343.1685.

2,3-Bis(4-methoxyphenyl)-5,6,7-trimethylpyrazolo[1,5-*a*]pyrimidine (17c). Following general procedure C, **9c** was reacted with 3-methyl-2,4-pentanedione **16** to yield **17c**. Isolated yield 81%; off-white solid; mp 201−203 °C; ^{1}H NMR (500 MHz, CDCl$_3$) δ 2.29 (s, 3H, pyrimidine−C*H*$_3$), 2.55 (s, 3H, pyrimidine−C*H*$_3$), 2.82 (s, 3H, pyrimidine−C*H*$_3$), 3.82 (s, 3H, Ar−OC*H*$_3$), 3.83 (s, 3H, Ar−OC*H*$_3$), 6.90 (AA′XX′, 2H, Ar−H), 6.93 (AA′XX′, 2H, Ar−H), 7.49 (AA′XX′, 2H, Ar−H), 7.61 (AA′XX′, 2H, Ar−H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 13.65 (pyrimidine−*C*H$_3$), 14.10 (pyrimidine−*C*H$_3$), 24.43 (pyrimidine−*C*H$_3$), 55.35 (2C, Ar−O*C*H$_3$), 107.01 (pyrazole−C), 113.94 (2C, Ar−C), 114.00 (2C, Ar−C), 114.53 (pyrimidine−*C*CH$_3$), 125.23 (Ar−C), 126.61 (Ar−C), 130.33 (2C, Ar−C), 131.19 (2C, Ar−C), 141.86 (pyrimidine−*C*CH$_3$), 145.15 (pyrazole−C), 152.00 (pyrazole−C), 158.27 (pyrimidine−*C*CH$_3$), 158.45 (Ar−*C*OCH$_3$), 159.74 (Ar−*C*OCH$_3$); LRMS *m/z* 373.2; HRMS ($C_{23}H_{23}N_3O_2$) calcd 373.1795, found 373.1790.

3-(3-Methoxyphenyl)-2-(4-methoxyphenyl)-5,6,7-trimethylpyrazolo[1,5-*a*]pyrimidine (17d). Following general procedure C, **9d** was reacted with 3-methyl-2,4-pentanedione **16** to yield **17d**. Isolated yield 78%; white solid; mp 143−145 °C; ^{1}H NMR (500 MHz, CDCl$_3$) δ 2.29 (s, 3H, pyrimidine−C*H*$_3$), 2.56 (s, 3H, pyrimidine−C*H*$_3$), 2.81 (s, 3H, pyrimidine−C*H*$_3$), 3.75 (s, 3H, Ar−OC*H*$_3$), 3.83 (s, 3H, Ar−OC*H*$_3$), 6.81 (ddd, 1H, J = 8.2, 2.6, 0.9 Hz, Ar−H), 6.91 (AA′XX′, 2H, Ar−H), 7.17 (dt, 1H, J = 7.5, 0.9 Hz, Ar−H), 7.21 (d, 1H, J = 1.3 Hz, Ar−H), 7.27 (t, 1H, J = 7.9 Hz, Ar−H), 7.62 (AA′XX′, 2H, Ar−H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 13.86 (pyrimidine−*C*H$_3$), 14.08 (pyrimidine−*C*H$_3$), 24.47 (pyrimidine−*C*H$_3$), 55.22 (Ar−O*C*H$_3$), 55.37 (Ar−O*C*H$_3$), 107.04 (pyrazole−C), 112.17 (Ar−C), 113.93 (2C, Ar−C), 114.72 (pyrimidine−*C*CH$_3$), 115.27 (Ar−C), 122.52 (Ar−C), 126.49 (Ar−C), 129.28 (Ar−C), 130.48 (2C, Ar−C), 134.15 (Ar−C), 141.95 (pyrimidine−*C*CH$_3$), 145.16 (pyrazole−C), 152.37 (pyrazole−C), 158.73 (pyrimidine−*C*CH$_3$), 159.56 (Ar−*C*OCH$_3$), 159.82 (Ar−*C*OCH$_3$); LRMS *m/z* 373.2; HRMS ($C_{23}H_{23}N_3O_2$) calcd 373.1794, found 373.1790.

2-(3-Methoxyphenyl)-3-(4-methoxyphenyl)-5,6,7-trimethylpyrazolo[1,5-*a*]pyrimidine (17e). Following general procedure C, **17e** was reacted with 3-methyl-2,4-pentanedione **16** to yield **17e**. Isolated yield 83%; off-white solid; mp 160−162 °C; ^{1}H NMR (500 MHz, CDCl$_3$) δ 2.28 (s, 3H, pyrimidine−C*H*$_3$), 2.54 (s, 3H, pyrimidine−C*H*$_3$), 2.80 (s, 3H, pyrimidine−C*H*$_3$), 3.72 (s, 3H, Ar−OC*H*$_3$), 3.81 (s, 3H, Ar−OC*H*$_3$), 6.89 (m, 3H, Ar−H), 7.24 (m, 3H, Ar−H), 7.47 (AA′XX′, 2H, Ar−H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 13.66 (pyrimidine−*C*H$_3$), 14.14 (pyrimidine−*C*H$_3$), 24.48 (pyrimidine−*C*H$_3$), 55.30 (Ar−O*C*H$_3$), 55.39 (Ar−O*C*H$_3$), 107.60 (pyrazole−C), 114.02 (2C, Ar−C), 114.09 (Ar−C), 114.44 (Ar−C), 114.83 (pyrimidine−*C*CH$_3$), 121.66 (Ar−C), 125.03 (Ar−C), 129.51 (Ar−C), 131.27 (2C, Ar−C), 135.43 (Ar−C), 141.93 (pyrimidine−*C*CH$_3$), 145.14 (pyrazole−C), 151.96 (pyrazole−C), 158.37 (Ar−*C*OCH$_3$), 158.62 (pyrimidine−*C*CH$_3$), 159.65 (Ar−*C*OCH$_3$); LRMS *m/z* 373.2; HRMS ($C_{23}H_{23}N_3O_2$) calcd 373.1791, found 373.1790.

General Procedure D for the Synthesis of Pyrazolo-[1,5-*a*]pyrimidines Using *p*-Toluenesulfonic Acid. The desired 3-amino-4,5-diarylpyrazole (0.5 mmol) was dissolved in 10 mL of dichlorobenzene. The diketone (0.7 mmol) and *p*-toluenesulfonic acid (0.7 mmol) were added, and the mixture was heated to 130 °C for 24 h. The dichlorobenzene was removed by rotary evaporation, and the resulting solid was purified by flash chromatography with 30% EtOAc/70% hexane.

5,7-Di-*tert*-butyl-2-(4-methoxyphenyl)-3-phenylpyrazolo-[1,5-*a*]pyrimidine (19a). Following general procedure D, **9a** was reacted with 2,2,6,6-tetramethyl-3,5-heptanedione **18a** to yield **19a**. Isolated yield 42%; light-yellow solid; mp 195−197 °C; ^{1}H NMR (500 MHz, CDCl$_3$) δ 1.41 (s, 9H, −C(C*H*$_3$)$_3$), 1.70 (s, 9H, −C(C*H*$_3$)$_3$), 3.86 (s, 3H, Ar−OC*H*$_3$), 6.79 (s, 1H, pyrimidine−H), 6.94 (AA′XX′, 2H, Ar−H), 7.26 (m, 1H, Ar−H), 7.38 (m, 2H, Ar−H), 7.68 (m, 4H, Ar−H); ^{13}C NMR (125

MHz, $CDCl_3$) δ 27.35 (3C, $-C(CH_3)_3$), 29.84 (3C, $-C(CH_3)_3$), 36.34 (pyrimidine$-C(CH_3)_3$), 38.44 (pyrimidine$-C(CH_3)_3$), 55.42 (Ar$-OCH_3$), 101.62 (pyrimidine−C), 106.56 (pyrazole−C), 113.90 (2C, Ar−C), 125.93 (Ar−C), 126.95 (Ar−C), 128.12 (2C, Ar−C), 130.08 (2C, Ar−C), 130.59 (2C, Ar−C), 133.17 (Ar−C), 147.54 (pyrazole−C), 152.02 (pyrazole−C), 155.14 (pyrimidine$-CC(CH_3)_3$), 159.82 (Ar$-COCH_3$), 168.90 (pyrimidine$-CC(CH_3)_3$); LRMS *m/z* 413.2; HRMS ($C_{27}H_{31}N_3O$) calcd 413.2473, found 413.2467.

5,7-Di-*tert*-butyl-3-(4-methoxyphenyl)-2-phenylpyrazolo-[1,5-*a*]pyrimidine (19b). Following general procedure D, **9b** was reacted with 2,2,6,6-tetramethyl-3,5-heptanedione **18a** to yield **19b**. Isolated yield 59%; off-white solid; mp 180−182 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.42 (s, 9H, $-C(CH_3)_3$), 1.71 (s, 9H, $-C(CH_3)_3$), 3.86 (s, 3H, Ar$-OCH_3$), 6.80 (s, 1H, pyrimidine−H), 6.94 (AA′XX′, 2H, Ar−H), 7.40 (m, 3H, Ar−H), 7.60 (AA′XX′, 2H, Ar−H), 7.75 (m, 2H, Ar−H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.34 (3C, $-C(CH_3)_3$), 29.84 (3C, $-C(CH_3)_3$), 36.33 (pyrimidine$-C(CH_3)_3$), 38.42 (pyrimidine$-C(CH_3)_3$), 55.33 (Ar$-OCH_3$), 101.67 (pyrimidine−C), 106.78 (pyrazole−C), 113.68 (2C, Ar−C), 125.36 (Ar−C), 128.17 (Ar−C), 128.42 (2C, Ar−C), 129.34 (2C, Ar−C), 131.16 (2C, Ar−C), 134.60 (Ar−C), 147.35 (pyrazole−C), 151.88 (pyrazole−C), 155.14 (pyrimidine$-CC(CH_3)_3$), 158.04 (Ar$-COCH_3$), 168.68 (pyrimidine$-CC(CH_3)_3$); LRMS *m/z* 413.3; HRMS ($C_{27}H_{31}N_3O$) calcd 413.2472, found 413.2467.

5,7-Di-*tert*-butyl-2,3-bis(4-methoxyphenyl)pyrazolo-[1,5-*a*]pyrimidine (19c). Following general procedure D, **9c** was reacted with 2,2,6,6-tetramethyl-3,5-heptanedione **18a** to yield **19c**. Isolated yield 84%; light-yellow solid; mp 158−161 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.41 (s, 9H, $-C(CH_3)_3$), 1.70 (s, 9H, $-C(CH_3)_3$), 3.86 (s, 6H, Ar$-OCH_3$), 6.77 (s, 1H, pyrimidine−H), 6.94 (m, 2H, Ar−H), 7.60 (AA′XX′, 2H, Ar−H), 7.68 (AA′XX′, 2H, Ar−H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.33 (3C, $-C(CH_3)_3$), 29.84 (3C, $-C(CH_3)_3$), 36.31 (pyrimidine$-C(CH_3)_3$), 38.39 (pyrimidine$-C(CH_3)_3$), 55.34 (Ar$-OCH_3$), 55.41 (Ar$-OCH_3$), 101.45 (pyrimidine−C), 106.29 (pyrazole−C), 113.67 (2C, Ar−C), 113.89 (2C, Ar−C), 125.55 (Ar−C), 127.08 (Ar−C), 130.51 (2C, Ar−C), 131.14 (2C, Ar−C), 147.38 (pyrazole−C), 151.70 (pyrazole−C), 155.03 (pyrimidine$-CC(CH_3)_3$), 157.99 (Ar$-COCH_3$), 159.76 (Ar$-COCH_3$), 168.57 (pyrimidine$-CC(CH_3)_3$); LRMS *m/z* 443.3; HRMS ($C_{28}H_{33}N_3O_2$) calcd 443.2568, found 443.2573.

5,7-Di-*tert*-butyl-3-(3-methoxyphenyl)-2-(4-methoxyphenyl)pyrazolo[1,5-*a*]pyrimidine (19d). Following general procedure D, **9d** was reacted with 2,2,6,6-tetramethyl-3,5-heptanedione **18a** to yield **19d**. Isolated yield 62%; white solid; mp 146−148 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.43 (s, 9H, $-C(CH_3)_3$), 1.70 (s, 9H, $-C(CH_3)_3$), 3.81 (s, 3H, Ar$-OCH_3$), 3.86 (s, 3H, Ar$-OCH_3$), 6.80 (s, 1H, pyrimidine−H), 6.83 (dd, 1H, J = 7.9, 1.3 Hz, Ar−H), 6.94 (AA′XX′, 2H, Ar−H), 7.23 (m, 2H, Ar−H), 7.43 (m, 1H, Ar−H), 7.69 (AA′XX′, 2H, Ar−H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.33 (3C, $-C(CH_3)_3$), 29.85 (3C, $-C(CH_3)_3$), 36.34 (pyrimidine$-C(CH_3)_3$), 38.45 (pyrimidine$-C(CH_3)_3$), 55.27 (Ar$-OCH_3$), 55.42 (Ar$-OCH_3$), 101.65 (pyrimidine−C), 106.35 (pyrazole−C), 112.58 (Ar−C), 113.88 (Ar−C), 114.61 (Ar−C), 122.39 (Ar−C), 126.92 (Ar−C), 127.90 (Ar−C), 128.96 (Ar−C), 130.69 (2C, Ar−C), 134.44 (Ar−C), 147.49 (pyrazole−C), 152.18 (pyrazole−C), 155.20 (pyrimidine$-CC(CH_3)_3$), 159.45 (Ar$-COCH_3$), 159.86 (Ar$-COCH_3$), 168.94 (pyrimidine$-CC(CH_3)_3$); LRMS *m/z* 443.3; HRMS ($C_{28}H_{33}N_3O_2$) calcd 443.2569, found 443.2573.

5,7-Di-*tert*-butyl-2-(3-methoxyphenyl)-3-(4-methoxyphenyl)pyrazolo[1,5-*a*]pyrimidine (19e). Following general procedure D, **9e** was reacted with 2,2,6,6-tetramethyl-3,5-heptanedione **18a** to yield **19e**. Isolated yield 63%; light-yellow solid; mp 144−145 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.40 (s, 9H, $-C(CH_3)_3$), 1.69 (s, 9H, $-C(CH_3)_3$), 3.77 (s, 3H, Ar$-OCH_3$), 3.85 (s, 3H, Ar$-OCH_3$), 6.78 (s, 1H, pyrimidine−H), 6.92 (m, 3H, Ar−H), 7.30 (m, 3H, Ar−H), 7.59 (AA′XX′, 2H, Ar−H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.34 (3C, $-C(CH_3)_3$), 29.83 (3C, $-C(CH_3)_3$), 36.33 (pyrimidine$-C(CH_3)_3$), 38.42 (pyrimidine$-C(CH_3)_3$), 55.34 (Ar$-OCH_3$), 55.36 (Ar$-OCH_3$), 101.73 (pyrimidine−C), 106.91 (pyrazole−C), 113.65 (2C, Ar−C), 113.99 (Ar−C), 114.61 (Ar−C), 121.85 (Ar−C), 125.30 (Ar−C), 129.42 (Ar−C), 131.25 (2C, Ar−C), 135.90 (Ar−C), 147.35 (pyrazole−C), 151.64 (pyrazole−C), 155.14 (pyrimidine$-CC(CH_3)_3$), 158.09 (Ar$-COCH_3$), 159.58 (Ar$-COCH_3$), 168.72 (pyrimidine$-CC(CH_3)_3$); LRMS *m/z* 443.3; HRMS ($C_{28}H_{33}N_3O_2$) calcd 443.2576, found 443.2573.

