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Pd/PTABS: Low Temperature Etherification of Chloroheteroarenes

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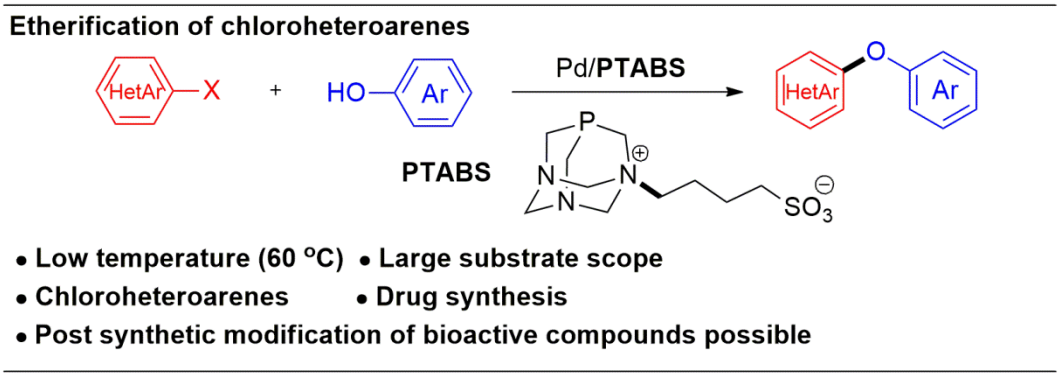
KEYWORDS Low Temperature, Etherification, Palladium-Catalyzed, ChloroHeteroarenes, PTABS.

Graphical abstract



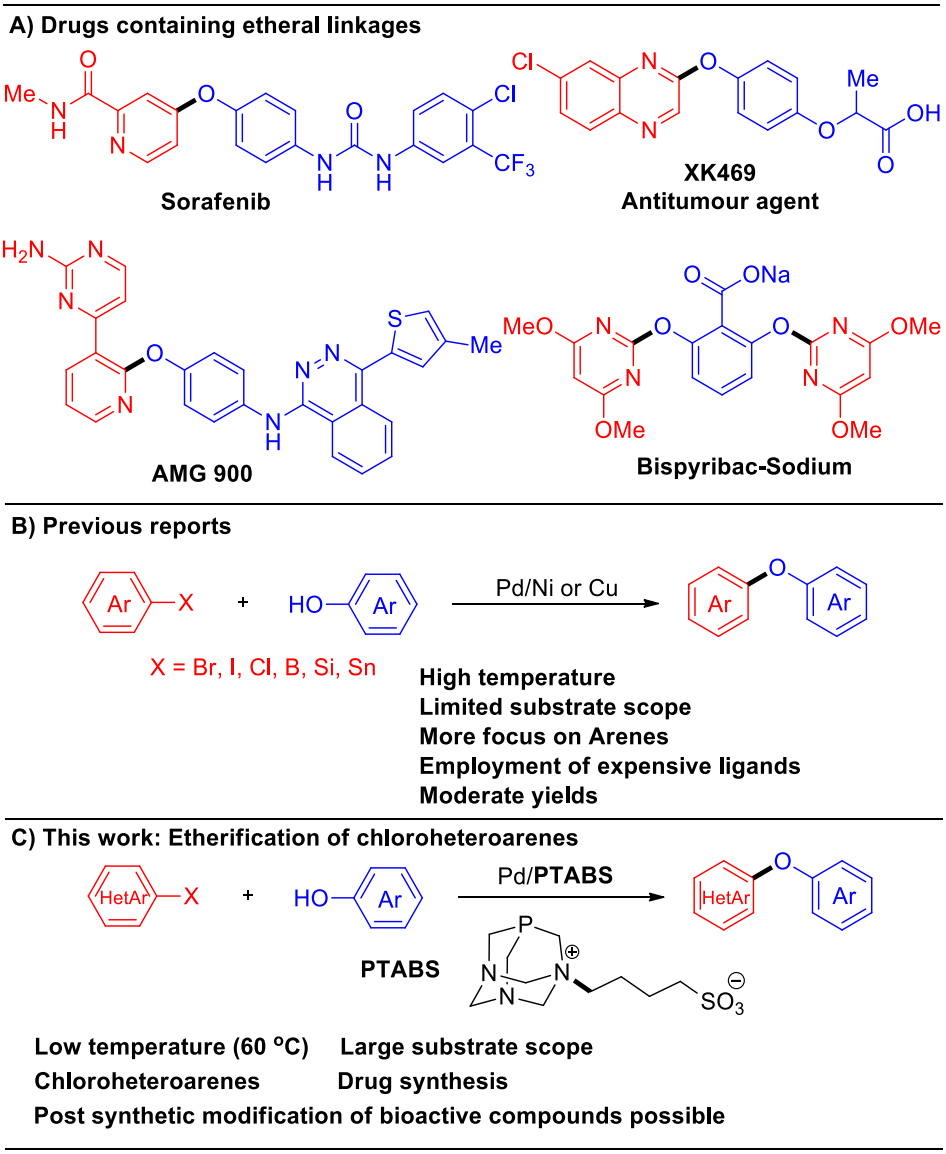
ABSTRACT: A mild, general and highly efficient catalytic etherification protocol for chloroheteroarenes has been developed using the Pd/PTABS catalytic system. The protocol is selective for the etherification of chloroheteroarenes using a large variety of electron-rich and electron-deficient phenol bearing synthons which include *inter alia* biologically and commercially important estrone, estradiol, tyrosine and several other molecules. The mildness of the new protocol is expected to be beneficial for the synthesis of complex drugs and drug intermediates offering late-stage modification of bioactive compounds.

1. **Introduction**

The etherification of heteroarenes is an important synthetic methodology due to the frequent occurrence of diaryl ether linkages in naturally occurring bioactive molecules and pharmaceutical drugs such as Sorafenib[1], AMG 900[2], anti-tumor agent XK469[3], herbicide such as Bispyribac-Sodium[4] and several others (Scheme 1A). The significance associated with this methodology has provided researchers with an increased impetus for the development of efficient metal-mediated routes for accessing these prized structural motifs. Copper-catalyzed Ullmann[5] and Chan-Lam-Evans-type[6] diaryl etherification protocols are well known, though, less attractive commercially due to the employment of stoichiometric amounts of copper as well as expensive boron reagents. Low to moderate yields associated with these transformations have further limited their utility and challenged researchers to develop more efficient, e.g. palladium-catalyzed etherification protocols.

The coupling of aryl halides (I, Br or Cl) with phenols has been explored extensively by researchers including Buchwald[7], Olofsson[8], Hierso[9] and Beller[10]. Several sterically hindered and electron-rich phosphines have been used as ligands in combination with common palladium

precursors to facilitate etherification reactions.[11]The possibility of using aryl silanes or stannanes as coupling partners has further fueled respective studies and improved their versatility. However, most of these protocols allow the formation of diaryl ethers (via coupling of Ar-X and phenols) while only a handful procedures are known which allow heteroaryl halides to be employed as coupling partners (Scheme 1B).[7a-b, 9] The importance of using the latter, though, is evident from their occurrence in a variety of naturally occurring bio-active molecules and pharmaceutical drugs. Recently, Yamaguchi and co-workers have reported the decarbonylative diaryl ether formation under Pd or Ni catalytic conditions.[12]Besides providing the desired diaryl ethers most of these protocols suffer from various process limitations such as high reaction temperature requirements, limited substrate scope and employment of expensive ligands often accompanied by only moderate yields. Difficulties in overcoming such challenges have impeded wider application of these protocols.



Scheme 1: A) Drugs containing ether linkages B) Previous reports C) This work: Etherification of chloroheteroarenes.

To address and overcome the above described limitations, we provide herein a sustainable catalytic solution with a low temperature etherification protocol for chloroheteroarenes utilizing a simple phosphatriazene ligand (PTABS- Phosphatriazene butane sulfonate). The method exhibits a large substrate scope (utility of the protocol demonstrated with >50 examples), providing the possibility of post-synthetic modifications of bioactive compounds and facilitates

the synthesis of an anti-tumor agent, XK469 (Scheme 1C). The developed protocol is superior to the existing etherification procedures available in literature and makes use of a bench stable Pd catalyst system which is easy to synthesize.[13] The inspiration for the current work came from our previous results in the employment of the PTA based complexes[14a-e] and Pd/PTABS catalytic system[14f] for the coupling of nucleosides under aqueous conditions and the room temperature amination of chloroheteroarenes[15].

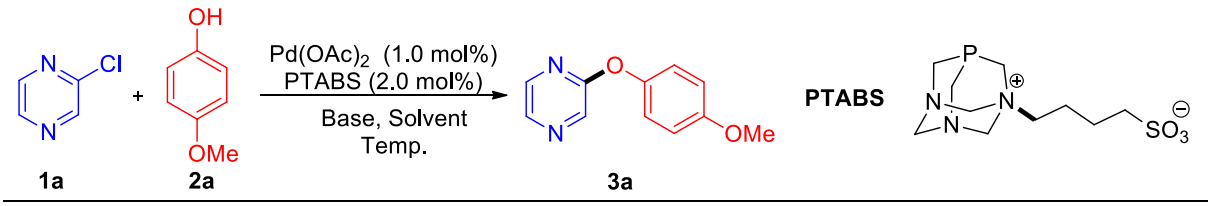
2. **Results and Discussion**

First, the coupling of, 2-chloropyrazine (**1a**) with 4-methoxyphenol (**2a**) was attempted using Pd/PTABS [$Pd(OAc)_2$ 1.0 mol%, PTABS 2.0 mol%] in DMF with Et_3N employed as the base at 60 °C providing <5% of the desired ether (Table 1, Entry 1). To assess the effect of the added base, the catalytic etherification reactions were performed with stronger inorganic bases such as NaOH, K_2CO_3 and K_3PO_4. The reaction solvent was also found to play an important role as polar aprotic solvents such as DMF or Acetonitrile (MeCN) provided higher yields of the product while non polar solvents such as toluene gave poor yields (Table 1, Entries 5-7). Only <5% of the coupled product could be obtained with water as the sole reaction solvent most likely due to the poor solubility of the starting material in this medium.

The temperature was also found to affect the outcome of the catalytic reaction. Although identical reactivity was observed at 80 °C (Table 1, Entry 8), performing the catalytic reaction at more ambient temperature (30 °C) led to lower catalytic activity and yield. The optimum concentration of catalyst components resulting in maximum yield was found to be 1.0 mol% Pd and 2.0 mol% PTABS. Although as a comparison to the previous reported[9] etherification methods, Pd/PTABS system at lower catalytic concentration was assessed at slightly elevated temperature of 100 °C. It was found that at such elevated temperatures the catalytic activity of

our system was high allowing the reduction of catalyst concentration to 0.1 mol% (better than 0.2 mol% achieved by Hierso and co-workers[9]). The extent of the reactivity enhancement of PTABS for the etherification of chloroheteroarenes versus other known and commonly used ligand systems was evaluated comparing the yields under otherwise identical conditions. Commercially available phosphine ligands such as PPh_3, $P(o\text{-}Tol)_3$, X-Phos, S-Phos as well as *N*-heterocyclic carbene ligands like IMes.HCl and IPr.HCl were tested (Table 1, Entries 17-22). In all cases including the highly electron-rich phosphines and N-heterocyclic carbenes, only minor amount of the desired product could be observed reaffirming the versatility and exceptional capability of the PTABS ligand system in catalyzing the transformation.

Table 1: Optimization of the Reaction Conditions.



Entry	Ligand	Catalyst loading (mol%) (Pd:Ligand)	Base (equiv.)	Solvent	Temp. (°C)	Yield[a] (%)
1	PTABS	1.0:2.0	NEt_3	DMF	60	<5%
2	PTABS	1.0:2.0	NaOH	DMF	60	<5%
3	PTABS	1.0:2.0	K_2CO_3	DMF	60	20
4	**PTABS**	**1.0:2.0**	**K_3PO_4**	**DMF**	**60**	**90**
5	PTABS	1.0:2.0	K_3PO_4	MeCN	60	75
6	PTABS	1.0:2.0	K_3PO_4	toluene	60	<5%
7	PTABS	1.0:2.0	K_3PO_4	H_2O	60	<5%
8	PTABS	1.0:2.0	K_3PO_4	DMF	80	90
9	PTABS	1.0:2.0	K_3PO_4	DMF	30	65
10	PTABS	0.1:0.2	K_3PO_4	DMF	60	20
11	PTABS	0.5:1.0	K_3PO_4	DMF	60	45
12	PTABS	0.5:1.0	K_3PO_4	DMF	100	98
13	PTABS	0.2:0.4	K_3PO_4	DMF	100	97
14	PTABS	0.1:0.2	K_3PO_4	DMF	100	99
15	PTABS	0.01:0.02	K_3PO_4	DMF	100	72

16	PTABS	1.0:2.0	K_3PO_4	DMF	60	85
17	PPh_3	1.0:2.0	K_3PO_4	DMF	60	<5%
18	P(o-Tolyl)$_3$	1.0:2.0	K_3PO_4	DMF	60	25
19	XPhos	1.0:2.0	K_3PO_4	DMF	60	<5%
20	SPhos	1.0:2.0	K_3PO_4	DMF	60	<5%
21	IMes.HCl	1.0:2.0	K_3PO_4	DMF	60	38
22	IPr.HCl	1.0:2.0	K_3PO_4	DMF	60	41
23	PTA	1.0:2.0	K_3PO_4	DMF	60	66
24	PTAMeI	1.0:2.0	K_3PO_4	DMF	60	81