2-(4-Methoxyphenyl)-3,5,7-triphenylpyrazolo[1,5-*a*]pyrimidine (20a). Following general procedure D, **9a** was reacted with dibenzoylmethane **18b** to yield **20a**. Isolated yield 93%; yellow solid; mp 191−193 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.84 (s, 3H, Ar$-OCH_3$), 6.90 (AA′XX′, 2H, Ar−H), 7.32 (m, 1H, Ar−H), 7.44 (m, 2H, Ar−H), 7.51 (m, 3H, Ar−H), 7.60 (m, 3H, Ar−H), 7.65 (AA′XX′, 2H, Ar−H), 7.73 (m, 2H, Ar−H), 8.21 (m, 4H, Ar−H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.43 (Ar$-OCH_3$), 105.26 (pyrimidine−C), 108.74 (pyrazole−C), 113.98 (2C, Ar−C), 126.18 (Ar−C), 126.52 (Ar−C), 127.43 (2C, Ar−C), 128.44 (2C, Ar−C), 128.81 (2C, Ar−C), 129.02 (2C, Ar−C), 129.68 (2C, Ar−C), 130.31 (2C, Ar−C), 130.37 (Ar−C), 130.64 (2C, Ar−C), 131.09 (Ar−C), 131.75 (Ar−C), 132.75 (Ar−C), 137.72 (Ar−C), 146.37 (pyrazole−C), 148.18 (pyrimidine−CPh), 154.18 (pyrazole−C), 155.85 (pyrimidine−CPh), 160.08 (Ar$-COCH_3$); LRMS *m/z* 453.2; HRMS ($C_{31}H_{23}N_3O$) calcd 453.1847, found 453.1841.

3-(4-Methoxyphenyl)-2,5,7-triphenylpyrazolo[1,5-*a*]pyrimidine (20b). Following general procedure D, **9b** was reacted with dibenzoylmethane **18b** to yield **20b**. Isolated yield 67%; orange solid; mp 220−223 °C dec; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.88 (s, 3H, Ar$-OCH_3$), 6.99 (AA′XX′, 2H, Ar−H), 7.37 (m, 3H, Ar−H), 7.41 (s, 1H, pyrimidine−H), 7.51 (m, 3H, Ar−H), 7.60 (m, 5H, Ar−H), 7.73 (m, 2H, Ar−H), 8.21 (m, 4H, Ar−H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.46 (Ar$-OCH_3$), 105.33 (pyrimidine−C), 109.07 (pyrazole−C), 114.07 (2C, Ar−C), 124.98 (Ar−C), 127.38 (Ar−C), 127.45 (2C, Ar−C), 128.51 (2C, Ar−C), 128.81 (2C, Ar−C), 128.88 (Ar−C), 129.03 (2C, Ar−C), 129.38 (2C, Ar−C), 129.69 (2C, Ar−C), 130.34 (Ar−C), 131.08 (Ar−C), 131.44 (2C, Ar−C), 131.82 (Ar−C), 137.83 (Ar−C), 146.44 (pyrazole−C), 148.08 (pyrimidine−CPh), 154.11 (pyrazole−C), 155.72 (pyrimidine−CPh), 158.61 (Ar$-COCH_3$); LRMS *m/z* 453.1; HRMS ($C_{31}H_{23}N_3O$) calcd 453.1839, found 453.1841.

2,3-Bis(4-methoxyphenyl)-5,7-diphenylpyrazolo[1,5-*a*]-pyrimidine (20c). Following general procedure D, **9c** was reacted with dibenzoylmethane **18b** to yield **20c**. Isolated yield 77%; orange solid; mp 206−208; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.83 (s, 3H, Ar$-OCH_3$), 3.88 (s, 3H, Ar$-OCH_3$), 6.90 (AA′XX′, 2H, Ar−H), 6.99 (AA′XX′, 2H, Ar−H), 7.39 (s, 1H, pyrimidine−H), 7.50 (m, 3H, Ar−H), 7.63 (m, 7H, Ar−H), 8.18 (m, 2H, Ar−H), 8.22 (m, 2H, Ar−H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.45 (2C, Ar$-OCH_3$), 105.15 (pyrimidine−C), 108.50 (pyrazole−C), 113.98 (2C, Ar−C), 114.03 (2C, Ar−C), 125.08 (Ar−C), 126.31 (Ar−C), 127.41 (2C, Ar−C), 128.81 (2C, Ar−C), 129.02 (2C, Ar−C), 129.66 (3C, Ar−C), 130.31 (Ar−C), 130.56 (2C, Ar−C), 131.06 (Ar−C), 131.40 (2C, Ar−C), 131.82 (Ar−C), 137.81 (2C, Ar−C), 146.29 (pyrazole−C), 149.07 (pyrimidine−CPh), 153.90 (pyrazole−C), 155.61 (pyrimidine−CPh), 158.47 (Ar$-COCH_3$), 160.02 (Ar$-COCH_3$); LRMS *m/z* 483.2; HRMS ($C_{32}H_{25}N_3O_2$) calcd 483.1944, found 483.1947.

3-(3-Methoxyphenyl)-2-(4-methoxyphenyl)-5,7-diphenylpyrazolo[1,5-*a*]pyrimidine (20d). Following general procedure D, **9d** was reacted with dibenzoylmethane **18b** to yield **20d**. Isolated yield 92%; yellow solid; mp 202−203 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.81 (s, 3H, Ar$-OCH_3$), 3.84 (s, 3H, Ar$-OCH_3$), 6.88 (ddd, 1H, J = 7.9, 2.6, 1.1 Hz), 6.92 (AA′XX′, 2H, Ar−H), 7.29 (dt, 1H, J = 7.5, 1.3 Hz, Ar−H), 7.33 (dd, 1H, J = 7.9, 7.7 Hz, Ar−H), 7.36 (dd, 1H, J = 2.6, 1.5 Hz), 7.41 (s, 1H, Ar−H), 7.51 (m, 3H, Ar−H), 7.60 (m, 3H, Ar−H), 7.67 (AA′XX′, 2H, Ar−H), 8.21 (m, 4H, Ar−H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.36 (Ar$-OCH_3$), 55.45 (Ar$-OCH_3$), 105.25 (pyrimidine−C), 108.53 (pyrazole−C), 112.74 (Ar−C), 113.97 (2C, Ar−C), 115.28 (Ar−C), 122.75 (Ar−C), 126.16 (Ar−C), 127.41 (2C, Ar−C), 128.81 (2C, Ar−C), 129.02 (2C, Ar−C), 129.35 (Ar−C), 129.68 (2C, Ar−C), 130.38 (Ar−C), 130.71 (2C, Ar−C), 131.11 (Ar−C), 131.72 (Ar−C), 134.02 (Ar−C), 137.71 (Ar−C), 146.40 (pyrazole−C), 148.14 (pyrimidine−CPh), 154.27

(pyrazole−C), 155.85 (pyrimidine−*C*Ph), 159.65 (Ar−*C*OCH$_3$), 160.11 (Ar−*C*OCH$_3$); LRMS *m/z* 483.2; HRMS ($C_{32}H_{25}N_3O_2$) calcd 483.1949, found 483.1947.

2-(3-Methoxyphenyl)-3-(4-methoxyphenyl)-5,7-diphenylpyrazolo[1,5-*a*]pyrimidine (20e). Following general procedure D, **9e** was reacted with dibenzoylmethane **18b** to yield **20e**. Isolated yield 86%; orange solid; mp 190−191 °C dec; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.75 (s, 3H, Ar−OC*H*$_3$), 3.88 (s, 3H, Ar−OC*H*$_3$), 6.92 (ddd, 1H, J = 7.7, 2.6, 1.3 Hz, Ar−H), 7.00 (AA′XX′, 2H, Ar−H), 7.30 (m, 3H, Ar−H), 7.41 (s, 1H, Ar−H), 7.50 (m, 3H, Ar−H), 7.60 (m, 3H, Ar−H), 7.65 (AA′XX′, 2H, Ar−H), 8.19 (m, 2H, Ar−H), 8.22 (m, 2H, Ar−H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.36 (Ar−O*C*H$_3$), 55.43 (Ar−O*C*H$_3$), 105.38 (pyrimidine−C), 109.09 (pyrazole−C), 113.98 (2C, Ar−C), 114.49 (2C, Ar−C), 121.86 (Ar−C), 124.82 (Ar−C), 127.39 (2C, Ar−C), 128.79 (2C, Ar−C), 129.00 (2C, Ar−C), 129.52 (Ar−C), 129.64 (2C, Ar−C), 130.34 (Ar−C), 131.08 (Ar−C), 131.45 (2C, Ar−C), 131.67 (Ar−C), 135.11 (Ar−C), 137.68 (Ar−C), 146.36 (pyrimidine−*C*Ph), 147.99 (pyrazole−C), 153.79 (pyrazole−C), 155.69 (pyrimidine−*C*Ph), 158.53 (Ar−*C*OCH$_3$), 159.63 (Ar−*C*OCH$_3$); LRMS *m/z* 483.2; HRMS ($C_{32}H_{25}N_3O_2$) calcd 483.1942, found 483.1947.

General Procedure E for the Deprotection of Pyrazolo[1,5-*a*]pyrimidines. The methoxyphenylpyrazolo[1,5-*a*]-pyrimidine (0.3 mmol) was dissolved in 5 mL of dry CH_2Cl_2 and cooled to 0 °C. A solution of BF_3·SMe_2 (1.8 mmol/methoxy) was added dropwise to the mixture. The solution was allowed to slowly warm to room temperature and stirred for a total of 18 h. The reaction was stopped by the addition of 2 mL of water and 8 mL of methanol. The mixture was placed under a nitrogen stream for 2 h to blow off the SMe_2. An additional 10 mL of water was added, and the solution was extracted with EtOAc (3 × 15 mL). The combined organic phases were washed with saturated NaCl (2 × 10 mL) and dried with Na_2SO_4. The resulting solid was purified by preparatory thin-layer chromatography. After isolation the sample was dried under vacuum in an Aberhalden apparatus in refluxing benzene for 24−48 h. Even after this process some samples still contained water in the crystals. This was confirmed by ^{1}H NMR, and suitable corrections are made for this water in evaluation of combustion microanalysis data.

2-(4-Hydroxyphenyl)-3-phenylpyrazolo[1,5-*a*]pyrimidine (21a). Following general procedure E, **11a** was deprotected to yield **21a**. Isolated yield 82%; light-yellow solid; mp 188−189 °C; ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 6.85 (AA′XX′, 2H, Ar−H), 6.97 (dd, 1H, J = 7.1, 4.1 Hz, pyrimidine−H), 7.27 (m, 1H, Ar−H), 7.36 (m, 2H, Ar−H), 7.49 (AA′XX′, 2H, Ar−H), 7.54 (m, 2H, Ar−H), 8.47 (dd, 1H, J = 4.1, 1.7 Hz, pyrimidine−H), 8.89 (dd, 1H, J = 7.1, 1.7 Hz, pyrimidine−H); ^{13}C NMR (125 MHz, $(CD_3)_3CO$) δ 108.55 (pyrazole−C), 109.31 (pyrimidine−C), 116.04 (2C, Ar−C), 125.30 (Ar−C), 127.22 (Ar−C), 128.92 (2C, Ar−C), 130.79 (2C, Ar−C), 131.08 (2C, Ar−C), 133.24 (Ar−C), 135.84 (pyrimidine−C), 147.81 (pyrazole−C), 150.35 (pyrimidine−C), 154.37 (pyrazole−C), 158.77 (Ar−*C*OH); LRMS *m/z* 287.1; HRMS ($C_{18}H_{13}N_3O$) calcd 287.1056, found 287.1059. Anal. ($C_{18}H_{13}N_3O$·0.1H_2O) C, H, N calcd: 74.78% C, 4.60% H, 14.53% N. Found: 74.87% C, 4.63% H, 14.12% N.

3-(4-Hydroxyphenyl)-2-phenylpyrazolo[1,5-*a*]pyrimidine (21b). Following general procedure E, **11b** was deprotected to yield **21b**. Isolated yield 89%; yellow solid; mp 219−221 °C; ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 6.87 (AA′XX′, 2H, Ar−H), 7.03 (dd, 1H, J = 7.1, 4.1 Hz, pyrimidine−H), 7.34 (AA′XX′, 2H, Ar−H), 7.39 (m, 3H, Ar−H), 7.67 (m, 2H, Ar−H), 8.50 (dd, 1H, J = 3.9, 1.7 Hz, pyrimidine−H), 8.93 (dd, 1H, J = 7.1, 1.9 Hz, pyrimidine−H); ^{13}C NMR (125 MHz, $(CD_3)_2CO$) δ 109.44 (pyrazole−C), 109.51 (pyrimidine−C), 115.99 (2C, Ar−C), 123.96 (Ar−C), 129.13 (2C, Ar−C), 129.19 (2C, Ar−C), 129.63 (2C, Ar−C), 132.07 (Ar−C), 135.95 (pyrimidine−C), 147.47 (pyrazole−C), 150.19 (pyrimidine−C), 153.87 (pyrazole−C), 157.23 (Ar−*C*OH); LRMS *m/z* 287.1; HRMS ($C_{18}H_{13}N_3O$) calcd 287.1055, found 287.1058. Anal. ($C_{18}H_{13}N_3O$·0.1H_2O) C, H, N calcd: 74.78% C, 4.60% H, 14.53% N. Found: 74.85% C, 4.57% H, 14.17% N.

2,3-Bis(4-hydroxyphenyl)pyrazolo[1,5-*a*]pyrimidine (21c). Following general procedure E, **11c** was deprotected to yield **21c**. Isolated yield 79%; yellow solid; mp >260 °C; ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 6.85 (m, 4H, Ar−H), 6.98 (dd, 1H, J = 6.9, 3.9 Hz, pyrimidine−H), 7.35 (AA′XX′, 2H, Ar−H), 7.52 (AA′XX′, 2H, Ar−H), 8.37 (s, 1H, Ar−O*H*), 8.46 (dd, 1H, J = 4.1, 1.7 Hz, pyrimidine−H), 8.58 (s, 1H, Ar−O*H*), 8.88 (dd, 1H, J = 6.9, 1.7 Hz, pyrimidine−H); ^{13}C NMR δ 108.07 (pyrimidine−C), 108.46 (pyrazole−C), 115.31 (2C, Ar−C), 115.36 (2C, Ar−C), 123.64 (Ar−C), 125.06 (Ar−C), 130.33 (2C, Ar−C), 131.42 (2C, Ar−C), 135.12 (pyrimidine−C), 146.87 (pyrazole−C), 149.28 (pyrimidine−C), 153.45 (pyrazole−C), 156.48 (Ar−*C*OH), 158.06 (Ar−*C*OH); LRMS *m/z* 303.1; HRMS (C_{18} $H_{13}N_3O_2$) calcd 303.1002, found 303.1008.