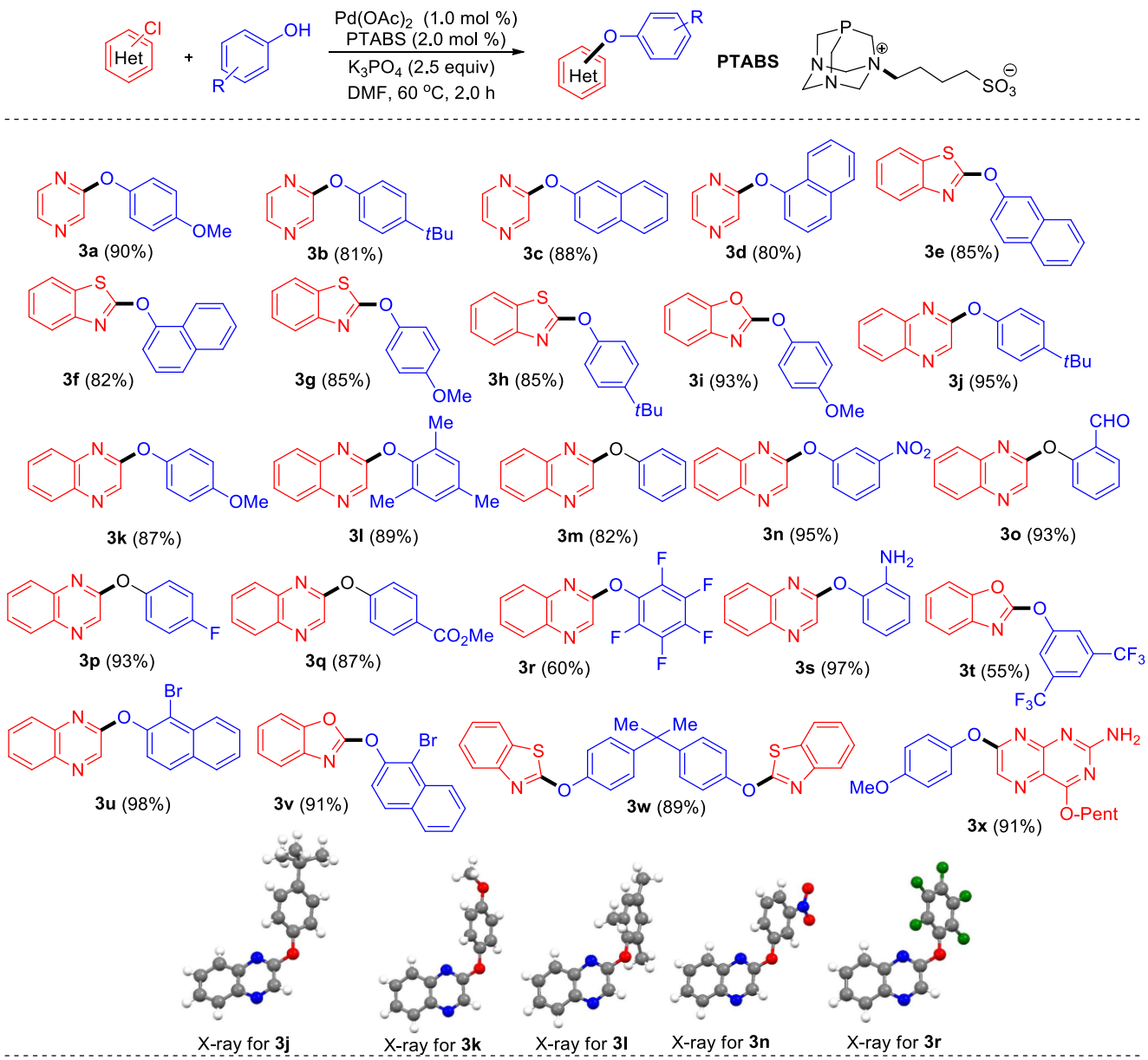
Reaction conditions: 1.0 mmol of **1a**, 1.5 mmol of **2a**, 1.0 mol% of $Pd(OAc)_2$and PTABS 2.0 mol%,3.0 mL of solvent, reaction time 2 hours under N_2 atmosphere unless stated otherwise, [a] isolated yields.

The employment of the parent PTA as well as methyl substituted PTA (PTAMeI) failed to provide comparable yields to that of PTABS (Table 1, entries 22,23). A rationale for the enhanced activity of PTABS compared to other PTA analogues points towards the activating influence of the substitution on the nitrogen atom of the parent PTA as well as the chain length and anionic counterpart. Further studies will be needed to ascertain the given assumption with DFT playing a crucial role in determining the exact influence of substituent's and electronics on the donation capacity of phosphorus atom in different PTA ligands, which will be reported at a later stage as it falls outside the purview of this manuscript.

With such a highly active catalytic system in hand, the substrate scope for the palladium-catalyzed diaryl ether synthesis was investigated (Scheme 2). It was decided to test the catalytic system for 5 different chloroheteroarenes: 2-chloropyrazine, 2-chloro benzothiazole, 2-chloro benzoxazole, 2-chloroquinoxaline and 7-chloro-4-(pentyloxy)pteridin-2-amine for ascertaining the extent of the utility. Initially, simple aromatic phenols such as 4-methoxyphenol, 4-*tert*-butylphenol and few others were employed as the nucleophilic coupling partners.

As a general trend, it could be observed that the employment of electronically activated phenols (OMe or *t*Bu as electron-releasing substituents) provided good to excellent yields of the

etherification product irrespective of the chloroheteroarene (Scheme 2). Even sterically demanding 2,4,6-trimethylphenol as substrate was well tolerated without any loss in reactivity (Scheme 2, **3l**). Electronically neutral phenol as well as several electronically deactivated phenols (3-NO_2, 2-CHO, 4-F, 4-CO_2Me) were also well tolerated, furnishing good to excellent yields of the etherified product. Pentafluoro phenol is an essential pharmacophore of high biological relevance[16] and therefore a desirable coupling partner. The reactivity of this phenol as synthon, though, was found to be comparably lower due to the deactivating nature of the fluoro substituents (Scheme 2, **3r**).



Scheme 2: Substrate scope for palladium-catalyzed etherification of chloroheteroarenes with diverse substituted arylphenols.

The catalytic efficiency and the mild nature of Pd/PTABS were further demonstrated by performing a chemoselective[17] etherification procedure using 1-bromo-2-naphthol as coupling partner (Scheme 2, **3u & 3v**) which did not lead to bromine induced homocoupling. This selectivity for the activation of the C–Cl over the C–Br bond by the catalytic system provides a useful handle for further functionalization. The selectivity towards chloro functionality has been

attributed to the possible coordination of the Pd-PTABS system to the nitrogen atom next to the chlorine atom directing it activation of C-Cl bond which is also more active due to the electronics on the heteroaromatic ring systems. It has also been observed that activation of C-Cl in 3rd position with regards to N atom does not occur. Some of the compounds synthesized were crystallized using suitable solvent to obtain single crystals allowing their characterization via x-ray analysis (**3j**, **3k**, **3l**, **3n** and **3r**).

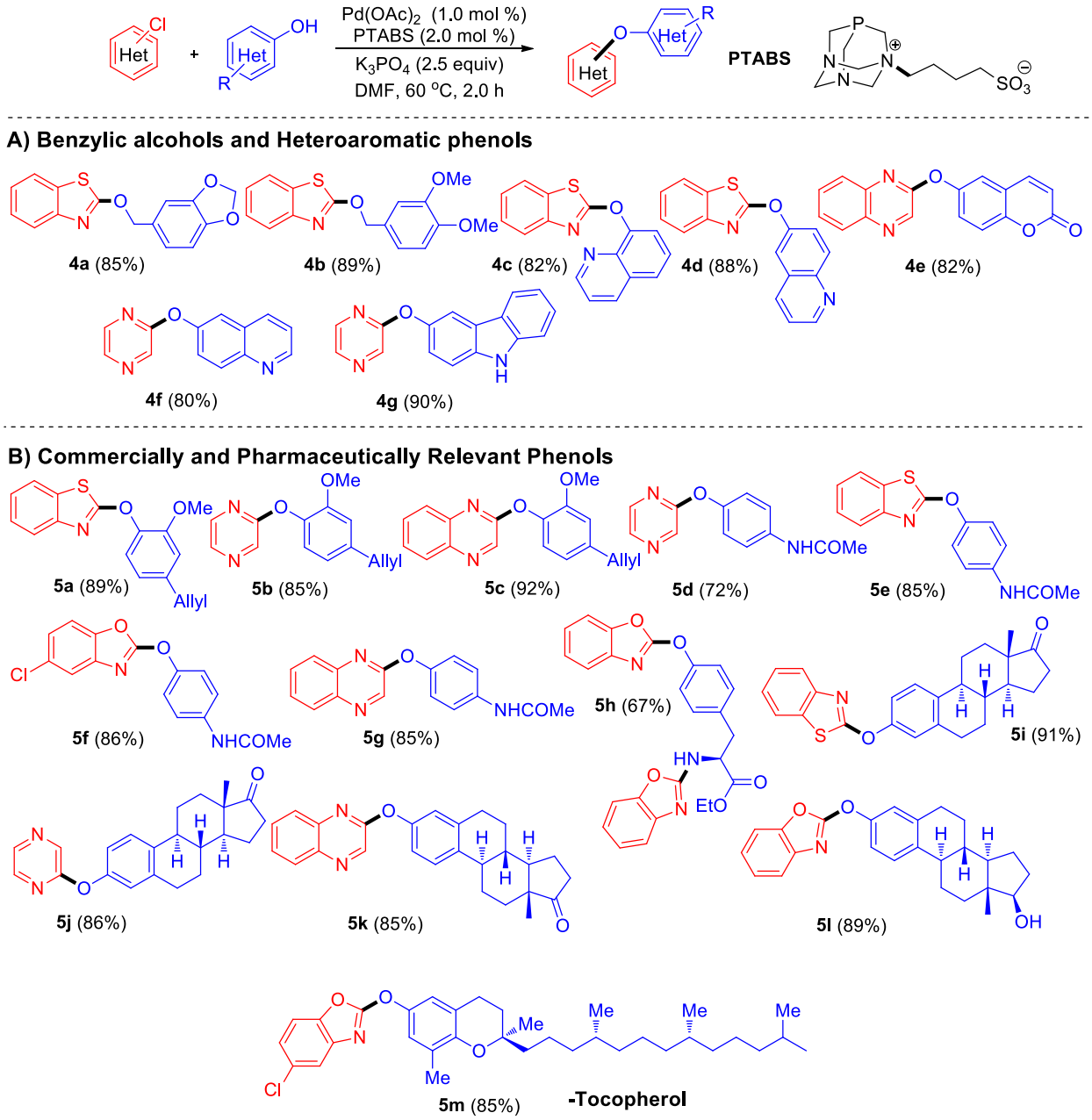
Given the success of the Pd/PTABS system with relatively simple phenols, we further explored the possibility of using benzylic alcohols as well as heteroaromatic phenols as coupling partners (Scheme 3A, **4a-g**). Good to excellent yields of the coupled products were obtained despite of a free-NH function in the case carbazole (**4g**).

With such a large substrate scope, efficiently allowing aromatic and heteroaromatic phenols to be readily coupled under the optimized conditions at relatively lower temperature, the Pd/PTABS etherification protocol was further envisioned to be beneficial for molecules bearing temperature sensitive functional groups and having commercial or pharmaceutical relevance. Eugenol with its extensive usage as an essential oil, in perfumery applications as well as a local anesthetic[18] was first chosen as a challenging candidate synthon for trying the etherification methodology. The etherification of eugenol was performed with three different chloroheteroarenes namely, 2-chlorobenzothiazole, 2-chloropyrazine and 2-chloro quinoxaline furnishing the respective products in excellent yields (Scheme 3B, **5a-c**). The lability of the allyl functional group under typical metal-mediated conditions[19] is well known; the mild nature of the new protocol, however, allowed the allyl group to be left unaffected. Another molecule of importance is the most commonly used pain reliever, paracetamol (acetaminophen) which was next to be coupled with four different chloroheteroarenes resulting in good to excellent yields (Scheme 3B, **5d-g**).

Tyrosine as particularly challenging substrate[20] with high biological relevance is a non-essential amino acid involved in protein synthesis. It was selected for etherification testing with 2-chlorobenzoxazole. The present free NH_2 group as part of the tyrosine structure has similar reactivity to the phenolic-OH and therefore rather than obtaining the selectively etherified product, the bis-arylation product of tyrosine was observed as the major component (the etherification product was obtained in significantly lower quantity of <5%; Scheme 3B, **5h**).

With a unique structural feature involving four fused carbocyclic rings, steroids are perhaps amongst the most widely applicable drugs for anesthetic usage besides their significance as hormones.[21] Estrone and estradiol are two such hormones with useful biological properties and several stereogenic centers that were next selected for coupling with different chloroheteroarenes. Even in these cases, the Pd/PTABS catalytic system was successful in providing very high yields of the coupled products (Scheme 3B, **estrone**: **5i-k**, **estradiol**: **5l**). A similar success was accomplished for δ-tocopherol as synthon, which represents the orally available δ form of essential vitamin E as well as possessing promising anti-oxidant properties. The palladium/PTABS-catalyzed etherification of 5-chlorobenzoxazole with δ-tocopherol proceeded smoothly providing the coupled product in good yield (Scheme 3B, **5m**).

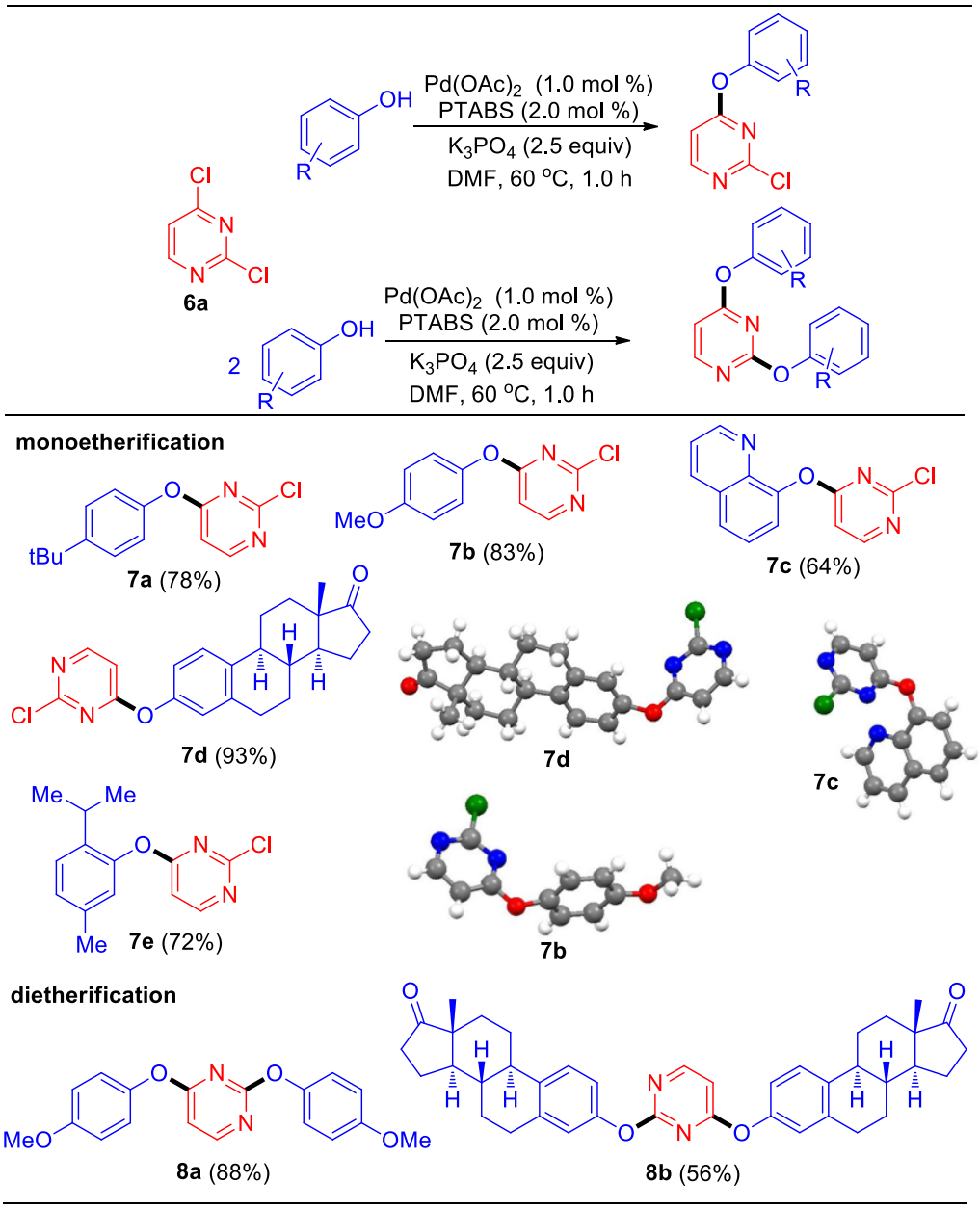
All results described above point towards the mild yet powerful nature of the novel catalytic system which not only allows the coupling to take place at significantly lower reaction temperature than the ones currently reported in literature but also provides ideal conditions for the late-stage modification of commercially and pharmaceutically useful compounds generating new leads for drug discovery.