2-(4-Hydroxyphenyl)-3-(3-hydroxyphenyl)pyrazolo[1,5-*a*]pyrimidine (21d). Following general procedure E, **11d** was deprotected to yield **21d**. Isolated yield 67%; light-yellow solid; mp >260 °C; ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 6.77 (ddd, 1H, J = 8.2, 2.6, 1.1 Hz, Ar−H), 6.85 (AA′XX′, 2H, Ar−H), 6.99 (ddd, 1H, J = 7.7, 1.5, 1.1 Hz, Ar−H), 7.01 (dd, 1H, J = 6.9, 4.1 Hz, pyrimidine−H), 7.06 (dd, 1H, J = 2.6, 1.7 Hz, Ar−H), 7.19 (t, 1H, J = 7.93 Hz, Ar−H), 7.51 (AA′XX′, 2H, Ar−H), 8.28 (s, 1H, Ar−O*H*), 8.49 (dd, 1H, J = 3.9, 1.7 Hz, pyrimidine−H), 8.59 (s, 1H, Ar−O*H*), 8.90 (dd, 1H, J = 6.9, 1.7 Hz, pyrimidine−H); ^{13}C NMR (125 MHz, $(CD_3)_2CO$) δ 108.67 (pyrazole−C), 109.31 (pyrimidine−C), 114.40 (Ar−C), 116.04 (2C, Ar−C), 117.78 (Ar−C), 122.19 (Ar−C), 125.54 (Ar−C), 129.94 (Ar−C), 131.12 (2C, Ar−C), 134.60 (Ar−C), 135.88 (pyrimidine−C), 147.63 (pyrazole−C), 150.25 (pyrimidine−C), 154.45 (pyrazole−C), 158.15 (Ar−*C*OH), 158.80 (Ar−*C*OH); LRMS *m/z* 303.1; HRMS ($C_{18}H_{13}N_3O_2$) calcd 303.0999, found 303.1008.

2-(3-Hydroxyphenyl)-3-(4-hydroxyphenyl)pyrazolo[1,5-*a*]pyrimidine (21e). Following general procedure E, **11e** was deprotected to yield **21e**. Isolated yield 59%; yellow solid; mp >260 °C; ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 6.77 (m, 3H, Ar−H), 6.97 (dt, 1H, J = 7.7, 1.3 Hz, Ar−H), 7.03 (dd, 1H, J = 2.4, 1.5 Hz, Ar−H), 7.05 (dd, 1H, J = 7.1, 4.1 Hz, pyrimidine−H), 7.16 (t, 1H, J = 7.8 Hz, Ar−H), 7.23 (AA′XX′, 2H, Ar−H), 8.51 (dd, 1H, J = 3.9, 1.7 Hz, pyrimidine−H), 9.11 (dd, 1H, J = 7.1, 1.7 Hz, pyrimidine−H), 9.43 (s, 1H, Ar−O*H*), 9.48 (dd, 1H, Ar−O*H*); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 108.01 (pyrazole−C), 108.89 (pyrimidine−C), 115.20 (2C, Ar−C), 115.29 (Ar−C), 115.49 (Ar−C), 119.29 (Ar−C), 122.03 (Ar−C), 129.41 (Ar−C), 130.91 (2C, Ar−C), 134.26 (Ar−C), 135.56 (pyrimidine−C), 145.99 (pyrazole−C), 149.77 (pyrimidine−C), 152.42 (pyrazole−C), 156.24 (Ar−*C*OH), 157.30 (Ar−*C*OH); LRMS *m/z* 303.1; HRMS ($C_{20}H_{13}N_3O_2$) calcd 303.1007, found 303.1008.

2-(4-Hydroxyphenyl)-5,7-dimethyl-3-phenylpyrazolo-[1,5-*a*]pyrimidine (22a). Following general procedure E, **12a** was deprotected to yield **22a**. Isolated yield 52%; white solid; mp 213-216 °C; ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 2.48 (s, 3H, pyrimidine−C*H*$_3$), 2.73 (d, 3H, J = 0.9 Hz, pyrimidine−C*H*$_3$), 6.77 (q, 1H, J = 0.9 Hz, pyrimidine−H), 6.83 (AA′XX′, 2H, Ar−H), 7.25 (m, 1H, Ar−H), 7.35 (m, 2H, Ar−H), 7.48 (AA′XX′, 2H, Ar−H), 7.53 (m, 2H, Ar−H), 8.59 (s, 1H, Ar−O*H*); ^{13}C NMR (125 MHz, $(CD_3)_2CO$) δ 16.78 (pyrimidine−*C*H$_3$), 24.64 (pyrimidine−*C*H$_3$), 107.65 (pyrazole−C), 109.44 (pyrimidine−C), 115.95 (2C, Ar−C), 126.01 (Ar−C), 126.91 (Ar−C), 128.85 (2C, Ar−C), 130.88 (2C, Ar−C), 131.06 (2C, Ar−C), 134.01 (Ar−C), 145.84 (pyrimidine−*C*CH$_3$), 147.47 (pyrazole−C), 153.80 (pyrazole−C), 158.64 (Ar−*C*OH), 159.41 (pyrimidine−*C*CH$_3$); LRMS *m/z* 315.2; HRMS ($C_{20}H_{17}N_3O$) calcd 315.1372, found 315.1372. Anal. ($C_{20}H_{17}N_3O$·0.1H_2O) C, H, N calcd: 75.74% C, 5.47% H, 13.25% N. Found: 75.65% C, 5.45% H, 12.90% N.

3-(4-Hydroxyphenyl)-5,7-dimethyl-2-phenylpyrazolo-[1,5-*a*]pyrimidine (22b). Following general procedure E, **12b** was deprotected to yield **22b**. Isolated yield 23%; white solid; mp 253−255 °C; ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 2.49 (s, 3H, pyrimidine−C*H*$_3$), 2.75 (d, 3H, J = 0.9 Hz, pyrimidine−C*H*$_3$), 6.81 (q, 1H, J = 1.1 Hz, pyrimidine−H), 6.85 (AA′XX′, 2H, Ar−H), 7.32 (AA′XX′, 2H, Ar−H), 7.37 (m, 3H, Ar−H), 7.66 (m, 2H, Ar−H), 8.35 (s, 1H, Ar−O*H*); ^{13}C NMR (125 MHz, $(CD_3)_2$-

CO), δ 16.75 (pyrimidine−*C*H$_3$), 24.66 (pyrimidine−*C*H$_3$), 109.57 (pyrimidine−C), 115.84 (pyrazole−C), 115.93 (2C, Ar−C), 124.64 (Ar−C), 128.85 (Ar−C), 129.04 (2C, Ar−C), 129.65 (2C, Ar−C), 132.13 (2C, Ar−C), 135.11 (Ar−C), 145.85 (pyrimidine−*C*CH$_3$), 147.39 (pyrazole−C), 153.28 (pyrazole−C), 158.15 (pyrimidine−*C*CH$_3$), 159.21 (Ar−*C*OH); LRMS *m/z* 315.2; HRMS ($C_{20}H_{17}N_3O$) calcd 315.1372, found 315.1372. Anal. ($C_{20}H_{17}N_3O$·0.1H_2O) C, H, N calcd: 75.74% C, 5.47% H, 13.25% N. Found: 75.40% C, 5.35% H, 13.02% N.

2,3-Bis(4-hydroxyphenyl)-5,7-dimethylpyrazolo[1,5-*a*]pyrimidine (22c). Following general procedure E, **12c** was deprotected to yield **22c**. Isolated yield 50%; light-yellow solid; mp 261−264 °C; ^{1}H NMR (500 MHz, (CD$_3$)$_2$CO) δ 2.47 (s, 3H, pyrimidine−C*H*$_3$), 2.73 (d, 3H, *J* = 0.9 Hz, pyrimidine−C*H*$_3$), 6.75 (q, 1H, *J* = 1.1 Hz, pyrimidine−H), 6.84 (m, 4H, Ar−H), 7.33 (AA′XX′, 2H, Ar−H), 7.52 (AA′XX′, 2H, Ar−H), 8.32 (s, 1H, Ar−O*H*), 8.53 (s, 1H, Ar−O*H*); ^{13}C NMR (125 MHz, (CD$_3$)$_2$CO) δ 16.75 (pyrimidine−*C*H$_3$), 24.62 (pyrimidine−*C*H$_3$), 107.81 (pyrazole−C), 109.16 (pyrimidine−C), 115.87 (2C, Ar−C), 115.91 (2C, Ar−C), 124.96 (Ar−C), 126.28 (Ar−C), 130.96 (2C, Ar−C), 132.12 (2C, Ar−C), 145.67 (pyrimidine−*C*CH$_3$), 147.39 (pyrazole−C), 153.49 (pyrazole−C), 156.91 (pyrimidine−*C*CH$_3$), 158.53 (Ar−*C*OH), 158.89 (Ar−*C*OH); LRMS *m/z* 331.1; HRMS ($C_{20}H_{17}N_3O_2$) calcd 331.1325, found 331.1321. Anal. ($C_{20}H_{17}N_3O_2$·0.4H_2O) C, H, N calcd: 70.95% C, 5.30% H, 12.41% N. Found: 70.77% C, 5.14% H, 12.02% N.

2-(4-Hydroxyphenyl)-3-(3-hydroxyphenyl)-5,7-dimethylpyrazolo[1,5-*a*]pyrimidine (22d). Following general procedure E, **12d** was deprotected to yield **22d**. Isolated yield 43%; off-white solid; mp 252−255 °C; ^{1}H NMR (500 MHz, (CD$_3$)$_2$CO) δ 2.48 (s, 3H, pyrimidine−C*H*$_3$), 2.72 (d, 3H, *J* = 0.6 Hz, pyrimidine−C*H*$_3$), 6.75 (ddd, 1H, *J* = 8.2, 2.6, 0.9 Hz, Ar−H), 6.77 (q, 1H, *J* = 0.9 Hz, pyrimidine−H), 6.84 (AA′XX′, 2H, Ar−H), 6.99 (dt, 1H, *J* = 7.5, 1.1 Hz, Ar−H), 7.06 (dd, 1H, *J* = 2.6, 1.6 Hz, Ar−H), 7.17 (t, 1H, *J* = 7.8 Hz, Ar−H), 7.51 (AA′XX′, 2H, Ar−H), 8.25 (s, 1H, Ar−O*H*), 8.54 (s, 1H, Ar−O*H*); ^{13}C NMR (125 MHz, (CD$_3$)$_2$CO) δ 16.78 (pyrimidine−*C*H$_3$), 24.65 (pyrimidine−*C*H$_3$), 107.76 (pyrazole−C), 109.38 (pyrimidine−C), 114.09 (Ar−C), 115.93 (2C, Ar−C), 117.87 (Ar−C), 122.31 (Ar−C), 126.10 (Ar−C), 129.81 (Ar−C), 131.08 (2C, Ar−C), 135.25 (Ar−C), 145.80 (pyrimidine−*C*CH$_3$), 147.49 (pyrazole−C), 153.78 (pyrazole−C), 158.06 (Ar−*C*OH), 158.59 (Ar−*C*OH), 159.28 (pyrimidine−*C*CH$_3$); LRMS *m/z* 331.1; HRMS ($C_{20}H_{17}N_3O_2$) calcd 331.1324, found 331.1321. Anal. ($C_{20}H_{17}N_3O_2$·0.1H_2O) C, H, N calcd: 72.10% C, 5.20% H, 12.61% N. Found: 71.79% C, 5.11% H, 12.61% N.

2-(3-Hydroxyphenyl)-3-(4-hydroxyphenyl)-5,7-dimethylpyrazolo[1,5-*a*]pyrimidine (22e). Following general procedure E, **12e** was deprotected to yield **22e**. Isolated yield 73%; light-yellow solid; mp 202−205 °C; ^{1}H NMR (500 MHz, (CD$_3$)$_2$CO) δ 2.48 (s, 3H, pyrimidine−C*H*$_3$), 2.72 (d, 3H, *J* = 0.9 Hz, pyrimidine−C*H*$_3$), 6.76 (q, 1H, *J* = 1.1 Hz, pyrimidine−H), 6.84 (m, 3H, Ar−H), 7.13 (dt, 1H, *J* = 7.7, 1.3 Hz, Ar−H), 7.19 (m, 2H, Ar−H), 7.34 (AA′XX′, 2H, Ar−H), 8.32 (s, 1H, Ar−O*H*), 8.37 (s, 1H, Ar−O*H*); ^{13}C NMR (125 MHz, (CD$_3$)$_2$CO) δ 16.74 (pyrimidine−*C*H$_3$), 24.64 (pyrimidine−*C*H$_3$), 108.46 (pyrazole−C), 109.49 (pyrimidine−C), 115.87 (2C, Ar−C), 116.00 (Ar−C), 116.53 (Ar−C), 121.00 (Ar−C), 124.68 (Ar−C), 130.05 (Ar−C), 132.12 (2C, Ar−C), 136.36 (Ar−C), 145.77 (pyrimdine-*C*CH$_3$), 147.31 (pyrazole−C), 153.27 (pyrazole−C), 156.92 (pyrimidine−*C*CH$_3$), 158.13 (Ar−*C*OH), 159.10 (Ar−*C*OH); LRMS *m/z* 331.1; HRMS ($C_{20}H_{17}N_3O_2$) calcd 331.1320, found 331.1320.

5,7-Diethyl-2-(4-hydroxyphenyl)-3-phenylpyrazolo[1,5-*a*]pyrimidine (23a). Following general procedure E, **13a** was deprotected to yield **23a**. Isolated yield 60%; peach solid; mp 92−95 °C; ^{1}H NMR (500 MHz, (CD$_3$)$_2$CO) δ 1.30 (t, 3H, *J* = 7.6 Hz, −CH$_2$C*H*$_3$), 1.45 (t, 3H, *J* = 7.5 Hz, −CH$_2$C*H*$_3$), 2.81 (q, 2H, *J* = 7.6 Hz, pyrimidine−C*H*$_2$CH$_3$), 3.20 (q, 2H, *J* = 7.5, 0.9 Hz, pyrimidine−C*H*$_2$CH$_3$), 6.82 (t, 1H, *J* = 0.9 Hz, pyrimidine−H), 6.85 (AA′XX′, 2H, Ar−H), 7.25 (m, 1H, Ar−H), 7.35 (m, 2H, Ar−H), 7.49 (AA′XX′, 2H, Ar−H), 7.57 (m, 2H, Ar−H), 8.55 (s, 1H, Ar−O*H*); ^{13}C NMR (125 MHz, (CD$_3$)$_2$CO) δ 10.29 (−CH$_2$*C*H$_3$), 12.65 (−CH$_2$*C*H$_3$), 23.63 (pyrimidine−*C*H$_2$CH$_3$), 31.47 (pyrimidine−*C*H$_2$CH$_3$), 106.19 (pyrimidine−H), 107.26 (pyrazole−C), 115.58 (2C, Ar−C), 125.72 (Ar−C), 126.44 (Ar−C), 128.43 (2C, Ar−C), 130.40 (2C, Ar−C), 130.74 (2C, Ar−C), 133.64 (Ar−C), 147.16 (pyrazole−C), 150.39 (pyrimidine−*C*CH$_2$CH$_3$), 153.41 (pyrazole−C), 158.24 (Ar−*C*OH), 163.90 (pyrimidine−*C*CH$_2$CH$_3$); LRMS *m/z* 343.2; HRMS ($C_{22}H_{21}N_3O$) calcd 343.1686, found 343.1685. Anal. ($C_{22}H_{21}N_3O$·0.2H_2O) C, H, N calcd: 76.14% C, 6.22% H, 12.11% N. Found: 76.09% C, 6.08% H, 11.96% N.

5,7-Diethyl-3-(4-hydroxyphenyl)-2-phenylpyrazolo[1,5-*a*]pyrimidine (23b). Following general procedure E, **13b** was deprotected to yield **23b**. Isolated yield 46%; off-white solid; mp 200 201 °C; ^{1}H NMR (500 MHz, (CD$_3$)$_2$CO) δ 1.31 (t, 3H, *J* = 7.5 Hz, −CH$_2$C*H*$_3$), 1.45 (t, 3H, *J* = 7.4 Hz, −CH$_2$C*H*$_3$), 2.82 (q, 2H, *J* = 7.6 Hz, pyrimidine−C*H*$_2$CH$_3$), 3.20 (qd, 2H, *J* = 7.5, 0.9 Hz, pyrimidine−C*H*$_2$CH$_3$), 6.82 (t, 1H, *J* = 0.9 Hz, pyrimidine−H), 6.85 (AA′XX′, 2H, Ar−H), 7.37 (m, 5H, Ar−H), 7.66 (m, 2H, Ar−H), 8.33 (s, 1H, Ar−O*H*); ^{13}C NMR (125 MHz, (CD$_3$)$_2$CO) δ 10.67 (−CH*C*H$_3$), 13.07 (−CH$_2$*C*H$_3$), 23.99 (pyrimidine−*C*H$_2$CH$_3$), 31.87 (pyrimidine−*C*H$_2$CH$_3$), 106.68 (pyrimidine−C), 108.47 (pyrazole−C), 115.90 (2C, Ar−C), 124.67 (Ar−C), 128.93 (2C, Ar−C), 129.02 (Ar−C), 129.71 (2C, Ar−C), 132.04 (2C, Ar−C), 135.17 (Ar−C), 147.41 (pyrazole−C), 150.75 (pyrimidine−*C*CH$_2$CH$_3$), 153.22 (pyrazole−C), 156.95 (Ar−*C*OH), 164.05 (pyrimidine−*C*CH$_2$CH$_3$); LRMS *m/z* 343.2; HRMS ($C_{22}H_{21}N_3O$) calcd 343.1687, found 343.1685. Anal. ($C_{22}H_{21}N_3O$) C, H, N calcd: 76.94% C, 6.16% H, 12.24% N. Found: 76.64% C, 6.16% H, 12.11% N.

5,7-Diethyl-2,3-bis(4-hydroxyphenyl)pyrazolo[1,5-*a*]pyrimidine (23c). Following general procedure E, **13c** was deprotected to yield **23c**. Isolated yield 56%; yellow solid; mp 148−152 °C; ^{1}H NMR (500 MHz, (CD$_3$)$_2$SO) δ 1.23 (t, 3H, *J* = 7.5, −CH$_2$C*H*$_3$), 1.37 (t, 3H, *J* = 7.5 Hz, −CH$_2$C*H*$_3$), 2.75 (q, 2H, *J* = 7.6 Hz, pyrimidine−C*H*$_2$CH$_3$), 3.11 (q, 2H, *J* = 7.5 Hz, pyrimidine−C*H*$_2$CH$_3$), 6.76 (m, 4H, Ar−H), 6.83 (s, 1H, pyrimidine−H), 7.22 (AA′XX′, 2H, Ar−H), 7.38 (AA′XX′, 2H, Ar−H), 9.38 (s, 1H, Ar−O*H*), 9.62 (s, 1H, Ar−H); ^{13}C NMR (125 MHz, (CD$_3$)$_2$SO) δ 10.23 (−CH$_2$*C*H$_3$), 12.79 (−CH$_2$*C*H$_3$), 22.91 (pyrimidine−*C*H$_2$CH$_3$), 30.72 (pyrimidine−*C*H$_2$CH$_3$), 105.66 (pyrimidine−C), 106.51 (pyrazole−C), 115.13 (2C, Ar−C), 115.17 (2C, Ar−C), 122.97 (Ar−C), 124.22 (Ar−C), 129.79 (2C, Ar−C), 130.88 (2C, Ar−C), 145.99 (pyrazole−C), 149.48 (pyrimidine−*C*CH$_2$CH$_3$), 152.08 (pyrazole−C), 155.93 (Ar−*C*OH), 157.64 (Ar−*C*OH), 162.89 (pyrimidine−*C*CH$_2$CH$_3$); LRMS *m/z* 359.2; HRMS ($C_{22}H_{21}N_3O_2$) calcd 359.1630, found 359.1634.

5,7-Diethyl-2-(4-hydroxyphenyl)-3-(3-hydroxyphenyl)-pyrazolo[1,5-*a*]pyrimidine (23d). Following general procedure E, **13d** was deprotected to yield **23d**. Isolated yield 63%; light-yellow solid; mp 218−219 °C; ^{1}H NMR (500 MHz, (CD$_3$)$_2$CO) δ 1.29 (t, 3H, *J* = 7.6 Hz, −CH$_2$C*H*$_3$), 1.45 (t, 3H, *J* = 7.5 Hz, −CH$_2$C*H*$_3$), 2.81 (q, 2H, *J* = 7.6 Hz, pyrimidine−C*H*$_2$CH$_3$), 3.19 (qd, 2H, *J* = 7.5. 0.9 Hz, pyrimidine−C*H*$_2$CH$_3$), 6.75 (ddd, 1H, *J* = 8.2, 2.6, 1.1 Hz, Ar−H), 6.81 (q, 1H, *J* = 0.9 Hz, pyrimidine−H), 6.84 (AA′XX′, 2H, Ar−H), 7.02 (dt, 1H, *J* = 7.7, 1.1 Hz, Ar−H), 7.10 (dd, 1H, *J* = 2.1, 1.7 Hz, Ar−H), 7.17 (t, 1H, *J* = 7.2 Hz, Ar−H), 7.52 (AA′XX′, 2H, Ar−H), 8.28 (s, 1H, Ar−O*H*), 8.58 (s, 1H, Ar−O*H*); ^{13}C NMR (125 MHz, (CD$_3$)$_2$CO) δ 10.69 (−CH$_2$*C*H$_3$), 13.13 (−CH$_2$*C*H$_3$), 24.03 (pyrimidine−*C*H$_2$CH$_3$), 31.89 (pyrimidine−*C*H$_2$CH$_3$), 106.50 (pyrimidine−C), 107.74 (pyrazole−C), 114.01 (Ar−C), 115.93 (2C, Ar−C), 117.79 (Ar−C), 122.21 (Ar−C), 126.17 (Ar−C), 129.76 (Ar−C), 131.14 (2C, Ar−C), 135.25 (Ar−C), 147.55 (pyrazole−C), 150.74 (pyrimidine−*C*CH$_2$CH$_3$), 153.79 (pyrazole−C), 158.08 (Ar−*C*OH), 158.61 (Ar−*C*OH), 164.19 (pyrimidine−*C*CH$_2$CH$_3$); LRMS *m/z* 359.3; HRMS ($C_{22}H_{21}N_3O_2$) calcd 359.1632, found 359.1634. Anal. ($C_{22}H_{21}N_3O_2$·0.2H_2O) calcd 72.79% C, 5.94% H, 11.57% N. Found: 72.42% C, 6.01% H, 11.74% N.

5,7-Diethyl-2-(3-hydroxyphenyl)-3-(4-hydroxyphenyl)-pyrazolo[1,5-*a*]pyrimidine (23e). Following general procedure E, **13e** was deprotected to yield **23e**. Isolated yield 61%; light-yellow solid; mp 190 °C dec; ^{1}H NMR (500 MHz, (CD$_3$)$_2$CO) δ 1.29 (t, 3H, *J* = 7.6 Hz, −CH$_2$C*H*$_3$), 1.45 (t, 3H, *J* = 7.4 Hz, −CH$_2$C*H*$_3$), 2.81 (q, 2H, *J* = 7.6 Hz, pyrimidine−C*H*$_2$CH$_3$),

3.19 (qd, 2H, J = 7.5, 0.9 Hz, pyrimidine−CH_2CH$_3$), 6.81 (t, 1H, J = 0.9 Hz, pyrimidine−H), 6.84 (m, 3H, Ar−H), 7.13 (dt, 1H, J = 7.7, 1.3 Hz, Ar−H), 7.19 (m, 2H, Ar−H), 7.38 (AA′XX′, 2H, Ar−H), 8.31 (s, 1H, Ar−OH), 8.36 (s, 1H, Ar−OH); ^{13}C NMR (125 MHz, (CD$_3$)$_2$CO) δ 10.69 (−CH$_2$$CH_3$), 13.07 (−CH$_2$-$CH_3$), 24.00 (pyrimidine−$CH_2CH_3$), 31.87 (pyrimidine−$CH_2$-CH$_3$), 106.64 (pyrimidine−C), 108.45 (pyrazole−C), 115.84 (2C, Ar−C), 115.98 (Ar−C), 116.59 (Ar−C), 121.05 (Ar−C), 124.71 (Ar−C), 130.06 (Ar−C), 132.04 (2C, Ar−C), 136.45 (Ar−C), 147.36 (pyrazole−C), 150.72 (pyrimidine−CCH$_2$CH$_3$), 153.24 (pyrazole−C), 156.87 (Ar−COH), 158.15 (Ar−COH), 163.98 (pyrimidine−CCH$_2$CH$_3$); LRMS *m/z* 359.2; HRMS ($C_{22}H_{21}N_3O_2$) calcd 359.1638, found 359.1634. Anal. ($C_{22}H_{21}N_3O_2$·0.4H$_2$O) C, H, N calcd: 72.07% C, 5.90% H, 11.46% N. Found: 71.71% C, 5.90% H, 11.22% N.

2-(4-Hydroxyphenyl)-3-phenyl-5,7-bis(trifluoromethyl)-pyrazolo[1,5-*a*]pyrimidine (24a). Following general procedure E, **14a** was deprotected to yield **24a**. Isolated yield 69%; yellow solid; mp 195−197 °C; ^{1}H NMR (500 MHz, (CD$_3$)$_2$CO) δ 6.88 (AA′XX′, 2H, Ar−H), 7.41 (m, 1H, Ar−H), 7.46 (m, 2H, Ar−C), 7.55 (m, 4H, Ar−H), 7.87 (s, 1H, pyrimidine−H), 8.78 (s, 1H, Ar−OH); ^{13}C NMR (125 MHz, (CD$_3$)$_2$CO), δ 104.06 (m, pyrimidine−C), 112.29 (pyrazole−C), 116.39 (2C, Ar−C), 120.39 (q, J = 274.3 Hz, −CF$_3$), 121.50 (q, J = 274.3 Hz, −CF$_3$), 123.90 (Ar−C), 128.59 (Ar−C), 129.46 (2C, Ar−C), 130.99 (2C, Ar−C), 131.33 (2C, Ar−C), 131.54 (Ar−C), 135.30 (q, J = 37.8 Hz, pyrimidine−CCF$_3$), 146.23 (q, J = 37.8 Hz, pyrimidine−CCF$_3$), 147.65 (pyrazole−C), 157.03 (pyrazole−C), 159.68 (Ar−COH); LRMS *m/z* 423.1; HRMS ($C_{20}H_{11}F_6N_3O$) calcd 423.0810, found 423.0806. Anal. ($C_{20}H_{11}F_6N_3O$) C, H, N calcd: 56.75% C, 2.62% H, 9.93% N. Found: 56.71% C, 2.55% H, 9.58% N.

3-(4-Hydroxyphenyl)-2-phenyl-5,7-bis(trifluoromethyl)-pyrazolo[1,5-*a*]pyrimidine (24b). Following general procedure E, **14b** was deprotected to yield **24b**. Isolated yield 79%; orange solid; mp 206−208 °C; ^{1}H NMR (500 MHz, (CD$_3$)$_2$CO) δ 6.93 (AA′XX′, 2H, Ar−H), 7.36 (AA′XX′, 2H, Ar−H), 7.44 (m, 3H, Ar−H), 7.72 (m, 2H, Ar−H), 7.88 (s, 1H, pyrimidine−H), 8.60 (s, 1H, Ar−OH); ^{13}C NMR (125 MHz, (CD$_3$)$_2$CO) δ 104.30 (m, pyrimidine−C), 113.32 (pyrazole−C), 116.45 (2C, Ar−C), 120.39 (q, J = 274.3 Hz, −CF$_3$), 121.50 (q, J = 274.3 Hz, −CF$_3$), 121.94 (Ar−C), 129.45 (2C, Ar−C), 129.77 (Ar−C), 130.16 (2C, Ar−C), 132.33 (2C, Ar−C), 133.06 (Ar−C), 135.54 (q, J = 37.8 Hz, pyrimidine−CCF$_3$), 145.99 (q, J = 37.8 Hz, pyrimidine−CCF$_3$), 147.38 (pyrazole−C), 156.52 (pyrazole−C), 158.25 (Ar−COH); LRMS *m/z* 423.1; HRMS ($C_{20}H_{11}F_6N_3O$) calcd 423.0809, found 423.0808. Anal. ($C_{20}H_{11}F_6N_3O$) C, H, N calcd: 56.75% C, 2.62% H, 9.93% N. Found: 56.45% C, 2.42% H, 9.68% N.

2,3-Bis(4-hydroxyphenyl)-5,7-bis(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidine (24c). Following general procedure E, **14c** was deprotected to yield **24c**. Isolated yield 90%; orange solid; mp 223−226 °C; ^{1}H NMR (500 MHz, (CD$_3$)$_2$CO) δ 6.89 (AA′XX′, 2H, Ar−H), 6.94 (AA′XX′, 2H, Ar−H), 7.37 (AA′XX′, 2H, Ar−H), 7.59 (AA′XX′, 2H, Ar−H), 7.82 (s, 1H, pyrimidine−H), 8.59 (s, 1H, Ar−OH), 8.77 (s, 1H, Ar−OH); ^{13}C NMR (125 MHz, (CD$_3$)$_2$CO) δ 103.73 (m, pyrimidine−C), 112.47 (pyrazole−C), 116.33 (2C, Ar−C), 116.42 (2C, Ar−C), 120.41 (q, CF$_3$, J = 274.3 Hz), 121.54 (q, CF$_3$, J = 274.3 Hz), 122.25 (Ar−C), 124.13 (Ar−C), 131.22 (2C, Ar−C), 132.22 (2C, Ar−C), 135.25 (q, J = 37.8 Hz, pyrimidine−CCF$_3$), 145.76 (q, J = 37.8 Hz, pyrimidine−CCF$_3$), 147.46 (pyrazole−C), 156.78 (pyrazole−C), 158.14 (Ar−COH), 159.57 (Ar−COH); LRMS *m/z* 439.2; HRMS ($C_{20}H_{11}F_6N_3O_2$) calcd 439.0748, found 439.0744. Anal. ($C_{20}H_{11}F_6N_3O_2$·0.1H$_2$O) C, H, N calcd: 54.46% C, 2.562% H, 9.53% N. Found: 54.23% C, 2.40% H, 9.24% N.