Scheme 3: Substrate scope for palladium-catalyzed etherification of chloroheteroarenes with diverse substituted heteroarylphenols (**A**) and pharmaceutically relevant phenols (**B**).

Regioselectivity in catalytic processes is an important and sought-after synthetic trait for the selective functionalization, i.e. tailored modification of substrates. The selective functionalization of polyhalogenated heteroarenes is therefore advantageous and in recent years

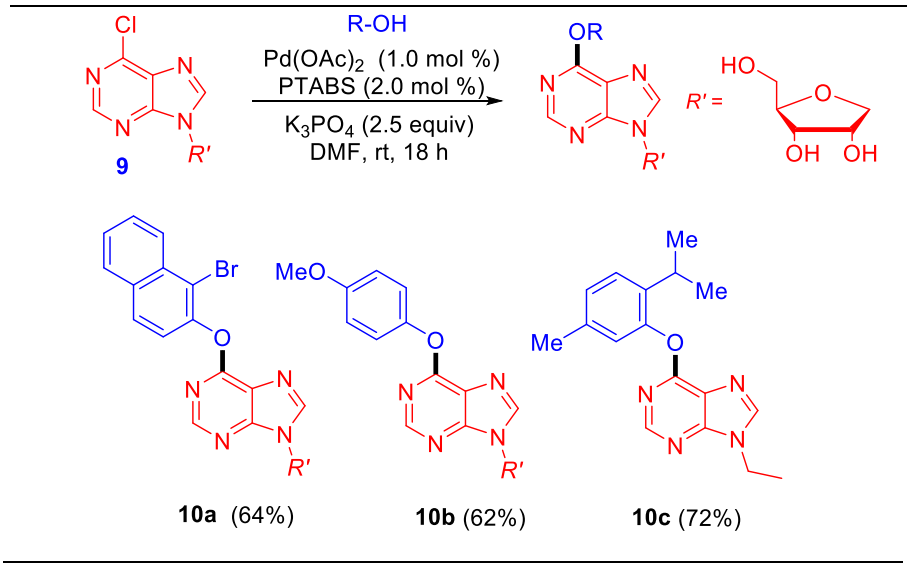
has been more extensively accomplished using palladium-catalyzed cross-coupling reactions.[22] To investigate whether the described Pd/PTABS catalyst system would foster selectivity, the mono-etherification of 2,4-dichloropyrimidine was tested with four different phenols being 4-*tert*-butylphenol, 4-methoxyphenol, 8-hydroxyquinoline, thymol and estrone (Scheme 4, 7a-e). Some of the compounds synthesized were crystallized using suitable solvent to obtain single crystals allowing their characterization via x-ray analysis (**7b-d**).



Scheme 4: Mono-selective etherification

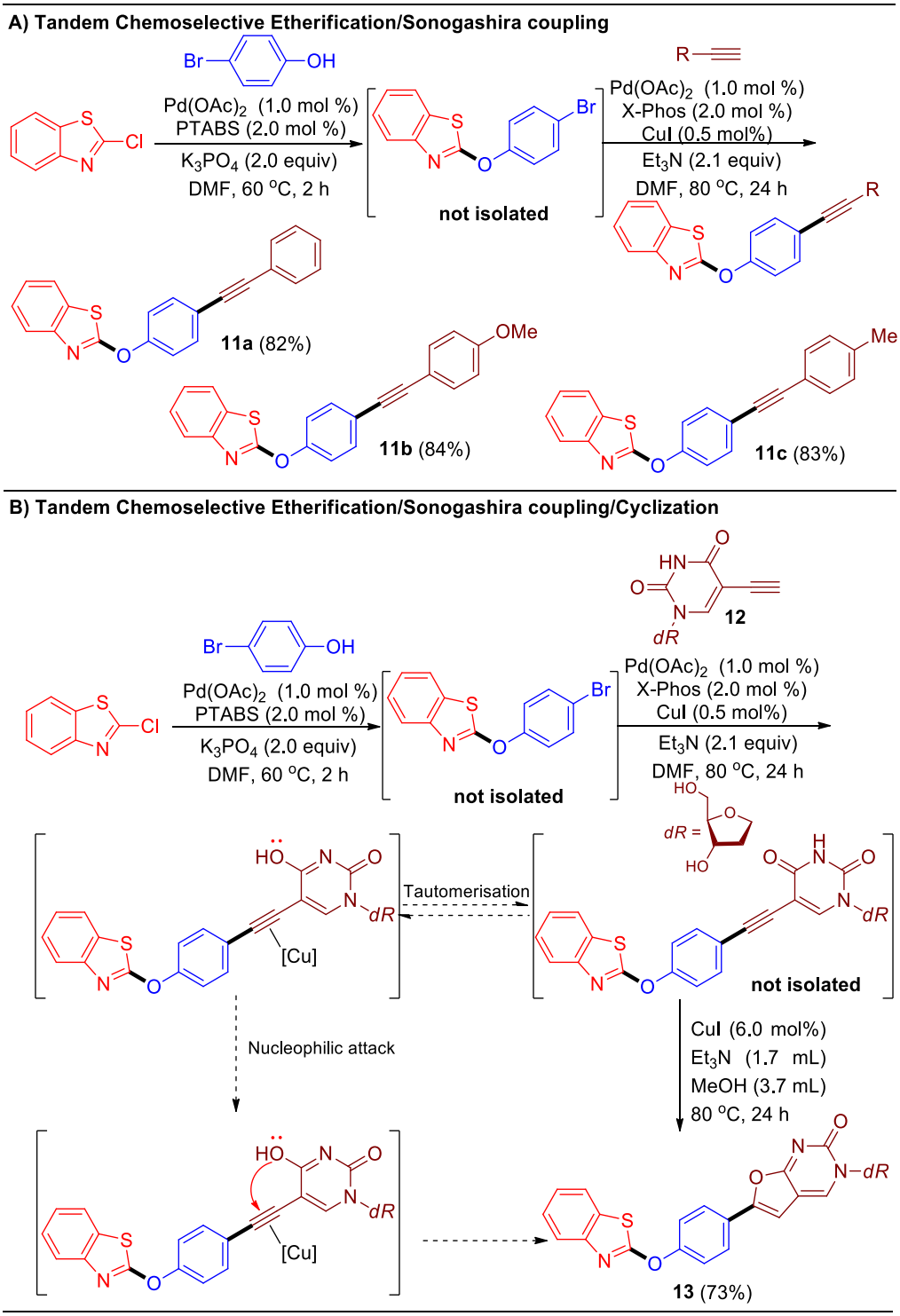
In each investigated case, the mono-etherification (selective towards the activation of the 4-Cl position) gave the major mono-ether product in good to excellent yield with a limited amount of di-etherification side product. To promote di-etherification specifically, an excess of the phenol synthons (4-methoxyphenol and estrone) resulted in excellent yield for 4-methoxyphenol while most likely steric effects reduced the product yield for estrone to 56% (Scheme 4, 8a-b).

Nucleosides comprise another example of biologically important molecules with a variety of applications.[23a-c] The four naturally occurring bases in the the 2'-deoxynucleosides exhibit only low fluorescence quantum yields and therefore, to enhance their applicability as fluorescent DNA probes, palladium-catalyzed coupling processes to attach or generate fluorophores have been extensively studied.[23d] 6-Chloro-9-β-D-ribofuranosyl-purine (**9**) for instance is one such substrate that has attracted a lot of attention in the respective synthetic community.



Scheme 5: Synthesis of 6-alkoxy functionalized purine

The mild and efficient nature of the developed Pd/PTABS catalytic system allows the coupling of the ribose nucleoside without the requirement of any form of protection of the sugar hydroxyl groups, providing the 6-phenoxy-9-β-D-ribofuranosyl-purine products with four different phenols in appreciable yields (Scheme 5, **10-d**).



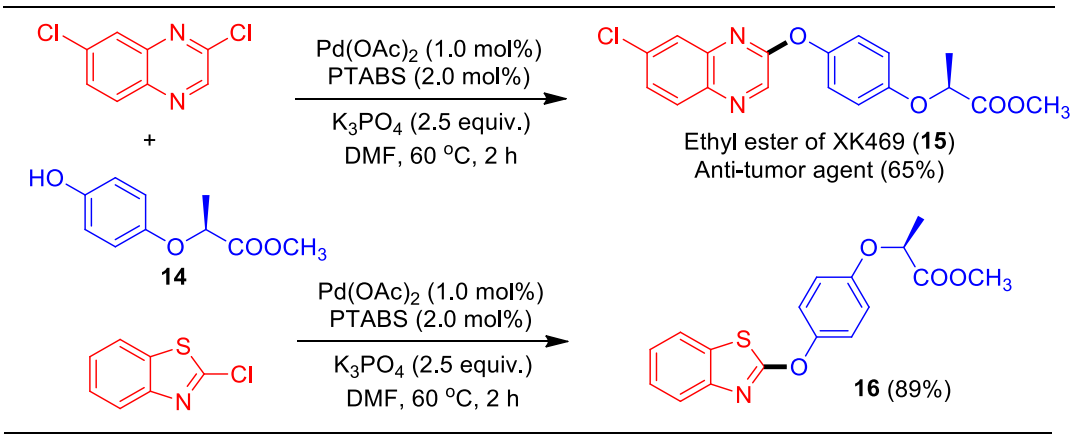
Scheme 6: Tandem catalytic processes using the Pd/TPABS system

Improving sustainability in synthesis is an important trait with which various environmental problems including waste generation and management are addressed. Tandem catalytic processes

involving the combination of two or several catalytic reactions (either with a single catalyst or multi-catalyst systems) in a single pot procedure without the isolation of the intermediates has come forth as a sustainable solution for waste reduction.[24] It provides multiple advantages over multi-step synthesis such as lower solvent usage for synthesis and purification, probable reduction in by-product formation and overall better efficiency. The Pd/PTABS catalytic system was, hence, tested for tolerating the combination of the etherification procedure with other catalytic processes giving access to functionalized molecules with improved synthetic applicability (Scheme 6).

A double tandem strategy was applied starting with the Pd/PTABS catalyzed etherification of 2-chlorobenzothiazole with 4-bromophenol activating chemoselectively the C–Cl bond and yielding 2-(4-bromophenoxy)benzothiazole (not isolated) bearing a handle for further functionalization. The Sonogashira alkynylation of the resultant 2-(4-bromophenoxy)benzothiazole with three different alkynes was enabled by introducing the Pd/X-Phos catalytic system providing highly functionalized 2-(4-(arylethynyl)phenoxy)benzothiazoles in good yields (Scheme 6A, **11a-d**). The success achieved with this double tandem procedure demonstrates the excellent compatibility of the Pd/PTABS catalytic system, which can readily be coupled with other catalysts (in this case Pd/X-Phos) with no interference. The next accepted challenge was to incorporate another catalytic system utilizing a different metal as part of the one-pot reaction sequence. This was achieved while changing the alkyne synthon from simple arylacetylenes to 5-ethynyl-2'-deoxyuridine, which itself is a useful 2'-deoxyuridine analog for Click chemistry.[25] First, the procedure applied to the installation of the alkyne was identical to the double tandem procedure discussed *vide supra*. This was followed by a copper-mediated cyclization strategy involving coordination of copper to the alkyne and the subsequent

isomerization of the amide to an imino-alcohol. Finally the nucleophilic attack of the alcohol on the electron-deficient alkyne furnished the cyclized product as a highly fluorescent furo-pyrimidine[26] analog in good yield (Scheme 6B, **13**).



Scheme 7: Palladium-catalyzed etherification for the synthesis of XK469 (anti-tumor agent).

To demonstrate the synthetic potential of the new catalytic system for the preparation of molecules of commercial relevance, the synthesis of an anti-tumor agent (**XK469**) was attempted. The **XK469** is a quinoxaline phenoxypropionic acid derivative the R enantiomer of which is capable of inducing reversible DNA crosslinks in mammalian cells, inhibiting the topoisomerase II as well as performing several other biological functions.[3] The synthetic strategy employed for XK469 involves the coupling of 2,7-dichloro quinoxaline with (*R*)-ethyl 2-(4-hydroxyphenoxy)propanoate under the palladium-catalyzed etherification conditions providing a good yield of the ethyl ester of the anti-tumor agent (Scheme 7, 15). A similar result was obtained when 2,7-dichloro quinoxaline was replaced by 2-chlorobenzothiazole to give the coupled product in very good yield (Scheme 7, 16).

3. Conclusion: In conclusion, the Pd/PTABS catalyst system was demonstrated to efficiently catalyze the etherification of chloroheteroarenes at relatively lower temperature (also works at

lower catalyst loading of 0.1 mol% at 100 °C), with a large substrate scope (electronically activated as well as deactivated phenols well-tolerated) and allowing the post synthetic functionalization of commercially important bio-active molecules such as estrones, estradiols, tryptophans, and δ-tocopherol for instance. The mild synthetic potential of the catalytic system was further explored for regioselectivity, ribonucleoside modification as well as the development of unique double and triple tandem protocols without inhibiting the reactivity of other reagents. Finally, the synthesis of the anti-tumor agent **XK469** was realized through the direct etherification of 2,7-dichloroquinoxaline and (R)-ethyl 2-(4-hydroxyphenoxy)propanoate in good yield. In summary, a mild catalytic system with the potential for generating a library of ethers for drug discovery efforts has been disclosed.