3-(3-Hydroxyphenyl)-2-(4-hydroxyphenyl)-5,7-bis(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidine (24d). Following general procedure E, **14d** was deprotected to yield **24d**. Isolated yield 76%; orange solid; mp 229−231 °C; ^{1}H NMR (500 MHz, (CD$_3$)$_2$CO) δ 6.88 (m, 3H, Ar−H), 7.00 (ddd, 1H, J = 7.5, 1.1, 0.4 Hz, Ar−H), 7.05 (dd, 1H, J = 2.04, 0.43 Hz), 7.28 (dd, 1H, J = 8.2, 7.5 Hz, Ar−H), 7.59 (AA′XX′, 2H, Ar−H), 7.86 (s, 1H, pyrimidine−H), 8.48 (s, 1H, Ar−OH), 8.77 (s, 1H, Ar−OH); ^{13}C NMR (125 MHz, (CD$_3$)$_2$CO) δ 103.98 (m, pyrimidine−C), 112.32 (pyrazole−C), 115.70 (Ar−C), 116.35 (2C, Ar−C), 117.84 (Ar−C), 120.39 (q, J = 274.3 Hz, −CF$_3$), 121.51 (q, J = 274.3 Hz, −CF$_3$), 122.23 (Ar−C), 123.96 (Ar−C), 130.52 (Ar−C), 131.34 (2C, Ar−C), 132.70 (Ar−C), 135.27 (q, J = 37.8 Hz, pyrimidine−CCF$_3$), 145.89 (q, J = 37.8 Hz, pyrimidine−CCF$_3$), 147.60 (pyrazole−C), 156.98 (pyrazole−C), 158.45 (Ar−COH), 159.63 (Ar−COH); LRMS *m/z* 439.1; HRMS ($C_{20}H_{11}F_6N_3O_2$) calcd 439.0756, found 439.0755. Anal. ($C_{20}H_{11}F_6N_3O_2$) C, H, N calcd: 54.68% C, 2.52% H, 9.57% N. Found: 54.32% C, 2.30% H, 9.29% N.

2-(3-Hydroxyphenyl)-3-(4-hydroxyphenyl)-5,7-bis(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidine (24e). Following general procedure E, **14e** was deprotected to yield **24e**. Isolated yield 68%; yellow solid; mp >260 °C; ^{1}H NMR (500 MHz, (CD$_3$)$_2$CO) δ 6.93 (m, 3H, Ar−H), 7.17 (dt, 1H, J = 7.7, 1.1 Hz, Ar−H), 7.25 (m, 2H, Ar−H), 7.38 (AA′XX′, 2H, Ar−H), 7.87 (s, 1H, pyrimidine−H), 8.59 (s, 1H, Ar−OH), 8.65 (s, 1H, Ar−OH); ^{13}C NMR (125 MHz, (CD$_3$)$_2$CO) δ 104.22 (m, pyrimidine−C), 113.29 (pyrazole−C), 116.39 (2C, Ar−C), 116.54 (Ar−C), 117.23 (Ar−C), 120.37 (q, J = 274.3 Hz, −CF$_3$), 121.03 (Ar−C), 121.50 (q, J = 274.3 Hz, −CF$_3$), 121.96 (Ar−C), 130.53 (Ar−C), 132.23 (2C, Ar−C), 134.25 (Ar−C), 135.42 (q, J = 37.8 Hz, pyrimidine−CCF$_3$), 145.84 (q, J = 37.8 Hz, pyrimidine−CCF$_3$), 147.35 (pyrazole−C), 156.49 (pyrazole−C), 158.18 (Ar−COH), 158.42 (Ar−COH); LRMS *m/z* 439.1; HRMS ($C_{20}H_{11}F_6N_3O_2$) calcd 439.0767, found 439.0755. Anal. ($C_{20}H_{11}F_6N_3O_2$) C, H, N calcd: 54.68% C, 2.52% H, 9.57% N. Found: 54.55% C, 2.46% H, 9.48% N.

2-(4-Hydroxyphenyl)-3-phenyl-5,7-diisopropylpyrazolo-[1,5-*a*]pyrimidine (25a). Following general procedure E, **15a** was deprotected to yield **25a**. Isolated yield 56%; peach solid; mp 190−193 °C; ^{1}H NMR (500 MHz, (CD$_3$)$_2$CO) δ 1.31 (d, 6H, J = 6.9 Hz, −CH(CH_3)$_2$), 1.48 (d, 6H, J = 6.9 Hz, −CH(CH_3)$_2$), 3.10 (sept, 1H, J = 6.9 Hz, pyrimidine−CH(CH$_3$)$_2$), 3.89 (sept, 1H, J = 6.9 Hz, pyrimidine−CH(CH$_3$)$_2$), 6.85 (m, 3H, Ar−H (2H), pyrimidine−H (1H)), 7.24 (m, 1H, Ar−H), 7.35 (m, 2H, Ar−H), 7.49 (AA′XX′, 2H, Ar−H), 7.59 (m, 2H, Ar−H), 8.55 (s, 1H, Ar−OH); ^{13}C NMR (500 MHz, (CD$_3$)$_2$CO) δ 20.06 (2C, −CH(CH$_3$)$_2$), 22.06 (2C, −CH(CH$_3$)$_2$), 29.27 (pyrimidine−C(CH$_3$)$_2$), 37.17 (pyrimidine−CH(CH$_3$)$_2$), 103.65 (pyrimidine−C), 107.63 (pyrazole−C), 116.01 (2C, Ar−C), 126.18 (Ar−C), 126.79 (Ar−C), 128.83 (2C, Ar−C), 130.72 (2C, Ar−C), 131.19 (2C, Ar−C), 134.02 (Ar−C), 147.57 (pyrazole−C), 153.84 (pyrazole−C), 155.08 (pyrimidine−CCH(CH$_3$)$_2$), 158.67 (Ar−COH), 168.13 (pyrimidine−CCH(CH$_3$)$_2$); LRMS *m/z* 371.2; HRMS ($C_{24}H_{25}N_3O$) calcd 371.1998, found 371.1998. Anal. ($C_{24}H_{25}N_3O$·0.2H$_2$O) C, H, N calcd: 76.85% C, 6.83% H, 11.20% N. Found: 76.86% C, 6.81% H, 10.97% N.

3-(4-Hydroxyphenyl)-3-phenyl-5,7-diisopropylpyrazolo-[1,5-*a*]pyrimidine (25b). Following general procedure E, **15b** was deprotected to yield **25b**. Isolated yield 81%; white solid; mp 201−202 °C; ^{1}H NMR (500 MHz, CD$_3$OD) δ 1.31 (d, 6H, J = 7.1 Hz, −CH(CH_3)$_2$), 1.46 (d, 6H, J = 7.1 Hz, −CH(CH_3)$_2$), 3.06 (sept, 1H, J = 6.9 Hz, −CH(CH$_3$)$_2$), 3.85 (sept, 1H, J = 6.9 Hz, −CH(CH$_3$)$_2$), 6.77 (m, 3H, Ar−H and pyrimidine−H), 7.27 (AA′XX′, 2H, Ar−H), 7.31 (m, 3H, Ar−H), 7.58 (m, 2H, Ar−H); ^{13}C NMR (125 MHz, CD$_3$OD) δ 20.25 (2C, −CH(CH$_3$)$_2$), 22.21 (2C, −CH(CH$_3$)$_2$), 29.66 (pyrimidine−CH(CH$_3$)$_2$), 37.70 (pyrimidine−CH(CH$_3$)$_2$), 103.59 (pyrimidine−C), 109.22 (pyrazole−C), 116.10 (2C, Ar−C), 124.75 (Ar−C), 129.24 (2C, Ar−C), 129.30 (Ar−C), 130.17 (2C, Ar−C), 132.42 (2C, Ar−C), 135.20 (Ar−C), 147.74 (pyrazole−C), 154.28 (pyrazole−C), 156.01 (pyrimidine−CCH(CH$_3$)$_2$), 157.30 (Ar−COH), 168.95 (pyrimidine−CCH(CH$_3$)$_2$); LRMS *m/z* 371.2; HRMS ($C_{24}H_{25}N_3O$) calcd 371.1996, found 371.1998. Anal. ($C_{24}H_{25}N_3O$) C, H, N calcd: 77.60% C, 6.78% N, 11.31% N. Found: 77.42% C, 6.75% H, 11.68% N.

2,3-Bis(4-hydroxyphenyl)-5,7-diisopropylpyrazolo[1,5-*a*]pyrimidine (25c). Following general procedure E, **15c** was deprotected to yield **25c**. Isolated yield 68%; light-yellow solid; mp 235−238 °C; ^{1}H NMR (500 MHz, (CD$_3$)$_2$CO) δ 1.30 (d, 6H, J = 6.9 Hz, −CH(CH_3)$_2$), 1.47 (d, 6H, J = 6.9 Hz, −CH(CH_3)$_2$), 3.07 (sept, 1H, J = 6.9 Hz, pyrimidine−CH(CH$_3$)$_2$), 3.87 (septd, 1H, J = 6.9, 0.4 Hz, pyrimidine−CH(CH$_3$)$_2$), 6.81 (t, 1H, J = 0.4 Hz, pyrimidine−H), 6.85 (m, 4H, Ar−H), 7.40 (AA′XX′, 2H,

Ar−H), 7.52 (AA′XX′, 2H, Ar−H), 8.30 (s, 1H, Ar−O*H*), 8.52 (s, 1H, Ar−O*H*); ^{13}C NMR (125 MHz, $(CD_3)_2CO$) δ 20.06 (2C, −CH(CH_3)$_2$), 22.08 (2C, −CH(CH_3)$_2$), 29.21 (−CH(CH_3)$_2$), 37.15 (−CH(CH_3)$_2$), 103.29 (pyrimidine−C), 107.77 (pyrazole−C), 115.84 (2C, Ar−C), 115.93 (2C, Ar−C), 124.98 (Ar−C), 126.41 (Ar−C), 131.07 (2C, Ar−C), 131.95 (2C, Ar−C), 147.41 (pyrazole−C), 153.43 (pyrazole−C), 154.88 (pyrimidine−CCH(CH_3)$_2$), 156.78 (Ar−COH), 158.53 (Ar−COH), 167.58 (pyrimidine−CCH(CH_3)$_2$); LRMS *m/z* 387.2; HRMS ($C_{24}H_{25}N_3O_2$) calcd 387.1941, found 387.1947.

3-(3-Hydroxyphenyl)-2-(4-hydroxyphenyl)-5,7-diisopropylpyrazolo[1,5-*a*]pyrimidine (25d). Following general procedure E, **15d** was deprotected to yield **25d**. Isolated yield 77%; white solid; mp 224−227 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 1.32 (d, 6H, J = 6.9 Hz, −CH(CH_3)$_2$), 1.46 (d, 6H, J = 6.9 Hz, −CH(CH_3)$_2$), 3.06 (sept, 1H, J = 6.9 Hz, pyrimidine−CH(CH_3)$_2$), 3.86 (sept, 1H, J = 6.9 Hz, pyrimidine−CH(CH_3)$_2$), 6.69 (ddd, 1H, J = 8.2, 2.6, 1.1 Hz, Ar−H), 6.77 (m, 3H, Ar−H and pyrimidine−H), 6.95 (dt, 1H, J = 7.5, 1.1 Hz, Ar−H), 6.99 (dd, 1H, J = 2.6, 1.3 Hz, Ar−H), 7.14 (t, 1H, J = 7.7 Hz, Ar−H), 7.43 (AA′XX′, 2H, Ar−H); ^{13}C NMR (125 MHz, CD_3OD) δ 20.27 (−CH(CH_3)$_2$), 22.24 (−CH(CH_3)$_2$), 29.65 (2C, pyrimidine−CH(CH_3)$_2$), 37.74 (2C, pyrimidine−CH(CH_3)$_2$), 103.40 (pyrimidine−C), 108.57 (pyrazole−C), 114.36 (Ar−C), 116.11 (2C, Ar−C), 118.13 (Ar−C), 122.77 (Ar−C), 126.09 (Ar−C), 130.11 (Ar−C), 131.57 (2C, Ar−C), 135.27 (Ar−C), 147.88 (pyrazole−C), 154.85 (pyrazole−C), 156 (pyrimidine−CCH(CH_3)$_2$), 158.22 (Ar−COH), 159.10 (Ar−COH), 169.17 (pyrimidine−CCH(CH_3)$_2$); LRMS *m/z* 387.2; HRMS ($C_{24}H_{25}N_3O_2$) calcd 387.1943, found 387.1947. Anal. ($C_{24}H_{25}N_3O_2$·0.2H_2O) C, H, N calcd: 73.71% C, 6.55% H, 10.74% N. Found: 73.44% C, 6.19% H, 10.52% N.

2-(3-Hydroxyphenyl)-3-(4-hydroxyphenyl)-5,7-diisopropylpyrazolo[1,5-*a*]pyrimidine (25e). Following general procedure E, **15e** was deprotected to yield **25e**. Isolated yield 73%; white solid; mp 189−190 °C; ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 1.31 (d, 6H, J = 6.9 Hz, −CH(CH_3)$_2$), 1.47 (d, 6H, J = 7.1 Hz, −CH(CH_3)$_2$), 3.08 (sept, 1H, J = 6.9 Hz, pyrimidine−CH(CH_3)$_2$), 3.88 (sept, 1H, J = 6.9 Hz, pyrimidine−CH(CH_3)$_2$), 6.85 (m, 4H, Ar−H), 7.13 (dt, 1H, J = 7.9, 1.1 Hz, Ar−H), 7.20 (m, 2H, Ar−H), 7.40 (AA′XX, 2H, Ar−H), 8.33 (s, 1H, Ar−O*H*), 8.40 (s, 1H, Ar−O*H*); ^{13}C NMR (125 MHz, $(CD_3)_2CO$) δ 20.04 (2C, −CH(CH_3)$_2$), 22.06 (2C, −CH(CH_3)$_2$), 29.23 (pyrimidine−CH(CH_3)$_2$), 37.16 (pyrimidine−CH(CH_3)$_2$), 103.67 (pyrimidine−C), 108.39 (pyrazole−C), 115.83 (2C, Ar−C), 115.98 (Ar−C), 116.64 (Ar−C), 121.10 (Ar−C), 124.68 (Ar−C), 130.08 (Ar−C), 131.95 (2C, Ar−C), 136.50 (Ar−C), 147.32 (pyrazole−C), 153.24 (pyrazole−C), 154.97 (pyrimidine−CCH(CH_3)$_2$), 156.82 (Ar−COH), 158.16 (Ar−COH), 167.76 (pyrimidine−CCH(CH_3)$_2$); LRMS *m/z* 387.2; HRMS ($C_{24}H_{25}N_3O_2$) calcd 387.1951, found 387.1947. Anal. ($C_{24}H_{25}N_3O_2$·0.2H_2O) C, H, N calcd: 73.71% C, 6.55% H, 10.74% N. Found: 73.41% C, 6.25%, 10.41% N.