4. EXPERIMENTAL SECTION

4.1 General:

All the reactions were performed under nitrogen atmosphere using oven dried standard schlenk glassware. The completely dried *N,N* Dimethylformamide (DMF, 99.8%, extra dry, stored over molecular sieves) was purchased from Acros organics was used as received for all air or moisture sensitive reactions. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded either on NMR EMAU Avance II-300 spectrometer or Agilent-400 MHz spectrometer. Chemical shifts δ are given in ppm and the solvent residual peak ($CDCl_3$: ^{1}H, δ = 7.27; ^{13}C, δ = 77.0 and DMSO-d6: ^{1}H, δ = 2.50; ^{13}C, δ = 40) was used as an internal standard. Peak multiplicities are specified as followed: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. APCI-MS (m/z) spectra were recorded on a Advion MS. Mechenary-Nagel silica gel 60 F254 plates were used for thin layer chromatography (TLC) and detection was achieved by UV light. Column chromatography was performed on silica gel 60 (40-63 μm) or on Acros Organics silica

gel 60 (35-70 μm). The X-ray single crystal structure experiments conducted by using "STOE IPDS2T" and diffraction source with fine- focus sealed molybdenum tube. "Elementar Vario MICRO cube" was used for the experimental determination of elemental configurations of final pure products.

1.1 General procedure (GP):

A 25 mL of oven dried schlenk tube was given with 1 mol% of $Pd(OAc)_2$, 2 mol% of PTABS (ligand, Phosphoadamantinebutylsaltone) and 1 mmol of chloroheterocyclic derivative under N_2 atmosphere and the resultant mixture dissolved in 3 mL of dry DMF. The reaction mixture stirred for 5 minutes and added by 1.2 eq. of corresponding phenol, 2.0 eq. of K_3PO_4 followed by stirring at 60^0C for 1-2hrs. After consumption of starting material (monitored by TLC / TLC-MS), the solvent was removed in vacuum and the resultant residue obtained was purified by column chromatography in Hexane: Ethyl Acetate (10% to 50%) solvent system to afford the desired product. In the case of riboside derivatives and purine substrate (10a-10C) $CHCl_3$:MeOH (9:1) was used as a mobile phase for column chromatography.

1.2 General procedure for Double Tandem Reactions (GPT):

A 25 mL of oven dried schlenk tube was charged with 1 mol % of $Pd(OAc)_2$, 2 mol % of PTABS (ligand) and 0.5 mmol of 2-Chlorobenzthiazole under N_2 atmosphere and the resultant mixture dissolved in 1.5 mL of dry DMF. The reaction mixture stirred for 5 minutes and was added 2.5 equiv. of Potassium phosphate, 1.2 equiv. of 4-Bromo phenol and 1.5 ml dry DMF. The resultant mixture was stirred at 60°C for 2 h. After consumption of starting material (monitored by TLC / TLC-MS), in the reaction mixture was added 1 mol % of $Pd(OAc)_2$, 2 mol% of XPhos, 1.5 equiv. of terminal alkyne, 0.5 mol % of Copper iodide and lastly 2.1 equiv. of triethyl amine and was stirred at 80°C for 24 h. Then the solvent was removed in vacuum and the resultant residue

obtained was purified by column chromatography in hexane: ethyl acetate (2.0% to 3.0%) solvent system to afford the desired product.

2.1 Substrate scope for palladium-catalyzed etherification of chloroheteroarenes with diverse substituted phenols

2-(4-Methoxyphenoxy)pyrazine (3a):

General Procedure (GP) was followed by using 2-chloropyrazine (1 mmol, 1 equiv.) and 4-methoxy phenol (1.1 mmol, 1.1 eq.) yielded a desired product (182 mg, 90**%**) as a white solid.Mp: 78-80 ^{o}C,^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.38 (d, *J* = 1.0 Hz, 1H), 8.21 (d, *J* = 2.5 Hz, 1H), 8.09 – 8.05 (m, 1H), 7.07 (dd, *J* = 6.8, 2.2 Hz, 2H), 6.95 – 6.91 (m, 2H), 3.80 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.5 (s), 157.0 (s), 146.2 (s), 141.0 (s), 138.1 (s), 135.6 (s), 122.2 (s), 114.8 (s), 55.5 (s). Anal.Calcd.for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.98; N, 13.85. Found: C, 65.23; H, 4.94; N, 13.87.

2-(4-(*tert*-Butyl)phenoxy)pyrazine (3b):

General Procedure (GP) was followed by using 2-chloropyrazine (1 mmol, 1 equiv.) and 4-*tert* butyl phenol (1.1 mmol, 1.1 eq.) yielded a desired product (184 mg, 81**%**) as a white solid.Mp: N.R,^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (s, 1H), 8.17 (d, *J* = 2.5 Hz, 1H), 8.04 (s, 1H), 7.36 (d, *J* = 8.7 Hz, 2H), 7.01 (d, *J* = 8.7 Hz, 2H), 1.27 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.3 (s), 149.5 (s), 147.1 (s), 140.0 (s), 137.2 (s), 134.8 (s), 125.7 (s), 119.4 (s), 33.4 (s), 30.4 (s). Anal.Calcd. For $C_{14}H_{16}N_2O$: C, 73.66; H, 7.06; N, 12.27. Found: C, 74.01; H, 7.21; N, 12.21.

2-(Naphthalen-2-yloxy)pyrazine (3c):

General Procedure (GP) was followed by using 2-chloropyrazine (1 mmol, 1 equiv.) and 2-naphthol (1.1 mmol, 1.1 eq.) yielded a desired product (195 mg, 88**%**) as a white solid. Mp:116-118 ^{o}C,^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (s, 1H), 8.28 (s, 1H), 8.10 (s, 1H), 7.88 (dd, *J* = 16.7, 8.2 Hz, 2H), 7.80 (d, *J* = 7.6 Hz, 1H), 7.61 (s, 1H), 7.52 – 7.44 (m, 2H), 7.29 (d, *J* = 8.8 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.3 (s), 150.6 (s), 141.1 (s), 138.5 (s), 135.9 (s), 134.0 (s), 131.2 (s), 129.8 (s), 127.8 (s), 127.5 (s), 126.6 (s), 125.5 (s), 120.9 (s), 117.8 (s).Anal.Calcd. For $C_{14}H_{10}N_2O$: C, 75.66; H, 4.54; N, 12.60. Found: C, 75.56; H, 4.56; N, 12.42.

2-(Naphthalen-1-yloxy)pyrazine (3d) :

General Procedure (GP) was followed by using 2-chloropyrazine (1 mmol, 1 equiv.) and 1-naphthol (1.1 mmol, 1.1 eq.) yielded a desired product (177 mg, 80**%**) as a white solid. Mp: 100-102 ^{o}C,^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, *J* = 2.9 Hz, 1H), 8.28 (d, *J* = 2.4 Hz, 1H), 8.07 (d, *J* = 1.3 Hz, 1H), 7.92 (dd, *J* = 5.2, 1.8 Hz, 2H), 7.82 – 7.75 (m, 1H), 7.56 – 7.44 (m, 3H), 7.30 – 7.23 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.9 (s), 141.3 (s), 138.5 (s), 135.3 (s), 134.9 (s), 128.1 (s), 127.1 (s), 126.5 (d), 125.68 (d), 121.5 (s), 117.3 (s). Anal.Calcd. For $C_{14}H_{10}N_2O$: C, 75.66; H, 4.54; N, 12.60. Found: C, 75.44; H, 4.70; N, 12.34.

2-(Naphthalen-2-yloxy)benzo[d]thiazole (3e):

General Procedure (GP) was followed by using 2-chlorobenzothiazole (1 mmol, 1 equiv.) and 2-naphthol (1.1 mmol, 1.1 eq.) yielded a desired product (235 mg, 85**%**) as a white solid.Mp:68-70 ^{o}C,^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 – 7.76 (m, 5H), 7.68 (d, *J* = 7.9 Hz, 1H), 7.51 (dd, *J* = 8.9, 5.4 Hz, 3H), 7.41 (t, *J* = 7.2 Hz, 1H), 7.28 (t, *J* = 7.3 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.0 (s), 152.3 (s), 149.1 (s), 133.9 (s), 132.4 (s), 131.6 (s), 130.1 (s), 127.8 (d), 126.8 (s), 126.3 (s), 126.0 (s), 124.1 (s), 121.8 (s), 121.3 (s), 120.1 (s), 117.5 (s). Anal.Calcd. For $C_{17}H_{11}NOS$: C, 73.62; H, 4.0; N, 5.05; S, 11.56. Found: C, 74.02; H, 4.04; N, 5.12; S, 11.77.

2-(Naphthalen-1-yloxy)benzo[d]thiazole (3f) :

General Procedure (GP) was followed by using 2-chlorobenzothiazole (1 mmol, 1 equiv.) and 1-naphthol (1.1 mmol, 1.1 eq.) yielded a desired product (227 mg, 82**%**) as a white solid.Mp: 100-102 ^{o}C,^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 7.3 Hz, 1H), 7.91 (d, *J* = 6.7 Hz, 1H), 7.82 (d, *J* = 6.6 Hz, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.63 (d, *J* = 7.9 Hz, 1H), 7.57 – 7.48 (m, 4H), 7.38 (t, *J* = 7.7 Hz, 1H), 7.25 (t, *J* = 7.6 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.6 (s), 150.7 (s), 149.1 (s), 134.9 (s), 132.3 (s), 128.0 (s), 127.0 – 126.5 (m), 126.3 (d), 125.5 (s), 124.0 (s), 121.7 (s), 121.3 (d), 117.1 (s). Anal.Calcd. For $C_{17}H_{11}NOS$: C, 73.62; H, 4.0; N, 5.05; S, 11.56. Found: C, 74.01; H, 4.14; N, 5.06; S, 12.00.

2-(4-Methoxyphenoxy)benzo[d]thiazole (3g) :[30]

General Procedure (GP) was followed by using 2-chlorobenzothiazole (1 mmol, 1 equiv.) and 4-methoxy phenol (1.1 mmol, 1.1 eq.) yielded a desired product (218 mg, 85**%**) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 7.6 Hz, 1H), 7.63 (d, *J* = 7.3 Hz, 1H), 7.39 – 7.32 (m, 1H), 7.29 – 7.22 (m, 3H), 6.98 – 6.90 (m, 2H), 3.82 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.9 (s), 157.6 (s), 149.2 (s), 148.3 (s), 132.2 (s), 126.1 (s), 123.8 (s), 121.8 (s), 121.6 (s), 121.2 (s), 114.8 (s), 55.6 (s). Anal.Calcd. For $C_{14}H_{11}NO_2S$: C, 65.35; H, 4.31; N, 5.44; S, 12.46. Found: C, 65.05; H, 4.36; N, 5.17; S, 12.33.The compound exhibited identical ^{1}H and ^{13}C NMR data to previous reports.[30]

2-(4-(tert-Butyl)phenoxy)benzo[d]thiazole (3h):

General Procedure (GP) was followed by using 2-chlorobenzothiazole (1 mmol, 1 equiv.) and 4-*tert* butyl phenol (1.1 mmol, 1.1 eq.) yielded a desired product (240 mg, 85**%**) as a white solid.Mp: 108-110 ^{o}C,^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.7 Hz, 1H), 7.64 (d, *J* = 7.5 Hz, 1H), 7.44 (d, *J* = 8.6 Hz, 2H), 7.37 (t, *J* = 7.2 Hz, 1H), 7.31 – 7.23 (m, 3H), 1.34 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.2 (s), 152.4 (s), 149.2 (s), 132.2 (s), 126.8 (s), 126.1 (s), 123.9 (s), 121.6 (s), 121.2 (s), 119.9 (s), 34.5 (s), 31.4 (s). Anal.Calcd. For $C_{17}H_{17}NOS$: C, 72.05; H, 6.05; N, 4.94; S, 11.31. Found: C, 72.42; H, 6.24; N, 4.66; S, 11.10.

2-(4-Methoxyphenoxy)benzo[d]oxazole (3i):

General Procedure (GP) was followed by using 2-chlorobenzo[d]oxazole (0.116 mL,1 mmol) and 4-methoxy phenol (149 mg, 1.2 mmol, 1.2 eq.) provided desired 2-(4-methoxyphenoxy)benzo[d]oxazole (224 mg, 0.93 mmol, 93%) as a colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.82 (s, 3 H), 6.92 - 6.99 (m, 2 H), 7.18 - 7.28 (m, 2 H), 7.28 - 7.35 (m, 2 H), 7.37 - 7.43 (m, 1 H), 7.47 - 7.53 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 55.6 (s, 1 C), 109.8 (s, 1 C), 114.8 (s, 1 C), 118.6 (s, 1 C), 121.2 (s, 1 C), 123.2 (s, 1 C), 124.4 (s, 1 C), 140.8 (s, 1 C), 146.3 (s, 1 C), 148.4 (s, 1 C), 157.6 (s, 1 C), 162.8 (s, 1 C); (+ve)APCI-MS m/z = 241.07 m/z calcd. for $C_{14}H_{11}NO_3$ [M]; found : 242.21[M+H].Anal.Calcd. For $C_{14}H_{11}NO_3$:C, 69.70; H, 4.60; N, 5.81; Found: C, 69.52; H, 4.44; N, 5.79.

2-(4-tert-Butylphenoxy)quinoxaline (3j):

General Procedure (GP) was followed by using 2-Chloroquinoxaline (164 mg,1 mmol) and 1-*tert*-butyl-4-methoxybenzene (180 mg, 1.2 mmol, 1.2 eq.) provided a desired 2-(4-tert-butylphenoxy)quinoxaline (265 mg, 0.949 mmol, 95%) as a colorless crystals. Mp: 66.7-68.7^{o}C, ^{1}H NMR (300 MHz, $CDCl_3$) δ : 1.37 (s, 9 H), 7.21 - 7.27 (m, 2 H), 7.43 - 7.51 (m, 2 H), 7.57 - 7.70 (m, 2 H), 7.76 - 7.83 (m, 1 H), 8.06 (dd, *J*=8.07, 1.56 Hz, 1 H), 8.68 (s, 1 H); ^{13}C NMR (75

MHz, $CDCl_3$) δ: 31.8 (s, 1 C), 31.9 (s, 1 C), 34.9 (s, 1 C), 121.0 (s, 1 C), 126.8 (s, 1 C), 126.9 (s, 1 C), 127.7 (s, 1 C), 128.1 (s, 1 C), 129.2 (s, 1 C), 130.7 (s, 1 C), 139.6 (s, 1 C), 139.9 (s, 1 C), 148.6 (s, 1 C), 150.8 (s, 1 C), 157.4 (s, 1 C); (+ve)APCI-MS *m/z* = 278.35 calcd. for $C_{18}H_{18}N_2O$[M], found : 279.4[M+H]. Anal.Calcd. For $C_{18}H_{18}N_2O$:C, 77.67; H, 6.52; N, 10.06; Found: C, 77.59; H, 6.48; N, 10.17.

2-(4-Methoxyphenoxy)quinoxaline (3k):

General Procedure (GP) was followed by using 2-Chloroquinoxiline (164 mg, 1 mmol) and 4-methoxy phenol (149 mg,1.2 mmol, 1.2 eq.) yielded a desired 2-(4-methoxyphenoxy)quinoxaline (219 mg, 0.79 mmol, 87%) as a white crystals. Mp: 144.7-146.7°C,^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.86 (s, 3 H), 6.96 - 7.02 (m, 2 H), 7.19 - 7.25 (m, 2 H), 7.57 - 7.70 (m, 2 H), 7.75 - 7.81 (m, 1 H), 8.07 (dd, *J*=7.98, 1.56 Hz, 1 H), 8.68 (s, 1 H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 55.6 (s, 1 C), 55.7 (s, 1 C), 114.6 (s, 1 C), 114.7 (s, 1 C), 116.0 (s, 1 C), 122.3 (s, 1 C), 127.2 (s, 1 C), 127.6 (s, 1 C), 128.8 (s, 1 C), 130.3 (s, 1 C), 139.1 (s, 1 C) 139.4 (s, 1 C), 140.0 (s, 1 C), 146.1 (s, 1 C), 156.9 (s, 1 C); (+ve)APCI-MS *m/z* = 252.27 [M]calcd. for $C_{15}H_{12}N_2O_2$ [M], found: 253.33[M+H]. Anal.Calcd. For $C_{15}H_{12}N_2O_2$: C, 71.42; H, 4.79; N, 11.10; Found: C, 71.09; H, 4.98; N, 11.07.

2-(Mesityloxy)quinoxaline (3l):

General Procedure (GP) was followed by using 2-Chloroquinoxaline (164 mg, 1 mmol) and 2,4,6-trimethylphenol (163 mg, 1.2 mmol, 1.2 eq.) provided desired 2-(mesityloxy)quinoxaline (243.25 mg, 0.92 mmol, 92%) as a shiny white needles; . Mp: 92.3-94.0 °C,^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.13 (s, 6 H), 2.36 (s, 3 H), 6.97 (s, 2 H), 7.62 (t_d, *J*=7.45, 1.79 Hz, 2 H), 7.71 - 7.81 (m, 1 H), 8.04 - 8.12 (m, 1 H), 8.73 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 16.5 (s, 1 C), 20.8 (s, 1 C), 127.0 (s, 1 C), 127.7 (s, 1 C), 128.8 (s, 1 C), 129.3 (s, 1 C), 130.1 (s, 1 C), 130.3 (s, 1 C),

135.0 (s, 1 C), 138.5 (s, 1 C), 139.4 (s, 1 C), 140.4 (s, 1 C), 147.4 (s, 1 C), 156.3 (s, 1 C); (+ve)APCI-MS *m/z* = 264.32 calcd. for $C_{17}H_{16}N_2O$ [M], found : 265.43 [M+H]. Anal.Calcd. For $C_{17}H_{16}N_2O$:C, 77.25; H, 6.10; N, 10.60; Found: C, 77.22; H, 6.48; N, 10.43.

2-Phenoxyquinoxaline (3m):

General Procedure (GP) was followed by using 2-Chloroquinoxaline (164 mg, 1 mmol) and phenol (119 mg, 1.2 mmol, 1.2 eq.) provided desired 2-phenoxyquinoxaline (182 mg, 0.82 mmol, 82%) as a colorless crystals.; ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ:7.19 - 7.33 (m, 3 H), 7.37 - 7.50 (m, 2 H), 7.52 - 7.68 (m, 2 H), 7.68 - 7.79 (m, 1 H), 8.03 (dd, *J*=7.98, 1.56 Hz, 1 H), 8.66 (s, 1 H); ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ:, 121.4 (s, 1 C), 125.4 (s, 1 C), 127.4 (s, 1 C), 127.7 (s, 1 C), 128.8 (s, 1 C), 129.6 (s, 1 C), 130.3 (s, 1 C), 139.2 (s, 1 C), 139.6 (s, 1 C), 140.0 (s, 1 C), 152.8 (s, 1 C), 156.9 (s, 1 C); (+ve)APCI-MS m/z = 222.24, calcd. for $C_{14}H_{10}N_2O$ [M], Found : 223.5 [M+H]. The compound exhibited identical ^{1}H and ^{13}C NMR data to previous reports[12].

2-(3-Nitrophenoxy)quinoxaline (3n):[31]

General Procedure (GP) was followed by using 2-Chloroquinoxaline (164 mg, 1 mmol) and 3-nitrophenol (208 mg, 1.5 mmol, 1.5 eq.) provided desired 2-(3-nitrophenoxy)quinoxaline(254 mg, 0.95 mmol, 95%) as a colorless crystals. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.61 - 7.72 (m, 4 H), 7.72 - 7.79 (m, 1 H), 8.07 - 8.15 (m, 1 H), 8.18 (dt, *J*=6.95, 2.21 Hz, 1 H), 8.23 - 8.28 (m, 1 H), 8.77 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 117.2 (s, 1 C), 120.3 (s, 1 C), 127.6 (s, 1 C), 127.9 (s, 1 C), 128.0 (s, 1 C), 129.0 (s, 1 C), 130.1 (s, 1 C), 130.7 (s, 1 C), 138.7 (s, 1 C), 139.4 (s, 1 C), 140.0 (s, 1 C), 149.0 (s, 1 C), 153.0 (s, 1 C), 155.9 (s, 1 C); (+ve)APCI-MS *m/z* = 267.24 calcd. for $C_{14}H_9N_3O_3$ [M], Found : 268.18 [M+H]. The compound exhibited identical ^{1}H and ^{13}C NMR data to previous reports.

2-(Quinoxalin-2-yloxy)benzaldehyde (3o):

General Procedure (GP) was followed by using 2-Chloroquinoxaline (164 mg, 1 mmol) and Salicylaldehyde (0.13 mL, 1.2 mmol, 1.2 eq.) provided desired 2-(quinoxalin-2-yloxy)benzaldehyde (232.8 mg, 0.93 mmol, 93%) as a colorless crystals.; ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ : 7.32 - 7.41 (m, 1 H), 7.45 (t, *J*=7.57 Hz, 1 H), 7.57 - 7.76 (m, 4 H), 7.98 - 8.17 (m, 2 H), 8.83 (s, 1 H), 10.26 (s, 1 H) ; ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ : 123.4 (s, 1 C), 126.5 (s, 1 C), 128.1 (s, 1 C), 128.3 (s, 1 C), 129.0 (s, 1 C), 129.4 (s, 1 C), 130.0 (s, 1 C), 131.0 (s, 1 C), 135.9 (s, 1 C), 139.0 (s, 1 C), 140.1 (s, 1 C), 140.3 (s, 1 C), 155.0 (s, 1 C), 157.3 (s, 1 C), 189.0 (s, 1 C) ;(+ve)APCI-MS *m/z* = 250.25 Anal.Calcd for $C_{15}H_{10}N_2O_2$ [M], Found : 251.4 [M+H]. The compound exhibited identical ^{1}H and ^{13}C NMR data to previous reports[12].

2-(4-Fluorophenoxy)quinoxaline (3p):

General Procedure (GP) was followed by using 2-Chloroquinoxaline (164 mg, 1 mmol) and 4-fluorophenol (146 mg, 1.3 mmol, 1.3 eq.) provided desired 2-(4-fluorophenoxy)quinoxaline (223.4 mg, 0.93 mmol, 93%) as a colorless crystals. ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ :7.08 - 7.20 (m, 2 H), 7.21 - 7.32 (m, 2 H), 7.56 - 7.70 (m, 2 H), 7.70 - 7.80 (m, 1 H), 8.06 (dd, *J*=8.02, 1.60 Hz, 1 H), 8.68 (s, 1 H); ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ: 116.1 (s, 1 C), 116.4 (s, 1 C), 122.9 (s, 1 C), 123.0 (s, 1 C), 127.5 (s, 1 C), 127.6 (s, 1 C), 128.9 (s, 1 C), 130.4 (s, 1 C), 139.0 (s, 1 C), 139.6 (s, 1 C), 139.8 (s, 1 C), 148.4 (s, 1 C), 148.4 (s, 1 C), 156.8 (s, 1 C), 158.3 (s, 1 C), 161.6 (s, 1 C); ^{19}F NMR (282 MHz, CHLOROFORM-*d*) δ :-117.3 (s, 1 F);(+ve)APCI-MS *m/z* = 240.23 calcd. for $C_{14}H_9FN_2O$ [M], found : 241.15 [M+H]. The compound exhibited identical ^{1}H and ^{13}C NMR data to previous reports.[32]

Ethyl 4-(quinoxalin-2-yloxy)benzoate (3q):

General Procedure (GP) was followed by using 2-Chloroquinoxaline (164 mg, 1 mmol) and ethyl 4-hydroxybenzoate (200 mg, 1.3 mmol, 1.3 eq.) provided desired ethyl 4-(quinoxalin-2-yloxy)benzoate (256 mg, 0.87 mmol, 87%) as a colorless crystals. ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ :1.42 (t, *J*=7.11 Hz, 3 H), 4.41 (q, *J*=7.15 Hz, 2 H), 7.34 - 7.44 (m, 2 H) 7.59 - 7.72 (m, 2 H), 7.74 - 7.82 (m, 1 H), 8.09 (dd, *J*=7.93, 1.70 Hz, 1 H), 8.13 - 8.21 (m, 2 H), 8.72 (s, 1 H); ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ :14.3 (s, 1 C), 61.0 (s, 1 C), 121.0 (s, 1 C), 127.5 (s, 1 C), 127.7 (s, 1 C), 127.8 (s, 1 C), 129.0 (s, 1 C), 130.5 (s, 1 C), 131.3 (s, 1 C), 139.0 (s, 1 C), 139.7 (s, 1 C), 139.8 (s, 1 C), 156.2 (s, 1 C), 156.5 (s, 1 C), 165.9 (s, 1 C); (+ve)APCI-MS *m/z* = 294.3 calcd. for $C_{17}H_{14}N_2O_3$ [M], found : 295 [M+H]. The compound exhibited identical ^{1}H and ^{13}C NMR data to previous reports.[33]

2-(Perfluorophenoxy)quinoxaline (3r):

General Procedure (GP) was followed by using 2-Chloroquinoxaline (164 mg, 1 mmol) and 2,3,4,5,6-pentafluorophenol (276.1 mg, 1.5 mmol, 1.5 eq.) provided desired 2-(perfluorophenoxy)quinoxaline (187 mg, 0.598 mmol, 60%) as a colorless crystals. . Mp: 83.1-84.3^{o}C ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.61 - 7.85 (m, 4 H), 8.09 - 8.24 (m, 1 H), 8.86 (s, 1 H) ; ^{13}C NMR (75 MHz, CDCl3) δ: 127.6 (s, 1 C), 128.3 (s, 1 C), 129.1 (s, 1 C), 130.9 (s, 1 C), 137.3 (s, 1 C), 139.3 (s, 1 C), 139.7 (s, 1 C), 140.0 (s, 1 C), 140.1 (s, 1 C), 140.4 (s, 1 C), 143.4 (s, 1 C), 143.5 (s, 1 C), 143.5 (s, 1 C), 154.4 (s, 1 C); ^{19}F NMR (282 MHz, $CDCl_3$) δ: -162.4 (s, 1 F), -162.4 (s, 1 F), -162.4 (s, 1 F), -162.3 (s, 1 F), -158.5 (s, 1 F), -158.4 (s, 1 F), -158.3 (s, 1 F), -152.1 (s, 1 F), -152.1 (s, 1 F), -152.0 (s, 1 F), -152.0 (s, 1 F) ;(+ve)APCI-MS *m/z* = 312.19 calcd. for $C_{14}H_5F_5N_2O$ [M], found : 313.22 [M+H]. Anal.Calcd. For $C_{14}H_5F_5N2O$:C, 53.86; H, 1.61; N, 8.97; Found: C, 53.89; H, 1.58; N, 8.93.

2-(Quinoxalin-2-yloxy)benzenamine (3s):

General Procedure (GP) was followed by using 2-Chloroquinoxaline (164 mg, 1 mmol) and 2-Aminophenol (121 mg, 1.1 mmol, 1.1 eq.) provided desired 2-(quinoxalin-2-yloxy)benzenamine(218 mg, 0.92 mmol, 92%) as a yellow needles. ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ :3.77 (br. s., 2H), 6.81 - 6.93 (m, 2 H), 7.08 - 7.21 (m, 2 H), 7.57 - 7.71 (m, 2 H), 7.77 - 7.86 (m, 1 H), 8.03 - 8.13 (m, 1 H), 8.71 (s, 1 H); ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ : 117.0 (s, 1 C), 118.8 (s, 1 C), 122.2 (s, 1 C), 126.4 (s, 1 C), 127.5 (s, 1 C), 127.8 (s, 1 C), 128.9 (s, 1 C), 130.4 (s, 1 C), 138.5 (s, 1 C), 138.9 (s, 1 C), 139.7 (s, 1 C), 140.0 (s, 1 C), 140.0 (s, 1 C), 156.4 (s, 1 C); (+ve)APCI-MS *m/z* = 237.26 calcd. for $C_{14}H_{11}N_3O$ [M], found : 238.48 [M+H]. The compound exhibited identical ^{1}H and ^{13}C NMR data to previous reports.[34]

2-(3,5-Bis(trifluoromethyl)phenoxy)benzo[d]oxazole (3t):[34]

General Procedure (GP) was followed by using 2-chlorobenzo[d]oxazole (0.116 mL,1 mmol) and 3,5-bis(trifluoromethyl)phenol (276 mg, 1.2 mmol, 1.2 eq.) provided desired 2-(3,5-bis(trifluoromethyl)phenoxy)benzo[d]oxazole (191 mg, 0.55 mmol, 55%) as a viscous liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.20 - 7.34 (m, 2 H), 7.38 - 7.46 (m, 1 H), 7.48 - 7.59 (m, 1 H), 7.81 (s, 1 H), 8.00 (s, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 110.1 (s, 1 C), 117.2 (s, 1 C), 119.1 (s, 1 C), 119.9 (s, 1 C), 119.9 (s, 1 C), 120.0 (s, 1 C), 120.0 (s, 1 C), 120.1 (s, 1 C), 120.7 (s, 1 C), 120.8 (s, 1 C), 124.2 (s, 1 C), 124.4 (s, 1 C), 124.9 (s, 1 C), 128.0 (s, 1 C), 132.7 (s, 1 C), 133.2 (s, 1 C), 133.7 (s, 1 C), 134.1 (s, 1 C), 140.1 (s, 1 C), 148.4 (s, 1 C), 152.9 (s, 1 C), 160.6 (s, 1 C); ^{19}F NMR (282 MHz, $CDCl_3$) δ: -63.0 (s, 1 F); (+ve)APCI-MS m/z = 347.04 m/z calcd. for $C_{15}H_7F_6NO_2$ [M]; found : 348.13[M+H].The compound exhibited identical ^{1}H and ^{13}C NMR data to previous reports.[34]

2-(1-Bromonaphthalen-2-yloxy)quinoxaline (3u):

General Procedure (GP) was followed by using 2-Chloroquinoxaline (164 mg, 1 mmol) and 1-bromonaphthalen-2-ol (334.6 mg, 1.5 mmol, 1.5 eq.) provided desired 2-(1-bromonaphthalen-2-yloxy)quinoxaline (344.2 mg, 0.98 mmol, 98%) as a brown Solid. . Mp: 183.9-185.3 ºC,1H NMR (300 MHz, CDCl3) δ: 7.46 (d, J=8.90 Hz, 1 H), 7.55 - 7.73 (m, 5 H), 7.94 (d, J=8.53 Hz, 2 H), 8.07 - 8.15 (m, 1 H), 8.33 (d, J=8.44 Hz, 1 H), 8.86 (s, 1 H); 13C NMR (75 MHz, CDCl3) δ: 115.1 (s, 1 C), 122.3 (s, 1 C), 126.3 (s, 1 C), 127.0 (s, 1 C), 127.5 (s, 1 C), 127.7 (s, 1 C), 127.7 (s, 1 C), 128.2 (s, 1 C), 128.8 (s, 1 C), 128.9 (s, 1 C), 130.4 (s, 1 C), 132.3 (s, 1 C), 133.0 (s, 1 C), 138.7 (s, 1 C), 139.8 (s, 1 C), 139.9 (s, 1 C), 148.0 (s, 1 C), 156.4 (s, 1 C); (+ve)APCI-MS m/z = 351.12 calcd. for $C_{18}H_{11}BrN_2O$ [M], found : 352.2 [M+H]. Anal.Calcd. For $C_{18}H_{11}BrN_2O$; C, 61.56; H, 3.16; N, 7.98; Found: C, 61.52; H, 3.18; N, 7.93.