2-(4-Hydroxyphenyl)-5,6,7-trimethyl-3-phenylpyrazolo[1,5-*a*]pyrimidine (26a). Following general procedure E, **17a** was deprotected to yield **26a**. Isolated yield 59%; white solid; mp 218−221 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 2.25 (s, 3H, pyrimidine−CH_3), 2.48 (s, 3H, pyrimidine−CH_3), 2.73 (s, 3H, pyrimidine−CH_3), 6.72 (AA′XX′, 2H, Ar−H), 7.23 (m, 1H, Ar−H), 7.31 (m, 2H, Ar−H), 7.35 (AA′XX′, 2H, Ar−H), 7.42 (m, 2H, Ar−H); ^{13}C NMR (125 MHz, CD_3OD) δ 13.66 (pyrimidine−CH$_3$), 13.95 (pyrimidine−CH$_3$), 23.80 (pyrimidine−CH$_3$), 108.22 (pyrazole−C), 116.10 (2C, Ar−C), 116.43 (pyrimidine−C), 125.96 (Ar−C), 127.39 (Ar−C), 129.25 (2C, Ar−C), 131.34 (2C, Ar−C), 131.43 (2C, Ar−C), 133.99 (Ar−C), 143.58 (pyrimidine−CCH$_3$), 146.05 (pyrazole−C), 153.96 (pyrazole−C), 159.05 (Ar−COH), 160.61 (pyrimidine−CCH$_3$); LRMS *m/z* 329.2; HRMS ($C_{21}H_{19}N_3O$) calcd 329.1524, found 329.1528. Anal. ($C_{21}H_{19}N_3O$·0.1H_2O) C, H, N calcd: 76.16% C, 5.84% H, 12.69% N. Found: 75.84% C, 5.83% H, 12.40% N.

3-(4-Hydroxyphenyl)-5,6,7-trimethyl-2-phenylpyrazolo[1,5-*a*]pyrimidine (26b). Following general procedure E, **17b** was deprotected to yield **26b**. Isolated yield 49%; white solid; mp 219−221 °C; ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 2.26 (s, 3H, pyrimidine−CH_3), 2.47 (s, 3H, pyrimidine−CH_3), 2.74 (s, 3H, pyrimidine−CH_3), 6.76 (AA′XX′, 2H, Ar−H), 7.20 (AA′XX′, 2H, Ar−H), 7.35 (m, 3H, Ar−H), 7.56 (m, 2H, Ar−H), 9.40 (s, 1H, Ar−O*H*); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 13.17 (pyrimidine−CH$_3$), 13.58 (pyrimidine−CH$_3$), 23.88 (pyrimidine−CH$_3$), 106.97 (pyrazole−C), 115.10 (pyrimidine−CCH$_3$), 115.18 (2C, Ar−C), 122.78 (Ar−C), 128.09 (Ar−C), 128.31 (2C, Ar−C), 128.37 (2C, Ar−C), 133.71 (Ar−C), 141.65 (pyrimidine−CCH$_3$), 144.35 (pyrazole−C), 150.64 (pyrazole−C), 156.03 (pyrimidine−CCH$_3$), 158.48 (Ar−COH); LRMS *m/z* 329.1; HRMS ($C_{21}H_{19}N_3O$) calcd 329.1525, found 329.1528. Anal. ($C_{21}H_{19}N_3O$) C, H, N calcd: 76.57% C, 5.81% H, 12.76% N. Found: 76.08% C, 5.96% H, 13.23% N.

2,3-Bis(4-hydroxyphenyl)-5,6,7-trimethylpyrazolo[1,5-*a*]pyrimidine (26c). Following general procedure E, **17c** was deprotected to yield **26c**. Isolated yield 52%; white solid; mp >260 °C; ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 2.29 (s, 3H, pyrimidine−CH_3), 2.48 (s, 3H, pyrimidine−CH_3), 2.75 (s, 3H, pyrimdine-CH_3), 6.83 (m, 4H, Ar−H), 7.35 (AA′XX′, 2H, Ar−H), 7.52 (AA′XX′, 2H, Ar−H), 8.29 (s, 1H, Ar−O*H*), 8.49 (s, 1H, Ar−O*H*); ^{13}C NMR (125 MHz, $(CD_3)_2CO$) δ 13.37 (pyrimidine−CH$_3$), 13.87 (pyrimidine−CH$_3$), 24.14 (pyrimidine−CH$_3$), 107.42 (pyrazole−C), 115.38 (pyrimidine−CCH$_3$), 115.84 (2C, Ar−C), 115.87 (2C, Ar−C), 125.15 (Ar−C), 126.53 (Ar−C), 130.89 (2C, Ar−C), 132.04 (2C, Ar−C), 142.43 (pyrimidine−CCH$_3$), 145.73 (pyrazole−C), 152.34 (pyrazole−C), 156.78 (pyrimidine−CCH$_3$), 158.37 (Ar−COH), 158.82 (Ar−COH); LRMS *m/z* 345.2; HRMS ($C_{21}H_{19}N_3O_2$) calcd 345.1479, found 345.1477. Anal. ($C_{21}H_{19}N_3O_2$·0.8H_2O) C, H, N calcd: 70.10% C, 5.77% H, 11.68% N. Found: 70.09% C, 5.85% H, 11.16% N.

3-(3-Hydroxyphenyl)-2-(4-hydroxyphenyl)-5,6,7-trimethylpyrazolo[1,5-*a*]pyrimidine (26d). Following general procedure E, **17d** was deprotected to yield **26d**. Isolated yield 43%; off-white solid; mp >260 °C; ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 2.26 (s, 3H, pyrimidine−CH_3), 2.48 (s, 3H, pyrimidine−CH_3), 2.73 (s, 3H, pyrimidine−CH_3), 6.65 (d, 1H, J = 7.9 Hz), 6.75 (AA′XX, 2H, Ar−H), 6.81 (d, 1H, J = 7.5 Hz, Ar−H), 6.89 (d, 1H, J = 1.5 Hz, Ar−H), 7.14 (t, 1H, 7.8 Hz, Ar−H), 7.38 (AA′XX′, 2H, Ar−H), 9.30 (s, 1H, Ar−O*H*), 9.60 (s, 1H, Ar−O*H*); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 13.20 (pyrimidine−CH$_3$), 13.54 (pyrimidine−CH$_3$), 23.87 (pyrimidine−CH$_3$), 106.12 (pyrazole−C), 113.22 (pyrimidine−CCH$_3$), 114.86 (Ar−C), 115.16 (2C, Ar−C), 116.69 (Ar−C), 120.66 (Ar−C), 124.20 (Ar−C), 129.03 (Ar−C), 129.80 (2C, Ar−C), 133.87 (Ar−C), 141.67 (pyrimidine−CCH$_3$), 144.41 (pyrazole−C), 151.30 (pyrazole−C), 157.11 (pyrimidine−CCH$_3$), 157.59 (Ar−COH), 158.51 (Ar−COH); LRMS *m/z* 345.2; HRMS ($C_{21}H_{19}N_3O_2$) calcd 345.1473, found 345.1477.

2-(3-Hydroxyphenyl)-3-(4-hydroxyphenyl)-5,6,7-trimethylpyrazolo[1,5-*a*]pyrimidine (26e). Following general procedure E, **17e** was deprotected to yield **26e**. Isolated yield 73%; white solid; mp 252−254 °C; ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 2.29 (s, 3H, pyrimidine−CH_3), 2.48 (s, 3H, pyrimidine−CH_3), 2.75 (s, 3H, pyrimidine−CH_3), 6.83 (m, 3H, Ar−H), 7.14 (dt, 1H, J = 7.7, 1.3 Hz, Ar−H), 7.17 (t, 1H, J = 7.7 Hz, Ar−H), 7.20 (dd, 1H, J = 2.5, 0.9 Hz, Ar−H), 7.35 (AA′XX′, 2H, Ar−H), 8.30 (s, 1H, Ar−O*H*), 8.35 (s, 1H, Ar−O*H*); ^{13}C NMR (125 MHz, $(CD_3)_2CO$) δ 13.37 (pyrimidine−CH$_3$), 13.89 (pyrimidine−CH$_3$), 24.17 (pyrimidine−CH$_3$), 108.09 (pyrazole−C), 115.75 (pyrimidine−CCH$_3$), 115.81 (Ar−C), 115.84 (2C, Ar−C), 116.48 (Ar−C), 120.96 (Ar−C), 124.87 (Ar−C), 130.01 (Ar−C), 132.05 (2C, Ar−C), 136.61 (Ar−C), 142.49 (pyrimidine−CCH$_3$), 145.66 (pyrazole−C), 152.12 (pyrazole−C), 156.80 (pyrimidine−CCH$_3$), 158.11 (Ar−COH), 159.05 (Ar−COH); LRMS *m/z* 345.2; HRMS ($C_{21}H_{19}N_3O_2$) calcd 345.1470, found 345.1477. Anal. ($C_{21}H_{19}N_3O_2$·0.5H_2O) C, H, N calcd: 71.01% C, 5.69% H, 11.86% N. Found: 71.06% C, 5.51% H, 11.72% N.

5,7-Di-*tert*-butyl-2-(4-hydroxyphenyl)-3-phenylpyrazolo[1,5-*a*]pyrimidine (27a). Following general procedure E, **19a** was deprotected to yield **27a**. Isolated yield 49%; white solid; mp 220−222 °C; ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 1.39 (s, 9H, −C(CH_3)$_3$), 1.70 (s, 9H, −C(CH_3)$_3$), 6.87 (AA′XX′, 2H, Ar−H), 6.99 (s, 1H, pyrimidine−H), 7.23 (m, 1H, Ar−H), 7.35 (m, 2H, Ar−H), 7.51 (AA′XX′, 2H, Ar−H), 7.61 (m, 2H, Ar−H), 8.58

(s, 1H, Ar−O*H*); ^{13}C NMR (125 MHz, $(CD_3)_2CO$) δ 27.30 (3C, −C(CH_3)$_3$), 29.80 (3C, −C(CH_3), 36.85 (pyrimidine−*C*(CH_3)$_3$), 38.88 (pyrimidine−*C*(CH_3)$_3$), 102.66 (pyrimidine−C), 107.13 (pyrazole−C), 116.05 (2C, Ar−C), 126.17 (Ar−C), 126.75 (Ar−C), 128.78 (2C, Ar−C), 130.69 (2C, Ar−C), 131.15 (Ar−C), 133.98 (Ar−C), 148.11 (pyrazole−C), 153.06 (pyrazole−C), 155.86 (pyrimidine−*C*C(CH_3)$_3$), 158.69 (Ar−*C*OH), 169.82 (pyrimidine−*C*C(CH_3)$_3$); LRMS *m/z* 399.3; HRMS ($C_{26}H_{29}N_3O$) calcd 399.2309, found 399.2311.

5,7-Di-*tert*-butyl-3-(4-hydroxyphenyl)-2-phenylpyrazolo-[1,5-*a*]pyrimidine (27b). Following general procedure E, **19b** was deprotected to yield **27b**. Isolated yield 82%; white solid; mp 241−244 °C; ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 1.39 (s, 9H, −C(C*H*$_3$)$_3$), 1.70 (s, 9H, −C(C*H*$_3$)$_3$), 6.86 (AA′XX′, 2H, Ar−H), 6.99 (s, 1H, pyrimidine−H), 7.39 (m, 5H, Ar−H), 7.69 (m, 2H, Ar−H), 8.31 (s, 1H, Ar−O*H*); ^{13}C NMR (125 MHz, $(CD_3)_2CO$) δ 27.29 (3C, −C(*C*H$_3$)$_3$), 29.80 (3C, −C(*C*H$_3$)$_3$), 36.84 (pyrimidine−*C*(CH_3)$_3$), 38.88 (pyrimidine−*C*(CH_3)$_3$), 102.77 (pyrimidine−C), 107.97 (pyrazole−C), 115.85 (2C, Ar−C), 124.62 (Ar−C), 128.96 (2C, Ar−C), 129.11 (2C, Ar−C), 129.74 (2C, Ar−C), 131.95 (Ar−C), 135.26 (Ar−C), 147.93 (pyrazole−C), 152.45 (pyrazole−C), 155.82 (pyrimidine−*C*C(CH_3)$_3$), 156.87 (Ar−*C*OH), 169.53 (pyrimidine−*C*C(CH_3)$_3$); LRMS *m/z* 399.2; HRMS ($C_{26}H_{29}N_3O$) calcd 399.2310, found 399.2311. Anal. ($C_{26}H_{29}N_3O\cdot 0.3H_2O$) C, H, N calcd: 77.12% C, 7.37% H, 10.38% N. Found: 76.96% C, 7.37% H, 10.15% N.

5,7-Di-*tert*-butyl-2,3-bis(4-hydroxyphenyl)pyrazolo[1,5-*a*]pyrimidine (27c). Following general procedure E, **19c** was deprotected to yield **27c**. Isolated yield 91%; yellow solid; mp 265−267 °C; ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 1.38 (s, 9H, −C(C*H*$_3$)$_3$), 1.69 (s, 9H, −C(C*H*$_3$)$_3$), 6.86 (m, 4H, Ar−H), 6.95 (s, 1H, pyrimidine−H), 7.42 (AA′XX′, 2H, Ar−H), 7.55 (AA′XX′, 2H, Ar−H), 8.28 (s, 1H, Ar−O*H*), 8.52 (s, 1H, Ar−H); ^{13}C NMR (125 MHz, $(CD_3)_2CO$) δ 27.30 (3C, −C(*C*H$_3$)$_3$), 29.82 (3C, −C(*C*H$_3$)$_3$), 36.81 (pyrimidine−*C*(CH_3)$_3$), 38.83 (pyrimidine−*C*(CH_3)$_3$), 102.35 (pyrimidine−C), 107.28 (pyrazole−C), 115.81 (2C, Ar−C), 116.00 (2C, Ar−C), 124.97 (Ar−C), 126.45 (Ar−C), 131.04 (2C, Ar−C), 131.93 (2C, Ar−C), 147.95 (pyrazole−C), 152.65 (pyrazole−C), 155.66 (pyrimidine−*C*C(CH_3)$_3$), 156.75 (Ar−*C*OH), 158.56 (Ar−*C*OH), 169.27; LRMS *m/z* 415.2; HRMS ($C_{26}H_{29}N_3O_2$) calcd 415.2265, found 415.2260. Anal. ($C_{26}H_{29}N_3O_2\cdot 0.5H_2O$) C, H, N calcd: 73.56% C, 7.12% H, 9.90% N. Found: 73.45% C, 6.94% H, 9.64% N.