2-(8-Bromonaphthalen-1-yloxy)benzo[d]oxazole (3v):

General Procedure (GP) was followed by using 2-chlorobenzo[d]oxazole (0.116 mL,1 mmol) and 1-bromo naphthol (268 mg, 1.2 mmol, 1.2 eq.) provided desired 2-(8-bromonaphthalen-1-yloxy)benzo[d]oxazole (308 mg, 0.909 mmol, 91%) as white amorphous solid.Mp: 139.6-140.5ºC, 1H NMR (300 MHz, CDCl3) δ: 7.27 (dd, J=7.24, 1.93 Hz, 2 H), 7.46 - 7.53 (m, 2 H), 7.55 - 7.62 (m, 2 H),7.67 (td, J=7.68, 1.24 Hz, 1 H), 7.88 - 7.99 (m, 2 H), 8.31 (d, J=8.44 Hz, 1 H); 13C NMR (75 MHz, CDCl3) δ: 110.0 (s, 1 C), 114.3 (s, 1 C), 118.8 (s, 1 C), 120.4 (s, 1 C), 123.5 (s, 1 C), 124.6 (s, 1 C), 126.8 (s, 1 C), 127.2 (s, 1 C), 128.1 (s, 1 C), 128.3 (s, 1 C), 129.5 (s, 1 C), 132.7 (s, 1 C), 132.8 (s, 1 C), 140.7 (s, 1 C),147.6 (s, 1 C), 148.8 (s, 1 C), 161.8 (s, 1 C); (+ve)APCI-MS m/z = 338.99m/z calcd. for $C_{17}H_{10}BrNO_2$[M]; found : 340.11[M+H]. Anal.Calcd. For $C_{17}H_{10}BrNO_2$: C, 60.02; H, 2.96; N, 4.12; Found: C, 59.99; H, 2.66; N, 4.18.

2,2'-((Propane-2,2-diylbis(4,1-phenylene))bis(oxy))bis(benzo[d]thiazole) (3w):

General Procedure (GP) was followed by using 2-Chlorobenzothiazole (2 mmol, 2 equiv.) and 4,4'-(propane-2,2-diyl)diphenol (1 mmol, 1 equiv.) yielded a desired product (440 mg, 89**%**) as a white solid.Mp: 122-124 ^{o}C,^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.1 Hz, 1H), 7.67 (d, *J* = 7.5 Hz, 1H), 7.42 – 7.36 (m, 1H), 7.35 – 7.26 (m, 5H), 1.74 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.9 (s), 152.7 (s), 149.1 (s), 148.1 (s), 132.2 (s), 128.3 (s), 126.2 (s), 124.0 (s), 121.6 (s), 121.2 (s), 120.0 (s), 42.6 (s), 30.9 (s). Anal.Calcd. For $C_{29}H_{22}N_2O_2S_2$: C, 70.42; H, 4.48; N, 5.66; S, 12.96. Found: C, 70.62; H, 4.63; N, 5.57; S, 13.17.

7-(4-Methoxyphenoxy)-4-(pentyloxy)pteridin-2-amine (3x) :

General Procedure (GP) was followed by using chloropterin (1 mmol, 1 equiv.) and 4-methoxy phenol (1.1 mmol, 1.1 eq.) yielded a desired product (244 mg, 91**%**) as a white solid.Mp: 194-196 ^{o}C,^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (d, *J* = 1.3 Hz, 1H), 7.21 – 7.15 (m, 2H), 6.92 (d, *J* = 7.4 Hz, 2H), 5.24 (s, 2H), 4.42 (t, *J* = 6.3 Hz, 2H), 3.81 (s, 3H), 1.85 – 1.77 (m, 2H), 1.37 (tt, *J* = 14.0, 6.9 Hz, 4H), 0.90 (t, *J* = 6.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.2 (d), 157.7 (s), 156.8 (s), 155.1 (s), 144.0 (s), 121.6 (s), 118.9 (s), 114.6 (s), 68.0 (s), 55.5 (s), 35.8 (s), 28.0 (s), 22.3 (s), 13.9 (s). Anal.Calcd. For $C_{18}H_{21}N_5O_3$: C, 60.83; H, 5.96; N, 19.71. Found: C, 60.97; H, 6.21; N, 19.80.

2-(Benzo[d][1,3]dioxol-5-ylmethoxy)benzo[d]thiazole (4a):

General Procedure (GP) was followed by using 2-Chlorobenzothiazole (1 mmol, 1 equiv.) and benzo[d][1,3]dioxol-5-ylmethanol (1.1 mmol, 1.1 eq.) yielded a desired product (242 mg, 85**%**) as a white solid.Mp: 96-98 ^{o}C,^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.36 (m, 1H), 7.24 – 7.18 (m, 1H), 7.16 – 7.07 (m, 1H), 7.01 – 6.93 (m, 1H), 6.86 – 6.67 (m, 3H), 5.90 (s, 2H), 5.03 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2 (s), 148.1 (s), 147.3 (s), 136.8 (s), 128.9 (s), 126.2 (s), 123.2 (s), 122.5 (s), 120.7 (s), 111.1 (s), 108.3 (s), 107.7 (s), 101.1 (s), 46.0 (s). Anal.Calcd. For $C_{15}H_{11}NO_3S$: C, 63.15; H, 3.89; N, 4.91; S, 11.24. Found: C, 63.01; H, 3.97; N, 5.12; S, 11.56.

2-((3,4-Dimethoxybenzyl)oxy)benzo[d]thiazole (4b):

General Procedure (GP) was followed by using 2-Chlorobenzothiazole (1 mmol, 1 equiv.) and (3,4-dimethoxyphenyl)methanol (1.1 mmol, 1.1 eq.) yielded a desired product (267 mg, 89**%**) as a white solid.Mp: 64-66 ^{o}C,^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, J = 8.0 Hz, 1H), 7.63 (d, J = 7.7 Hz, 1H), 7.36 (t, J = 7.6 Hz, 1H), 7.23 (d, J = 7.9 Hz, 1H), 6.62 (s, 2H), 6.44 (s, 1H), 5.51 (s, 2H), 3.79 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.5 (s), 160.9 (s), 149.1 (s), 140.6 (s), 137.3 (s), 132.0 (s), 125.9 (s), 123.5 (s), 121.2 (s), 120.8 (s), 106.1 (s), 100.5 (s), 73.2 (s), 55.3 (s). Anal.Calcd. For $C_{16}H_{15}NO_3S$: C, 63.77; H, 5.02; N, 4.65; S, 10.64. Found: C, 63.71; H, 4.88; N, 4.70; S, 10.87.

2-(Quinolin-8-yloxy)benzo[d]thiazole (4c):[35]

General Procedure (GP) was followed by using 2-Chlorobenzothiazole (1 mmol, 1 equiv.) and 8-hydroxy quinoline (1.1 mmol, 1.1 eq.) yielded a desired product (228 mg, 82**%**) as a white solid.^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (d, J = 3.9 Hz, 1H), 8.19 (d, J = 8.2 Hz, 1H), 7.76 (t, J = 7.8 Hz, 2H), 7.68 – 7.62 (m, 2H), 7.61 – 7.56 (m, 1H), 7.43 (dd, J = 7.9, 3.9 Hz, 1H), 7.33 (t, J = 7.7 Hz, 1H), 7.26 – 7.22 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.6 (s), 150.7 (s), 150.5

(s), 149.0 (s), 140.8 (s), 136.0 (s), 132.6 (s), 129.9 (s), 126.3 (s), 126.1 (d), 123.87 (s), 121.9 (s), 121.6 (s), 121.2 (s), 120.7 (s). Anal.Calcd. For $C_{16}H_{10}N_2OS$: C, 69.05; H, 3.62; N, 10.07; S, 11.52. Found: C, 69.02; H, 3.92; N, 9.80; S, 11.40.The compound exhibited identical ^{1}H and ^{13}C NMR data to previous reports.[35]

2-(Quinolin-6-yloxy)benzo[d]thiazole (4d):

General Procedure (GP) was followed by using 2-Chlorobenzothiazole (1 mmol, 1 equiv.) and 6-hydroxy quinoline (1.1 mmol, 1.1 eq.) yielded a desired product (244 mg, 88**%**) as a white solid.Mp: 68-70 ^{o}C ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (dd, *J* = 1.5, 0.8 Hz, 1H), 8.21 – 8.13 (m, 2H), 7.84 (dd, *J* = 1.6, 0.6 Hz, 1H), 7.71 (td, *J* = 7.7, 4.1 Hz, 3H), 7.45 – 7.36 (m, 2H), 7.28 (ddd, *J* = 8.1, 2.5, 1.4 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.3 (s), 152.2 (s), 150.3 (s), 148.8 (s), 146.3 (s), 135.8 (s), 132.3 (s), 131.6 (s), 128.7 (s), 126.3 (s), 124.3 (s), 123.7 (s), 121.8 (d), 121.3 (s), 117.0 (s). Anal.Calcd. For $C_{16}H_{10}N_2OS$: C, 69.05; H, 3.62; N, 10.07; S, 11.52. Found: C, 69.02; H, 3.95; N, 10.34; S, 11.91.

6-(Quinoxalin-2-yloxy)-2H-chromen-2-one (4e):

General Procedure (GP) was followed by using 2-Chloroquinoxaline (164 mg, 1 mmol) and 6-hydroxy coumarin (194.6 mg, 1.2 mmol, 1.2 eq.) provided desired 6-(quinoxalin-2-yloxy)-2H-chromen-2-one (238 mg, 0.82 mmol, 82%) as a white shiny feathery needles. . Mp: 207.2-208.9 ^{o}C,^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ : 6.51 (d, *J*=9.63 Hz, 1 H), 7.42 - 7.52 (m, 3 H), 7.64 - 7.78 (m, 4 H), 8.07 - 8.13 (m, 1 H), 8.75 (s, 1 H);^{13}C NMR (75 MHz, $CDCl_3$) δ: 117.4 (s, 1 C), 118.1 (s, 1 C), 119.4 (s, 1 C), 119.9 (s, 1 C), 125.6 (s, 1 C), 127.6 (s, 1 C), 127.7 (s, 1 C), 129.0 (s, 1 C), 130.6 (s, 1 C), 138.9 (s, 1 C), 139.6 (s, 1 C), 139.8 (s, 1 C), 142.8 (s, 1 C), 148.6 (s, 1 C), 151.3 (s, 1 C), 156.6 (s, 1 C), 160.5 (s, 1 C); (+ve)APCI-MS m/z = 290.07 calcd. for

$C_{17}H_{10}N_2O_3$ [M], found : 291.3 [M+H]. Anal.Calcd. For$C_{17}H_{10}N_2O_3$: C, 70.34; H, 3.47; N, 9.65; Found: C, 70.13; H, 3.27; N, 9.35.

6-(Pyrazin-2-yloxy)quinoline (4f):

General Procedure (GP) was followed by using 2-Chloropyrazine (1 mmol, 1 equiv.) and 6-hydroxy quinoline (1.1 mmol, 1.1 eq.) yielded a desired product (178 mg, 80**%**) as a white solid.Mp: 104-106 ^{o}C,^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 – 8.85 (m, 1H), 8.50 (s, 1H), 8.30 (s, 1H), 8.15 (dd, *J* = 9.2, 0.6 Hz, 1H), 8.11 (d, *J* = 8.0 Hz, 2H), 7.59 (s, 1H), 7.55 – 7.50 (m, 1H), 7.40 (ddd, *J* = 4.2, 3.4, 2.3 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.9 (s), 150.8 (s), 150.0 (s), 146.1 (s), 141.0 (s), 138.9 (s), 136.0 (s), 135.5 (s), 131.3 (s), 128.8 (s), 124.5 (s), 121.5 (s), 117.4 (s). Anal.Calcd. For $C_{13}H_9N_3O$: C, 69.95; H, 4.06; N, 18.82. Found: C, 69.99; H, 4.09; N, 18.71.

3-(Pyrazin-2-yloxy)-9H-carbazole (4g):

General Procedure (GP) was followed by using 2-Chloropyrazine (1 mmol, 1 equiv.) and 4-hydroxy carbazole (1.1 mmol, 1.1 eq.) yielded a desired product (235 mg, 90**%**) as a white solid.Mp: 230-232 ^{o}C,^{1}H NMR (400 MHz, DMSO-d_6) δ 11.50 (s, 1H), 8.70 (d, *J* = 0.9 Hz, 1H), 8.34 (d, *J* = 2.5 Hz, 1H), 8.10 (dd, *J* = 2.3, 1.3 Hz, 1H), 7.60 (d, *J* = 7.5 Hz, 1H), 7.47 (d, *J* = 8.1 Hz, 1H), 7.41 – 7.38 (m, 2H), 7.33 (dd, *J* = 11.1, 4.0 Hz, 1H), 7.01 (dd, *J* = 11.0, 3.9 Hz, 1H), 6.94 (dd, *J* = 5.5, 2.9 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 160.1 (s), 147.9 (s), 142.1 (s), 141.8 (s), 140.0 (s), 139.3 (s), 135.6 (s), 126.6 (s), 126.0 (s), 121.9 (s), 120.4 (s), 119.4 (s), 115.4 (s), 111.5 (d), 108.8 (s). Anal.Calcd. For $C_{16}H_{11}N_3O$: C, 73.55; H, 4.24; N, 16.08. Found: C, 73.39; H, 4.36; N, 16.02.

2-(4-Allyl-2-methoxyphenoxy)benzo[d]thiazole (5a):[12]

General Procedure (GP) was followed by using 2-Chlorobenzothiazole (1 mmol, 1 equiv.) and eugenol (1.1 mmol, 1.1 eq.) yielded a desired product (264 mg, 89**%**) as a liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 – 7.69 (m, 1H), 7.62 (d, *J* = 7.9 Hz, 1H), 7.35 (t, *J* = 7.7 Hz, 1H), 7.23 (dd, *J* = 7.8, 3.0 Hz, 2H), 6.90 – 6.81 (m, 2H), 6.04 – 5.93 (m, 1H), 5.20 – 5.09 (m, 2H), 3.79 (s, 3H), 3.41 (d, *J* = 6.1 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.9 (s), 151.0 (s), 149.3 (s), 141.9 (s), 139.8 (s), 136.7 (s), 132.4 (s), 126.0 (s), 123.6 (s), 122.3 (s), 121.6 (s), 121.2 (s), 120.9 (s), 116.3 (s), 113.5 (s), 55.9 (s), 40.1 (s). Mass *m/z* = 297.08 calcd. for $C_{17}H_{15}NO_2S$ [M], found : 298.20 [M+H].The compound exhibited identical ^{1}H and ^{13}C NMR data to previous reports.[12]

2-(4-Allyl-2-methoxyphenoxy)pyrazine (5b):

General Procedure (GP) was followed by using 2-Chloropyrazine (1 mmol, 1 equiv.) and eugenol (1.1 mmol, 1.1 eq.) yielded a desired product (205mg, 85**%**) as a liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (s, 1H), 8.20 (d, *J* = 2.5 Hz, 1H), 8.07 – 8.02 (m, 1H), 7.11 – 7.05 (m, 1H), 6.83 (d, *J* = 7.4 Hz, 2H), 6.03 – 5.94 (m, 1H), 5.16 – 5.08 (m, 2H), 3.73 (s, 3H), 3.41 (d, *J* = 5.0 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.1 (s), 151.2 (s), 141.0 (s), 139.6 (s), 138.7 (s), 137.9 (s), 136.9 (s), 135.2 (s), 122.6 (s), 120.9 (s), 116.2 (s), 113.0 (s), 55.7 (s), 40.0 (s). Mass *m/z* = 242.11 calcd. for $C_{14}H_{14}N_2O_2$ [M], found : 243.48 [M+H].Anal.Calcd. For $C_{14}H_{14}N_2O_2$: C, 69.41; H, 5.82; N, 11.56; Found: C, 69.69; H, 5.74; N, 11.56.

2-(5-allyl-2-methoxyphenoxy)quinoxaline(5c):

General Procedure (GP) was followed by using 2-Chloroquinoxaline (164 mg, 1 mmol) and Eugenol (0.23 mL, 1.5 mmol, 1.5 eq.) provided desired2-(5-allyl-2-methoxyphenoxy)quinoxaline (248.5 mg, 0.85 mmol, 85%) as a brown oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.42 (d, *J*=6.69 Hz, 2 H), 3.78 (s, 3 H), 5.09 - 5.16 (m, 2 H), 5.96 - 6.03 (m, 1 H), 6.85 - 6.88 (m, 2 H), 7.19 (d, *J*=7.79 Hz, 1 H), 7.50 - 7.63 (m, 2 H), 7.70 - 7.79 (m, 1 H), 8.04 - 8.13 (m, 1 H), 8.73 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 39.7 (s, 1 C), 55.3 (s, 1 C), 55.4 (s, 1 C),

115.1 (s, 1 C), 115.8 (s, 1 C), 120.7 (s, 1 C), 122.4 (s, 1 C), 127.3 (s, 1 C), 128.4 (s, 1 C), 129.8 (s, 1 C), 131.3 (s, 1 C), 136.7 (s, 1 C), 137.5 (s, 1 C), 138.3 (s, 1 C), 139.1 (s, 1 C), 139.4 (s, 1 C), 139.9 (s, 1 C), 150.9 (s, 1 C), 156.7 (s, 1 C); (+ve)APCI-MS *m/z* =292,33 calcd. for$C_{18}H_{16}N_2O_2$[M], found : 293.5 [M+H].

N-(4-(Pyrazin-2-yloxy)phenyl)acetamide (5d):

General Procedure (GP) was followed by using 2-Chloropyrazine (1 mmol, 1 equiv.) and paracetamol (1.1 mmol, 1.1 eq.) yielded a desired product (165 mg, 72**%**) as a white solid.Mp: 176-178 ^oC,^1H NMR (400 MHz, $CDCl_3$) δ 8.34 (s, 1H), 8.18 (d, *J* = 1.5 Hz, 1H), 8.02 (d, *J* = 0.9 Hz, 1H), 7.50 (d, *J* = 8.6 Hz, 3H), 7.08 – 7.02 (m, 2H), 2.11 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.3 (s), 160.2 (s), 149.0 (s), 141.0 (s), 138.4 (s), 135.7 (s), 135.2 (s), 121.7 (s), 121.2 (s), 24.4 (s). Anal.Calcd. For $C_{12}H_{11}N_3O_2$: C, 62.87; H, 4.84; N, 18.33. Found: C, 62.78; H, 5.13; N, 18.01.

N-(4-(Benzo[d]thiazol-2-yloxy)phenyl)acetamide (5e):

General Procedure (GP) was followed by using 2-Chlorobenzothiazole (1 mmol, 1 equiv.) and paracetamol (1.1 mmol, 1.1 eq.) yielded a desired product (241 mg, 85**%**) as a white solid.Mp: 160-162 ^oC,^1H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.67 (dd, *J* = 14.4, 7.9 Hz, 2H), 7.56 (d, *J* = 8.6 Hz, 2H), 7.36 (t, *J* = 7.4 Hz, 1H), 7.28 – 7.22 (m, 3H), 2.13 (s, 3H) ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.4 (s), 168.5 (s), 150.6 (s), 148.8 (s), 136.2 (s), 132.1 (s), 126.3 (s), 124.1 (s), 121.3 (d), 24.4 (s). Anal.Calcd. For $C_{15}H_{12}N_2O_2S$: C, 63.36; H, 4.25; N, 9.85; S, 11.28. Found: C, 63.32; H, 4.32; N, 10.06; S, 11.11.

***N*-(4-((5-Chlorobenzo[d]oxazol-2-yl)oxy)phenyl)acetamide (5f):**

General Procedure (GP) was followed by using 2,5-dichlorobenzo[d]oxazole (1 mmol, 1 equiv.) and paracetamol (1.1 mmol, 1.1 eq.) yielded a desired product (260 mg, 86**%**) as a white solid.Mp: 158-160 ^{o}C,^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 – 7.56 (m, 2H), 7.48 – 7.44 (m, 1H), 7.38 – 7.30 (m, 4H), 7.22 – 7.17 (m, 1H), 2.17 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.2 (s), 146.8 (s), 136.2 (s), 129.9 (s), 123.6 (s), 121.1 (s), 120.6 (s), 118.8 (s), 110.6 (s), 24.5 (s). Anal.Calcd. For $C_{15}H_{11}ClN_2O_3$: C, 59.52; H, 3.66; N, 9.25. Found: C, 59.29; H, 3.92; N, 9.50.

***N*-(4-(Quinoxalin-2-yloxy)phenyl)acetamide (5g):**

General Procedure (GP) was followed by using 2-chloroquinoxaline (1 mmol, 1 equiv.) and paracetamol (1.1 mmol, 1.1 eq.) yielded a desired product (237 mg, 85%) as a white solid.Mp: 124-126 ^{o}C,^{1}H NMR (400 MHz, DMSO-d6) δ 10.00 (s, 1H), 8.80 (s, 1H), 8.03 (d, J = 7.7 Hz, 1H), 7.71 – 7.60 (m, 5H), 7.22 (d, J = 8.8 Hz, 2H), 2.03 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d6) δ 168.6 (s), 157.4 (s), 148.0 (s), 140.1 (s), 139.6 (s), 139.4 (s), 137.1 (s), 131.1 (s), 129.0 (s), 128.0 (s), 127.5 (s), 122.2 (s), 120.6 (s), 24.3 (s). Anal.Calcd. For $C_{16}H_{13}N_3O_2$: C, 68.81; H, 4.69; N, 15.05. Found: C, 68.50; H, 4.80; N, 15.20.

Ethyl-2-(benzo[d]oxazol-2-ylamino)-3-(4-(benzo[d]oxazol-yloxy)phenyl)propanoate (5h):

General Procedure (GP) was followed by using 2-chlorobenzo[d]oxazole (0.116 mL,1 mmol) and L-Tyrosin ester(251 mg, 1.2 mmol, 1.2 eq.) provided desired Ethyl-2-(benzo[d]oxazol-2-ylamino)-3-(4-(benzo[d]oxazol-yloxy)phenyl)propanoate (296 mg, 0.669 mmol, 67%) as pale yellow solid. . Mp: 136-138 ^{o}C,^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.21 - 1.31 (m, 3 H), 3.28 (d, *J*=6.14 Hz, 1 H), 3.35 (d, *J*=5.69 Hz, 1 H), 4.21 (q, *J*=7.12 Hz, 2 H), 4.89 (br. s., 1 H), 6.25 (br. s., 1 H), 7.03 (dd, *J*=7.66, 1.24 Hz, 1 H), 7.11 - 7.29 (m, 6 H), 7.29 - 7.35 (m, 2 H), 7.35 - 7.41 (m, 2 H), 7.44 - 7.51 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.9 (s, 1 C), 37.0 (s, 1 C), 56.4 (s, 1 C), 61.7 (s, 1 C), 108.8 (s, 1 C), 109.7 (s, 1 C), 116.5 (s, 1 C), 118.5 (s, 1 C), 119.9 (s, 1 C),

121.0 (s, 1 C), 123.2 (s, 1 C), 123.8 (s, 1 C), 124.3 (s, 1 C), 130.7 (s, 1 C), 133.9 (s, 1 C), 140.5 (s, 1 C), 142.4 (s, 1 C), 148.2 (s, 1 C), 148.4 (s, 1 C), 151.7 (s, 1 C), 160.7 (s, 1 C), 161.8 (s, 1 C), 171.1 (s, 1 C); (+ve)APCI-MS m/z = 443.15m/z calcd. for $C_{25}H_{21}N_3O_5$ [M]; found : 444.72 [M+H]. Anal.Calcd. For $C_{25}H_{21}N_3O_5$:C, 67.71; H, 4.77; N, 9.48; Found: C, 67.72; H, 4.98; N, 9.44.

3-(Benzo[d]thiazol-2-yloxy)-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-17*H*-cyclopenta[a]phenanthren-17-one (5i):

General Procedure (GP) was followed by using 2-chlorobenzothiazole (1 mmol, 1 equiv.) and estrone (1.1 mmol, 1.1 eq.) yielded a desired product (367 mg, 91%) as a white solid.Mp: 166-168 ^oC,1H NMR (400 MHz, CDCl3) δ 7.72 (d, J = 7.9 Hz, 1H), 7.64 (d, J = 7.8 Hz, 1H), 7.35 (dd, J = 15.0, 7.8 Hz, 2H), 7.24 (t, J = 7.1 Hz, 1H), 7.11 (d, J = 8.2 Hz, 1H), 7.06 (s, 1H), 2.93 (d, J = 4.3 Hz, 2H), 2.54 – 2.46 (m, 1H), 2.44 – 2.39 (m, 1H), 2.34 – 2.27 (m, 1H), 2.20 – 1.91 (m, 5H), 1.59 – 1.40 (m, 5H), 0.91 (s, 3H). 13C NMR (101 MHz, CDCl3) δ 220.6 (s), 172.2 (s), 152.6 (s), 149.1 (s), 138.6 (s), 137.9 (s), 132.2 (s), 126.8 (s), 126.1 (s), 123.9 (s), 121.6 (s), 121.2 (s), 120.5 (s), 117.8 (s), 77.3 (s), 77.0 (s), 76.6 (s), 50.4 (s), 47.9 (s), 44.1 (s), 37.9 (s), 35.8 (s), 31.5 (s), 29.4 (s), 26.2 (s), 25.7 (s), 21.5 (s), 13.8 (s). Anal.Calcd. For $C_{25}H_{25}NO_2S$: C, 74.41; H, 6.24; N, 3.47; S, 7.94. Found: C, 74.79; H, 6.55; N, 3.38; S, 7.97.

13-Methyl-3-(pyrazin-2-yloxy)-6,7,8,9,11,12,13,14,15,16-decahydro-17*H*-cyclopentaphenanthren-17-one (5j):

General Procedure (GP) was followed by using 2-chloropyrazine (1 mmol, 1 equiv.) and estrone (1.1 mmol, 1.1 eq.) yielded a desired product (300 mg, 86**%**) as a white solid.Mp: 136-138 ^oC,^1H NMR (400 MHz, $CDCl_3$) δ 8.39 (s, 1H), 8.22 (d, *J* = 2.4 Hz, 1H), 8.09 (s, 1H), 7.32 (d, *J* = 8.4 Hz, 1H), 6.94 – 6.89 (m, 1H), 6.88 (s, 1H), 2.94 – 2.88 (m, 2H), 2.53 – 2.46 (m, 1H), 2.43 – 2.37

(m, 1H), 2.30 (ddd, *J* = 9.9, 6.0, 2.6 Hz, 1H), 2.14 (ddd, *J* = 9.9, 9.3, 3.9 Hz, 1H), 2.09 – 1.93 (m, 4H), 1.63 (s, 2H), 1.54 (d, *J* = 5.3 Hz, 1H), 1.49 – 1.42 (m, 2H), 0.90 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 220.7 (s), 160.3 (s), 150.7 (s), 141.1 (s), 138.4 (s), 138.2 (s), 136.9 (s), 135.8 (s), 126.7 (s), 121.2 (s), 118.4 (s), 50.4 (s), 47.9 (s), 44.1 (s), 37.9 (s), 35.8 (s), 31.5 (s), 29.4 (s), 26.3 (s), 25.7 (s), 21.5 (s), 13.8 (s). Anal.Calcd. For $C_{22}H_{24}N_2O_2$: C, 75.83; H, 6.94; N, 8.04. Found: C, 76.01; H, 6.55; N, 7.92.