5,7-Di-*tert*-butyl-3-(3-hydroxyphenyl)-2-(4-hydroxyphenyl)pyrazolo[1,5-*a*]pyrimidine (27d). Following general procedure E, **19d** was deprotected to yield **27d**. Isolated yield 77%; yellow solid; mp 227−230 °C; ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 1.40 (s, 9H, −C(C*H*$_3$)$_3$), 1.69 (s, 9H, −C(C*H*$_3$)$_3$), 6.74 (ddd, 1H, J = 8.2, 2.6, 1.1 Hz, Ar−H), 6.87 (AA′XX′, 2H, Ar−H), 6.97 (s, 1H, pyrimidine−H), 7.08 (dt, 1H, J = 7.7, 1.5 Hz, Ar−H), 7.16 (dd, 1H, J = 2.6, 1.9 Hz, Ar−H), 7.18 (t, 1H, J = 7.9 Hz, Ar−H), 7.54 (AA′XX′, 2H, Ar−H), 8.21 (s, 1H, Ar−O*H*), 8.52 (s, 1H, Ar−O*H*); ^{13}C NMR (125 MHz, $(CD_3)_2CO$) δ 27.39 (3C, −C(*C*H$_3$)$_3$), 29.89 (3C, −C(*C*H$_3$)$_3$), 36.88 (pyrimidine−*C*(CH_3)$_3$), 38.92 (pyrimidine−*C*(CH_3)$_3$), 102.55 (pyrimidine−C), 107.30 (pyrazole−C), 113.98 (Ar−C), 116.06 (2C, Ar−C), 117.79 (Ar−C), 122.22 (Ar−C), 126.39 (Ar−C), 129.69 (Ar−C), 131.22 (2C, Ar−C), 135.30 (Ar−C), 148.20 (pyrazole−C), 153.14 (pyrazole−C), 155.87 (pyrimidine−*C*C(CH_3)$_3$), 158.09 (Ar−*C*OH), 158.67 (Ar−*C*OH), 169.74 (pyrimidine−*C*C(CH_3)$_3$); LRMS *m/z* 415.2; HRMS ($C_{26}H_{29}N_3O_2$) calcd 415.2264, found 415.2260. Anal. ($C_{26}H_{29}N_3O_2\cdot 0.5H_2O$) C, H, N calcd: 73.56% C, 7.12% H, 9.90% N. Found: 73.32% C, 6.87% H, 9.61% N.

5,7-Di-*tert*-butyl-2-(3-hydroxyphenyl)-3-(4-hydroxyphenyl)pyrazolo[1,5-*a*]pyrimidine (27e). Following general procedure E, **19e** was deprotected to yield **27e**. Isolated yield 60%; white solid; mp 232−236 °C; ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 1.39 (s, 9H, −C(C*H*$_3$)$_3$), 1.69 (s, 9H, −C(C*H*$_3$)$_3$), 6.85 (m, 3H, Ar−H), 6.98 (s, 1H, pyrimidine−H), 7.15 (dt, 1H, J = 7.7, 1.2 Hz, Ar−H), 7.22 (m, 1H, Ar−H), 7.43 (AA′XX′, 2H, Ar−H), 8.28 (s, 1H, Ar−O*H*), 8.39 (s, 1H, Ar−O*H*); ^{13}C NMR (125 MHz, $(CD_3)_2CO$) δ 27.37 (3C, −C(*C*H$_3$)$_3$), 29.84 (3C, −C(*C*H$_3$)$_3$), 36.87 (pyrimidine−*C*(CH_3)$_3$), 38.90 (pyrimidine−*C*(CH_3)$_3$), 102.69 (pyrimidine−C), 108.01 (pyrazole−C), 115.85 (2C, Ar−C), 116.06 (Ar−C), 116.68 (Ar−C), 121.14 (Ar−C), 124.78 (Ar−C), 130.15 (Ar−C), 132.00 (2C, Ar−C), 136.62 (Ar−C), 147.96 (pyrazole−C), 152.55 (pyrazole−C), 155.85 (pyrimidine−*C*C(CH_3)$_3$), 156.84 (Ar−*C*OH), 158.28 (Ar−CO*H*), 169.49 (pyrimidine−*C*C(CH_3)$_3$); LRMS *m/z* 415.3; HRMS ($C_{26}H_{29}N_3O_2$) calcd 415.2253, found 415.2260.

2-(4-Hydroxyphenyl)-3,5,7-triphenylpyrazolo[1,5-*a*]pyrimidine (28a). Following general procedure E, **20a** was deprotected to yield **28a**. Isolated yield 68%; yellow solid; mp 198−200 °C dec; ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 6.84 (AA′XX′, 2H, Ar−H), 7.31 (m, 1H, Ar−H), 7.41 (m, 2H, Ar−H), 7.49 (m, 5H, Ar−H), 7.60 (m, 2H, Ar−H), 7.67 (m, 3H, Ar−H and pyrimidine−H), 8.30 (m, 4H, Ar−H), 8.58 (s, 1H, Ar−O*H*); ^{13}C NMR (125 MHz, $(CD_3)_2CO$) δ 105.58 (pyrimidine−C), 108.89 (pyrazole−C), 116.03 (2C, Ar−C), 125.76 (Ar−C), 127.14 (Ar−C), 128.08 (2C, Ar−C), 128.99 (2C, Ar−C), 129.22 (2C, Ar−C), 129.58 (2C, Ar−C), 130.64 (2C, Ar−C), 130.94 (2C, Ar−C), 131.20 (2C, Ar−C), 131.65 (Ar−C), 132.42 (Ar−C), 133.76 (Ar−C), 138.27 (Ar−C), 146.98 (pyrazole−C), 148.68 (pyrimidine−*C*Ph), 154.70 (pyrazole−C), 156.38 (Ar−*C*OH), 158.81 (pyrimidine−*C*Ph); LRMS *m/z* 439.1; HRMS ($C_{30}H_{21}N_3O$) calcd 439.1680, found 439.1685. Anal. ($C_{30}H_{21}N_3O$) C, H, N calcd: 81.98% C, 4.82% H, 9.56% N. Found: 81.68% C, 4.85% H, 9.52% N.

3-(4-Hydroxyphenyl)-2,5,7-triphenylpyrazolo[1,5-*a*]pyrimidine (28b). Following general procedure E, **20b** was deprotected to yield **28b**. Isolated yield 72%; orange solid; mp 237−240 °C; ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 6.92 (AA′XX′, 2H, Ar−H), 7.37 (m, 3H, Ar−H), 7.49 (m, 5H, Ar−H), 7.61 (m, 3H, Ar−H), 7.67 (m, 2H, Ar−H), 7.70 (s, 1H, pyrimidine−H), 8.31 (m, 4H, Ar−H), 8.41 (s, 1H, Ar−O*H*); ^{13}C NMR (125 MHz, $(CD_3)_2CO$) δ 106.00 (pyrimidine−C), 109.77 (pyrazole−C), 116.06 (2C, Ar−C), 124.72 (Ar−C), 128.10 (2C, Ar−C), 129.09 (2C, Ar−C), 129.13 (Ar−C), 129.24 (2C, Ar−C), 129.61 (2C, Ar−C), 129.74 (2C, Ar−C), 130.64 (2C, Ar−C), 131.03 (Ar−C), 131.67 (Ar−C), 132.18 (2C, Ar−C), 132.41 (Ar−C), 134.83 (Ar−C), 138.31 (Ar−C), 147.02 (pyrazole−C), 148.53 (pyrimidine−*C*Ph), 154.13 (pyrazole−C), 156.20 (pyrimidine−*C*Ph), 157.19 (Ar−*C*OH); LRMS *m/z* 439.3; HRMS ($C_{30}H_{21}N_3O$) calcd 439.1682, found 439.1685. Anal. ($C_{30}H_{21}N_3O\cdot 0.7H_2O$) C, H, N calcd: 79.70% C, 4.99% H, 9.29% N. Found: 79.55% C, 4.64% H, 9.10% N.

2,3-Bis(4-hydroxyphenyl)-5,7-diphenylpyrazolo[1,5-*a*]-pyrimidine (28c). Following general procedure E, **20c** was deprotected to yield **28c**. Isolated yield 75%; orange solid; mp 139−141 °C; ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 6.84 (AA′XX′, 2H, Ar−H), 6.93 (AA′XX′, 6.93 Ar−H), 7.48 (m, 5H, Ar−H), 7.55 (AA′XX′, 2H, Ar−H), 7.61 (m, 3H, Ar−H), 7.66 (s, 1H, pyrimidine−H), 8.31 (m, 4H, Ar−H), 8.40 (s, 1H, Ar−O*H*), 8.57 (s, 1H, Ar−O*H*); ^{13}C NMR (125 MHz, $(CD_3)_2CO$) δ 105.60 (pyrimidine−C), 109.08 (pyrazole−C), 115.98 (2C, Ar−C), 116.02 (2C, Ar−C), 124.69 (Ar−C), 125.98 (Ar−C), 128.04 (2C, Ar−C), 129.21 (2C, Ar−C), 129.58 (2C, Ar−C), 130.61 (2C, Ar−C),130.93 (Ar−C), 131.08 (2C, Ar−C), 131.60 (Ar−C), 132.17 (2C, Ar−C), 132.52 (Ar−C), 138.39 (Ar−C), 146.83 (pyrazole−C), 154.36 (pyrazole−C), 155.94 (pyrimidine−*C*Ph), 157.08 (2C, Ar−*C*OH), 158.70 (pyrimidine−*C*Ph); LRMS *m/z* 455.2; HRMS ($C_{30}H_{21}N_3O_2$) calcd 455.1625, found 455.1634.

3-(3-Hydroxyphenyl)-2-(4-hydroxyphenyl)-5,7-diphenylpyrazolo[1,5-*a*]pyrimidine (28d). Following general procedure E, **20d** was deprotected to yield **28d**. Isolated yield 83%; orange solid; mp 151−152 °C; ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 6.81 (ddd, 1H, J = 7.7, 1.9, 0.9 Hz, Ar−H), 6.86 (AA′XX′, 2H, Ar−H), 7.15 (d, 1H, J = 7.5 Hz, Ar−H), 7.24 (m, 2H, Ar−H), 7.49 (m, 3H, Ar−H), 7.54 (AA′XX′, 2H, Ar−H), 7.60 (m, 3H, Ar−H), 7.67 (pyrimidine−H), 8.29 (m, 4H, Ar−H), 8.34 (s, 1H, Ar−O*H*), 8.58 (s, 1H, Ar−O*H*); ^{13}C NMR (125 MHz, $(CD_3)_2CO$) δ 105.82 (pyrimidine−C), 108.94 (pyrazole−C), 114.30 (Ar−C), 115.98 (2C, Ar−C), 117.84 (Ar−C), 122.29 (Ar−C), 125.82 (Ar−C), 128.11 (2C, Ar−C), 129.19 (2C, Ar−C), 129.57 (2C, Ar−C), 129.95 (Ar−C), 130.62 (2C, Ar−C), 131.01 (Ar−C), 131.21 (2C, Ar−C), 131.62 (Ar−C), 132.43 (Ar−C), 134.96 (Ar−C), 138.31 (Ar−C), 146.94 (pyrazole−C), 148.65 (pyrimidine−*C*Ph), 154.70 (pyrazole−C), 156.31 (pyrimidine−

*C*Ph), 158.16 (Ar−*C*OH), 158.74 (Ar−*C*OH); LRMS *m/z* 455.2; HMRS ($C_{30}H_{21}N_3O_2$) calcd 455.1629, found 455.1634. Anal. ($C_{30}H_{21}N_3O_2 \cdot 0.5\%H_2O$) C, H, N calcd: 77.57% C, 4.77% H, 9.05% N. Found: 77.34%C, 4.60% H, 8.97% N.

2-(3-Hydroxyphenyl)-3-(4-hydroxyphenyl)-5,7-diphenylpyrazolo[1,5-*a*]pyrimidine (28e). Following general procedure E, **20e** was deprotected to yield **28e**. Isolated yield 49%; orange solid; mp 190−191 °C dec; ^{1}H NMR (500 MHz, $(CD_3)_2$-CO) δ 6.85 (ddd, 1H, J = 7.7, 2.4, 1.1 Hz, Ar−H), 6.92 (AA′XX′, 2H, Ar−H), 7.15 (dt, 1H, J = 7.5, 1.3 Hz, Ar−H), 7.20 (m, 2H, Ar−H), 7.50 (m, 5H, Ar−H), 7.62 (m, 3H, Ar−H), 7.70 (s, 1H, pyrimidine−H), 8.31 (m, 4H, Ar−H), 8.38 (s, 1H, Ar−O*H*), 8.39 (s, 1H, Ar−O*H*); ^{13}C NMR (125 MHz, $(CD_3)_2CO$) δ 105.98 (pyrimidine−C), 109.85 (pyrazole−C), 116.07 (2C, Ar−C), 116.25 (Ar−C), 116.68 (Ar−C), 121.16 (Ar−C), 124.53 (Ar−C), 128.14 (2C, Ar−C), 129.27 (2C, Ar−C), 129.64 (2C, Ar−C), 130.15 (Ar−C), 130.67 (2C, Ar−C), 131.03 (Ar−C), 131.68 (Ar−C), 132.23 (2C, Ar−C), 132.53 (Ar−C), 136.18 (Ar−C), 138.44 (Ar−C), 147.07 (pyrazole−C), 148.58 (pyrimidine−*C*Ph), 154.26 (pyrazole−C), 156.22 (pyrimidine−*C*Ph), 157.17 (Ar−*C*OH), 158.23 (Ar−*C*OH); LRMS (EI, 70 eV) *m/z* 455.1; HMRS ($C_{30}H_{21}N_3O_2$) calcd 455.1628, found 455.1634. Anal. ($C_{30}H_{21}N_3O_2 \cdot 0.9H_2O$) C, H, N calcd: 76.38% C, 4.87% H, 8.91% N. Found: 76.25% C, 4.61% H, 8.79% N.

Estrogen Receptor Binding Affinity Assays. Relative binding affinities were determined by a competitive radiometric binding assay as previously described,[41,49] using 10 nM [^{3}H]-estradiol as tracer ([6,7-^{3}H]estra-1,3,5(10)triene-3,17-β-diol, 51−53 Ci/mmol, Amersham Biosciences, Piscataway, NJ) and purified full-length human ERα and ERβ receptors purchased from Pan Vera (Madison, WI). Incubations were for 18−24 h at 0 °C. Hydroxyapatite (BioRad, Hercules, CA) was used to absorb the receptor/ligand complexes, and free ligand was washed away. The binding affinities are expressed as relative binding affinity (RBA) values with the RBA of estradiol set to 100%. The values given are the average ± range or SD of two to three independent determinations. Estradiol binds to ERα with a K_d of 0.2 nM and to ERβ with a K_d of 0.5 nM.

Cell Culture and Transient Transfections. Human endometrial cancer (HEC-1) cells were maintained in minimum essential medium (MEM) plus phenol red supplemented with 5% calf serum and 5% fetal calf serum. Cells were plated in phenol-red-free improved MEM and 5% charcoal dextran-treated calf serum (CDCS) and were given fresh medium 24 h before transfection. Transfection assays were performed in 24-well plates using a mixture of 0.35 mL of serum-free improved MEM medium and 0.15 mL of Hank's balanced salt solution containing 5 μL of lipofectin (Life Technologies, Inc., Gaithersburg, MD), 1.6 μg of transferrin (Sigma, St. Louis, MO), 0.5 μg of pCMV β-galactosidase as internal control, 1 μg of 2ERE-pS2-Luc, and 100 ng of ER expression vector per well. The cells were incubated at 37 °C in a 5% CO_2-containing incubator for 5 h. The medium was then replaced with fresh improved MEM supplemented with 5% CDCS plus the desired concentrations of ligands. Cells were harvested 24 h later. Luciferase and β-galactosidase activity was assayed as described.[50]

Molecular Modeling. Small-molecule geometry optimization and modeling of ligand/protein complexes were carried out in Sybyl (version 6.7, Tripos). For ERα, the estradiol−ERα ligand binding domain (1ERE) crystal structure was used. For ERβ, the genistein−ERβ ligand binding domain (1QKM) crystal structure was used. The ligand **24c** was prepositioned by overlaying a *p*-hydroxyphenyl ring with the A-ring of estradiol or genistein. Estradiol or genistein was then deleted, and ligand **24c** was merged into its place. The rotatable bonds of ligand **24c** were set, and the **24c** was then allowed to reposition itself in the binding pocket while the protein remained fixed. The best docked ligand/receptor complexes were then subjected to a three-part minimization process. In the first step, the torsional bonds were minimized using the torsmin command. In the second step, the ligand **24c** and amino acids within 8 Å of the ligand were minimized while holding the protein backbone fixed. In the final step, the ligand/receptor complex was minimized with the anneal command, utilizing a hot radius of 8 Å and an interesting radius of 16 Å. All minimizations used the MMFF94 force field with the Powell gradient (final rms less than 0.1 kcal mol^{-1} Å^{-1}).

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Supporting Information Available: Elemental analysis results, HPLC results, and HPLC spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Katzenellenbogen, B. S.; Katzenellenbogen, J. A. Estrogen receptor transcription and transactivation: Estrogen receptor alpha and estrogen receptor beta: regulation by selective estrogen receptor modulators and importance in breast cancer. *Breast Cancer Res.* **2000**, *2*, 335−344.
(2) Katzenellenbogen, J. A.; Katzenellenbogen, B. S. Nuclear hormone receptors: ligand-activated regulators of transcription and diverse cell responses. *Chem. Biol.* **1996**, *3*, 529−536.
(3) Jensen, E. V.; Jordan, V. C. The Estrogen Receptor: A Model for Molecular Medicine. *Clin. Cancer Res.* **2003**, *9*, 1980−1989.
(4) Jordan, V. C. Antiestrogens and Selective Estrogen Receptor Modulators as Multifunctional Medicines. 2. Clinical Considerations and New Agents. *J. Med. Chem.* **2003**, *46*, 1081−1111.
(5) Jordan, V. C. Antiestrogens and Selective Estrogen Receptor Modulators as Multifunctional Medicines. 1. Receptor Interactions. *J. Med. Chem.* **2003**, *46*, 883−908.
(6) Grese, T. A.; Dodge, J. A. Selective estrogen receptor modulators (SERMs). *Curr. Pharm. Des.* **1998**, *4*, 71−92.
(7) McDonnell, D. P. The molecular pharmacology of SERMs. *Trends Endocrinol. Metab.* **1999**, *10*, 301−311.
(8) Kuiper, G. G.; Enmark, E.; Pelto-Huikko, M.; Nilsson, S.; Gustafsson, J. A. Cloning of a novel receptor expressed in rat prostate and ovary. *Proc. Natl. Acad. Sci. U.S.A.* **1996**, *93*, 5925−5930.
(9) McInerney, E. M.; Weis, K. E.; Sun, J.; Mosselman, S.; Katzenellenbogen, B. S. Transcription activation by the human estrogen receptor subtype beta (ER beta) studied with ER beta and ER alpha receptor chimeras. *Endocrinology* **1998**, *139*, 4513−4522.
(10) Pike, A. C. W.; Brzozowski, A. M.; Hubbard, R. E.; Bonn, T.; Thorsell, A.-G.; et al. Structure of the ligand-binding domain of oestrogen receptor beta in the presence of a partial agonist and a full antagonist. *EMBO J.* **1999**, *18*, 4608−4618.
(11) Anstead, G. M.; Carlson, K. E.; Katzenellenbogen, J. A. The estradiol pharmacophore: ligand structure−estrogen receptor binding affinity relationships and a model for the receptor binding site. *Steroids* **1997**, *62*, 268−303.
(12) Gao, H.; Katzenellenbogen, J. A.; Garg, R.; Hansch, C. Comparative QSAR Analysis of Estrogen Receptor Ligands. *Chem. Rev.* **1999**, *99*, 723−744.
(13) Meegan, M. J.; Lloyd, D. G. Advances in the science of estrogen receptor modulation. *Curr. Med. Chem.* **2003**, *10*, 181−210.
(14) Fink, B. E.; Mortensen, D. S.; Stauffer, S. R.; Aron, Z. D.; Katzenellenbogen, J. A. Novel structural templates for estrogen-receptor ligands and prospects for combinatorial synthesis of estrogens. *Chem. Biol.* **1999**, *6*, 205−219.
(15) Mortensen, D. S.; Rodriguez, A. L.; Carlson, K. E.; Sun, J.; Katzenellenbogen, B. S.; et al. Synthesis and biological evaluation of a novel series of furans: ligands selective for estrogen receptor α. *J. Med. Chem.* **2001**, *44*, 3838−3848.
(16) Stauffer, S. R.; Huang, Y.; Coletta, C. J.; Tedesco, R.; Katzenellenbogen, J. A. Estrogen pyrazoles: defining the pyrazole core structure and the orientation of substituents in the ligand binding pocket of the estrogen receptor. *Bioorg. Med. Chem.* **2001**, *9*, 141−150.
(17) Ghosh, U.; Ganessunker, D.; Sattigeri, V. J.; Carlson, K. E.; Mortensen, D. J.; et al. Estrogenic diazenes: heterocyclic non-steroidal estrogens of unusual structure with selectivity for estrogen receptor subtypes. *Bioorg. Med. Chem.* **2003**, *11*, 629−657.
(18) Grese, T. A.; Pennington, L. D.; Sluka, J. P.; Adrian, M. D.; Cole, H. W.; et al. Synthesis and pharmacology of conformationally restricted raloxifene analogues: highly potent selective estrogen receptor modulators. *J. Med. Chem.* **1998**, *41*, 1272−1283.
(19) Palkowitz, A. D.; Glasebrook, A. L.; Thrasher, K. J.; Hauser, K. L.; Short, L. L.; et al. Discovery and synthesis of [6-hydroxy-3-[4-[2-(1-piperidinyl)ethoxy]phenoxy]-2-(4-hydroxyphenyl)]b enzo-[b]thiophene: a novel, highly potent, selective estrogen receptor modulator. *J. Med. Chem.* **1997**, *40*, 1407−1416.

(20) von Angerer, E.; Knebel, N.; Kager, M.; Ganss, B. 1-(aminoalkyl)-2-phenylindoles as novel pure estrogen antagonists. *J. Med. Chem.* **1990**, *33*, 2635−2640.
(21) Teo, C. C.; Kon, O. L.; Sim, K. Y.; Ng, S. C. Synthesis of 2-(*p*-chlorobenzyl)-3-aryl-6-methoxybenzofurans as selective ligands for antiestrogen-binding sites. Effects on cell proliferation and cholesterol synthesis. *J. Med. Chem.* **1992**, *35*, 1330−1339.
(22) Mehta, L. K.; Parrick, J. The synthesis of three indolizine derivatives of interest as non-isomerizable analogs of tamoxifen. *J. Heterocycl. Chem.* **1995**, *32*, 391−394.
(23) Jorgensen, A. S.; Jacobsen, P.; Christiansen, L. B.; Bury, P. S.; Kanstrup, A.; et al. Synthesis and estrogen receptor binding affinities of novel pyrrolo[2,1,5-*cd*]indolizine derivatives. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2383−2386.
(24) Malamas, M. S.; Gunawan, I.; Harris, H. A.; Keith, J. C.; Albert, L. M. Preparation of naphthyl benzoxazoles and benzisoxazoles as estrogenic agents. In *U.S. Patent Application Publishers*; (Wyeth, John, and Brother Ltd., 2003 (28 pages).
(25) Barlaam, B.; Bernstein, P.; Dantzman, C.; Warwick, P. Preparation of benzoxazoles and benzothiazoles as selective ligands for human b-estrogen receptor. PCT Int. Appl. WO, 2002 (Astrazeneca AB, Sweden).
(26) Bernstein, P. Preparation of aminobenzothiazoles as selective ER-b ligands for treatment of Alzheimer's disease, anxiety disorders, depressive disorders, osteoporosis, cardiovascular disease, rheumatoid arthritis or prostate cancer. PCT Int. Appl. WO, 2003 (Astrazeneca AB, Sweden).
(27) Gilligan, P. J.; Baldauf, C.; Cocuzza, A.; Chidester, D.; Zaczek, R.; et al. The discovery of 4-(3-pentylamino)-2,7-dimethyl-8-(2-methyl-4-methoxyphenyl)-pyrazolo-[1,5-*a*]-pyrimidine: a corticotropin-releasing factor (hCRF1) antagonist. *Bioorg. Med. Chem.* **2000**, *8*, 181−189.
(28) Almansa, C.; de Arriba, A. F.; Cavalcanti, F. L.; Gomez, L. A.; Miralles, A.; et al. Synthesis and SAR of a new series of COX-2-selective inhibitors: pyrazolo[1,5-*a*]pyrimidines. *J. Med. Chem.* **2001**, *44*, 350−361.
(29) Novinson, T.; Miller, J. P.; Scholten, M.; Robins, R. K.; Simon, L. N.; et al. Adenosine cyclic 3′,5′,-monophosphate phosphodiesterase inhibitors. 2.3-Substituted 5,7-dialkylpyrazolo [1,5-*a*]-pyrimidines. *J. Med. Chem.* **1975**, *18*, 460−464.
(30) Senga, K.; Novinson, T.; Springer, R. H.; Rao, R. P.; O'Brien, D. E.; et al. Synthesis and antitrichomonal activity of certain pyrazolo (1,5-a) pyrimidines. *J. Med. Chem.* **1975**, *18*, 312−314.
(31) Compton, D. R.; Carlson, K. E.; Katzenellenbogen, J. A. Pyrazolo-[1,5-*a*]pyrimidines as Estrogen Receptor Ligands: Defining the Orientation of a Novel Heterocyclic Core. *Bioorg. Med. Chem. Lett.*, submitted.
(32) Kohno, H.; Bocchinfuso, W. P.; Gandini, O.; Curtis, S. W.; Korach, K. S. Mutational analysis of the estrogen receptor ligand-binding domain: influence of ligand structure and stereochemistry on transactivation. *J. Mol. Endocrinol.* **1996**, *16*, 277−285.
(33) Chae, K.; Gibson, M. K.; Korach, K. S. Estrogen receptor stereochemistry: ligand binding orientation and influence on biological activity. *Mol. Pharmacol.* **1991**, *40*, 806−811.
(34) Anstead, G. M.; Peterson, C. S.; Katzenellenbogen, J. A. Hydroxylated 2,3-diarylindenes: Synthesis, estrogen receptor binding affinity, and binding orientation considerations. *J. Steroid Biochem.* **1989**, *33*, 877−887.
(35) Pike, A. C.; Brzozowski, A. M.; Walton, J.; Hubbard, R. E.; Bonn, T.; et al. Structural aspects of agonism and antagonism in the oestrogen receptor. *Biochem. Soc. Trans.* **2000**, *28*, 396−400.
(36) Kayaleh, N. E.; Gupta, R. C.; Johnson, F. Enolate ions as β-activators of ortho-metalation: direct synthesis of 3-aminoindenones. *J. Org. Chem.* **2000**, *65*, 4515−4522.
(37) Bellec, C.; Maitte, P.; Armand, J.; Pinson, J. Deaminative electrochemical reduction of pyrazolo[1,5-*a*]pyrimidine-7-amines. *Can. J. Chem.* **1981**, *59*, 2826−2832.
(38) Al-Afaleq, E. I. Heterocyclic synthesis via enaminonitriles: an efficient, one step synthesis of some novel azolo[1,5-*a*]pyrimidine, pyrimido[1,2-*a*]benzimidazole, pyrido[1,2-*a*]benzimidazole, pyrimidine and pyrazole derivatives. *Synth. Commun.* **2000**, *30*, 1985−1999.
(39) Elnagdi, M. H.; Erian, A. W. Synthesis of substituted azaindenes: synthesis of new pyrazolo[1,5-*a*]pyrimidine derivatives. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1854−1856.
(40) Okabe, T.; Bhooshan, B.; Novinson, T.; Hillyard, I. W.; Garner, G. E.; et al. Dialkyl bicyclic heterocycles with a bridgehead nitrogen as purine analogs possessing significant cardiac inotropic activity. *J. Heterocycl. Chem.* **1983**, *20*, 735−751.
(41) Katzenellenbogen, J. A.; Johnson, H. J., Jr.; Myers, H. N. Photoaffinity labels for estrogen binding proteins of rat uterus. *Biochemistry* **1973**, *12*, 4085−4092.
(42) Stauffer, S. R.; Coletta, C. J.; Tedesco, R.; Nishiguchi, G.; Carlson, K.; et al. Pyrazole ligands: structure−affinity/activity relationships and estrogen receptor-α-selective agonists. *J. Med. Chem.* **2000**, *43*, 4934−4947.
(43) Shiau, A. K.; Barstad, D.; Radek, J. T.; Meyers, M. J.; Nettles, K. W.; et al. Structural characterization of a subtype-selective ligand reveals a novel mode of estrogen receptor antagonism. *Nat. Struct. Biol.* **2002**, *9*, 359−364.
(44) Muthyala, R. S.; Sheng, S.; Carlson, K. E.; Katzenellenbogen, B. S.; Katzenellenbogen, J. A. Bridged bicyclic cores containing a 1,1-diarylethylene motif are high-affinity subtype-selective ligands for the estrogen receptor. *J. Med. Chem.* **2003**, *46*, 1589−1602.
(45) Meyers, M. J.; Sun, J.; Carlson, K. E.; Katzenellenbogen, B. S.; Katzenellenbogen, J. A. Estrogen receptor subtype-selective ligands: asymmetric synthesis and biological evaluation of *cis*- and *trans*-5,11-dialkyl-5,6,11,12-tetrahydrochrysenes. *J. Med. Chem.* **1999**, *42*, 2456−2468.
(46) Nishiguchi, G. A.; Rodriguez, A. L.; Katzenellenbogen, J. A. Diaryl-dialkyl-substituted pyrazoles: regioselective synthesis and binding affinity for the estrogen receptor. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 947−950.
(47) Wolohan, P.; Reichert, D. E. CoMFA and docking study of novel estrogen receptor subtype selective ligands. *J. Comput.-Aided. Mol. Des.* **2003**, *17*, 313−328.
(48) Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. Safe and Convenient Procedure for Solvent Purification. *Organometallics* **1996**, *15*, 1518−1520.
(49) Carlson, K. E.; Choi, I.; Gee, A.; Katzenellenbogen, B. S.; Katzenellenbogen, J. A. Altered ligand binding properties and enhanced stability of a constitutively active estrogen receptor: evidence that an open pocket conformation is required for ligand interaction. *Biochemistry* **1997**, *36*, 14897−14905.
(50) McInerney, E. M.; Tsai, M. J.; O'Malley, B. W.; Katzenellenbogen, B. S. Analysis of estrogen receptor transcriptional enhancement by a nuclear hormone receptor coactivator. *Proc. Natl. Acad. Sci. U.S.A.* **1996**, *93*, 10069−10073.

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