(8R,9S,13S,14S)-13-methyl-3-(quinoxalin-2-yloxy)-6,7,8,9,11,12,13,14,15,16-decahydro-17H-cyclopenta[a]phenanthren-17-one (5k):

General Procedure (GP) was followed by using 2-chloroquinoxaline (1 mmol, 1 equiv.) and estrone (1.1 mmol, 1.1 eq.) yielded a desired product (338 mg, 85%) as a white solid.Mp: 206-208 ^{o}C,^{1}H NMR (400 MHz, CDCl3) δ 8.60 (s, 1H), 8.01 – 7.96 (m, 1H), 7.72 (dd, J = 7.7, 0.7 Hz, 1H), 7.61 – 7.50 (m, 2H), 7.29 (d, J = 8.3 Hz, 1H), 7.00 (ddd, J = 4.9, 1.9, 0.7 Hz, 1H), 6.94 (s, 1H), 2.92 – 2.84 (m, 2H), 2.49 – 2.36 (m, 2H), 2.32 – 2.24 (m, 1H), 2.14 – 2.06 (m, 1H), 2.04 – 1.91 (m, 3H), 1.58 (dd, J = 13.2, 8.0 Hz, 3H), 1.50 – 1.40 (m, 3H), 0.87 (s, 3H). ^{13}C NMR (101 MHz, CDCl3) δ 220.6 (s), 156.9 (s), 150.6 (s), 140.0 (s), 139.5 (s), 139.2 (s), 138.2 (s), 136.8 (s), 130.2 (s), 128.8 (s), 127.7 (s), 127.3 (s), 126.5 (s), 121.1 (s), 118.5 (s), 50.4 (s), 47.9 (s), 44.2 (s), 38.0 (s), 35.8 (s), 31.5 (s), 29.4 (s), 26.3 (s), 25.7 (s), 21.5 (s), 13.8 (s). (+ve)APCI-MS m/z = 398.5 m/z calcd. for$C_{26}H_{26}N_2O_2$[M]; found : 399.7 [M+H]. Anal.Calcd. For $C_{26}H_{26}N_2O_2$: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.09; H, 6.28; N, 7.06.

(13S)-3-(Benzo[d]oxazol-2-yloxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-17-ol (5l):

General Procedure (GP) was followed by using 2-chlorobenzo[d]oxazole (0.116 mL,1 mmol) and estradiol (327 mg, 1.2 mmol, 1.2 eq.) provided desired (13S)-3-(benzo[d]oxazol-2-yloxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-17-ol (346 mg,

0.89 mmol, 89%) as a white solid. Mp: 108.3-110 °C,^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.68 - 0.84 (m, 3 H), 1.08 - 1.23 (m, 1 H), 1.23 - 1.39 (m, 3 H), 1.39 - 1.60 (m, 3 H), 1.60 - 1.74 (m, 1 H), 1.83 - 2.00 (m, 2 H), 2.00 - 2.14 (m, 1 H), 2.14 - 2.36 (m, 2 H), 2.51 (br. s., 1 H), 2.87 (d, *J*=4.49 Hz, 2 H), 3.68 (t, *J*=8.48 Hz, 1 H), 7.06 (d, *J*=2.48 Hz, 1 H), 7.08 - 7.17 (m, 1 H), 7.17 - 7.26 (m, 2 H), 7.30 - 7.42 (m, 2 H), 7.46 - 7.53 (m, 1 H);^{13}C NMR (75 MHz, $CDCl_3$) δ: 10.8 (s, 1 C) 22.8 (s, 1 C) 25.9 (s, 1 C) 26.7 (s, 1 C) 29.3 (s, 1 C) 30.1 (s, 1 C) 36.4 (s, 1 C) 38.1 (s, 1 C) 42.9 (s, 1 C) 43.9 (s, 1 C) 49.8 (s, 1 C) 81.2 (s, 1 C) 109.5 (s, 1 C) 116.9 (s, 1 C) 118.3 (s, 1 C) 119.8 (s, 1 C) 123.0 (s, 1 C) 124.1 (s, 1 C) 126.6 (s, 1 C) 138.5 (s, 1 C) 138.6 (s, 1 C) 140.5 (s, 1 C) 148.1 (s, 1 C) 150.2 (s, 1 C);(+ve)APCI-MS m/z = 389.2 m/z calcd. for $C_{25}H_{27}NO_3$ [M]; found : 390.3 [M+H]. Anal.Calcd. For $C_{25}H_{27}NO_3$: C, 77.09; H, 6.99; N, 3.60; Found: C, 77.02; H, 6.98; N, 3.44.

5-Chloro-2-(((R)-2,8-dimethyl-2-((4R,8R)-4,8,12-trimethyltridecyl)chroman-6-yl)oxy)benzo[d]oxazole (5m):

General Procedure (GP) was followed by using 2,5-dichlorobenzo[d]oxazole (1 mmol, 1 equiv.) and tocopherol (1.1 mmol, 1.1 eq.) yielded a desired product (470 mg, 85**%**) as a white solid.Mp:NA^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 1.9 Hz, 1H), 7.27 – 7.21 (m, 1H), 7.10 (dd, *J* = 8.5, 2.0 Hz, 1H), 6.85 (d, *J* = 15.8 Hz, 2H), 2.69 (s, 3H), 2.11 (s, 3H), 1.80 – 1.65 (m, 3H), 1.51 (s, 2H), 1.21 (s, 10H), 1.09 – 0.97 (m, 7H), 0.78 (t, *J* = 6.8 Hz, 14H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.9 (s), 150.4 (s), 146.9 (s), 144.4 (s), 142.1 (s), 129.7 (s), 127.9 (s), 123.2 (s), 121.3 (s), 119.8 (s), 118.7 (s), 117.8 (s), 110.4 (s), 76.4 (s), 40.2 (s), 39.3 (s), 37.3 (s), 32.7 (d), 30.8 (s), 27.9 (s), 24.7 (s), 24.3 (d), 22.8 – 22.3 (m), 20.9 (s), 19.6 (d), 16.2 (s). Mass *m/z* = 553.33 calcd. for $C_{34}H_{48}ClNO_3$ [M], found : 554.97 [M+H].Anal.Calcd. For $C_{34}H_{48}ClNO_3$: C, 73.68; H, 8.73; N, 2.53; Cl, 6.40; Found: C, 73.79; H, 8.56; N, 2.41.

2.2 Mono-selective etherification:

4-(4-tert-Butylphenoxy)-2-chloropyrimidine (7a):

General Procedure (GP) was followed by using 2,4 dichloropyrimidine (149 mg, 1 mmol) and 4-tertiary butyl phenol (165 mg, 1.1 mmol, 1.1 eq.) provided desired 4-(4-tert-butylphenoxy)-2-chloropyrimidine (205 mg, 0.78 mmol, 78%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.36 (s, 9 H), 6.75 (d, *J*=5.69 Hz, 1 H), 7.07 - 7.11 (m, 2 H), 7.42 - 7.48 (m, 2 H), 8.42 (d, *J*=5.69 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 31.3 (s, 1 C), 31.5 (s, 1 C), 34.5 (s, 1 C), 106.3 (s, 1 C), 120.4 (s, 1 C), 120.7 (s, 1 C), 126.2 (s, 1 C), 126.3 (s, 1 C), 126.8 (s, 1 C), 149.1 (s, 1 C), 149.4 (s, 1 C), 160.1 (s, 1 C), 170.6 (s, 1 C); (+ve)APCI-MS *m/z* =262.73; m/z calcd. for $C_{14}H_{15}ClN_2O$ [M]; found : 263.52 [M+H]. The compound exhibited identical ^{1}H and ^{13}C NMR data to previous reports.[33]

2-chloro-4-(4-methoxyphenoxy)pyrimidine(7b):

General Procedure (GP) was followed by using 2,4 dichloropyrimidine (149 mg,1 mmol) and 4-Methoxyphenol (0.092 mL, 1.1 mmol, 1.1 eq.) provided desired 2-chloro-4-(pyrrolidin-1-yl)pyrimidine (159, 0.87 mmol, 83%) as a colorless needles. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.82 (s, 3 H), 6.74 (d, *J*=5.78 Hz, 1 H), 6.90 - 6.99 (m, 2 H), 7.03 - 7.13 (m, 2 H), 8.40 (d, *J*=5.69 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 55.5 (s, 1 C), 106.2 (s, 1 C), 114.8 (s, 1 C), 122.0 (s, 1 C), 145.1 (s, 1 C), 157.5 (s, 1 C), 160.1 (s, 1 C), 160.6 (s, 1 C), 170.7 (s, 1 C); (+ve)APCI-MS *m/z* = 236,04 m/z calcd. for $C_{11}H_9ClN_2O_2$ [M]; found : 237.1[M+H]. The compound exhibited identical ^{1}H and ^{13}C NMR data to previous reports.[12]

8-(2-Chloropyrimidin-4-yloxy)quinolone (7c):

General Procedure (GP) was followed by using 2,4 dichloropyrimidine (149 mg,1 mmol) and quinolin-8-ol (159.6 mg, 1.1 mmol, 1.1 eq.) provided desired 8-(2-chloropyrimidin-4-yloxy)quinoline (164 mg, 0.64 mmol, 64%) as a bright yellow cubic crystals. . Mp: 176.5-177.7 ^{o}C,^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.97 (d, *J*=5.69 Hz, 1 H), 7.44 (dd, *J*=8.34, 4.22 Hz, 1 H), 7.52 - 7.63 (m, 2 H), 7.79 (dd, *J*=7.79, 1.83 Hz, 1 H), 8.21 (dd, *J*=8.34, 1.65 Hz, 1 H), 8.45 (d, *J*=5.69 Hz, 1 H), 8.82 (dd, *J*=4.22, 1.65 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 106.8 (s, 1 C), 121.3 (s, 1 C), 121.8 (s, 1 C), 126.2 (s, 1 C), 126.3 (s, 1 C), 129.8 (s, 1 C), 136.1 (s, 1 C), 140.9 (s, 1 C), 148.0 (s, 1 C), 150.4 (s, 1 C), 159.9 (s, 1 C), 160.3 (s, 1 C), 171.0 (s, 1 C); (+ve)APCI-MS *m/z* = 257.68, m/z calcd. for $C_{13}H_8ClN_3O$ [M]; found : 258.72[M+H]; Anal. Calcd. For $C_{13}H_8ClN_3O$: C, 60.60; H, 3.13; N, 16.31; Found: C, 60.82; H, 3.18; N, 16.43.

(13S)-2-(2-Chloropyrimidin-4-yloxy)-13-methyl-7,8,9,11,12,13,15,16-octahydro-6H-cyclopenta[a]phenanthren-17(14H)-one (7d):

General Procedure (GP) was followed by using 2,4 dichloropyrimidine (149 mg,1 mmol) and estrone (298 mg, 1.1 mmol, 1.1 eq.) provided desired (13S)-2-(2-chloropyrimidin-4-yloxy)-13-methyl-7,8,9,11,12,13,15,16-octahydro-6H-cyclopenta[a]phenanthren-17(14H)-one (368.8 mg, 0.93 mmol, 93%) as a white sharp needles. Mp: 153-155^{o}C,^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.94 (s, 3 H), 1.41 - 1.74 (m, 6 H), 1.95 - 2.25 (m, 4 H), 2.27 - 2.37 (m, 1 H), 2.37 - 2.61 (m, 2 H), 2.94 (dd, *J*=8.48, 3.90 Hz, 2 H), 6.76 (d, *J*=5.78 Hz, 1 H), 6.85 - 6.98 (m, 2 H), 7.35 (d, *J*=8.53 Hz, 1 H), 8.41 (d, *J*=5.69 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.8 (s, 1 C), 21.5 (s, 1 C),

25.7 (s, 1 C), 26.2 (s, 1 C), 29.4 (s, 1 C), 31.5 (s, 1 C), 35.8 (s, 1 C), 37.9 (s, 1 C), 44.1 (s, 1 C), 47.9 (s, 1 C), 50.4 (s, 1 C), 106.4 (s, 1 C), 118.3 (s, 1 C), 121.0 (s, 1 C), 126.6 (s, 1 C), 137.8 (s, 1 C), 138.6 (s, 1 C), 149.7 (s, 1 C), 160.1 (s, 1 C), 160.6 (s, 1 C), 170.6 (s, 1 C); (+ve)APCI-MS *m/z* = 382.14; m/z calcd. for $C_{22}H_{23}ClN_2O_2$ [M]; found : 383.23[M+H]; Anal. Calcd. For $C_{22}H_{23}ClN_2O_2$: C, 69.42; H, 6.59; N, 7.04; Found: C, 69.22; H, 6.48; N, 7.14.

2-Chloro-4-(2-isopropyl-4-methylphenoxy)pyrimidine (7e):

General Procedure (GP) was followed by using 2,4 dichloropyrimidine (149 mg,1 mmol) and Thymol (151 mg, 1.0 mmol, 1.0 eq.) provided desired 2-chloro-4-(2-isopropyl-4-methylphenoxy)pyrimidine (165.4 mg, 0.63 mmol, 63%) as a green oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.16 (d, J=6.88 Hz, 6 H), 2.32 (s, 3 H), 2.84 - 3.03 (m, 1 H), 6.68 (d, J=5.69 Hz, 1 H), 7.07 (dd, J=7.20, 5.36 Hz, 2 H), 7.26 (d, J=7.89 Hz, 1 H), 8.38 (d, J=5.69 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 20.7 (s, 1 C), 22.9 (s, 1 C), 23.0 (s, 1 C), 26.8 (s, 1 C), 105.7 (s, 1 C), 115.9 (s, 1 C), 127.0 (s, 1 C), 127.6 (s, 1 C), 137.2 (s, 1 C), 137.3 (s, 1 C), 148.9 (s, 1 C), 152.8 (s, 1 C), 160.1 (s, 1 C), 170.9 (s, 1 C); (+ve)APCI-MS *m/z* =262.73; m/z calcd. for $C_{14}H_{15}ClN_2O$ [M]; found : 263.52[M+H]..

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2,4-bis(4-methoxyphenoxy)pyrimidine (8a):

General Procedure (GP) was followed by using 2,4 dichloropyrimidine (149 mg,1 mmol) and 4-methoxy phenol (273mg, 2.2 mmol, 2.2 eq.) provided desired 2,4-bis(4-methoxyphenoxy)pyrimidine (285 mg, 0.88 mmol, 88%) as a white solid. Mp: 141.2-143.7^{o}C,^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.82 (s, 3 H), 3.81 (s, 3 H), 6.50 (d, *J*=5.69 Hz, 1 H), 6.85 - 6.97 (m, 4 H), 7.01 - 7.13 (m, 4 H), 8.30 (d, *J*=5.69 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$)

δ: 55.5 (s, 1 C), 55.5 (s, 1 C), 102.2 (s, 1 C), 114.4 (s, 1 C), 114.7 (s, 1 C), 122.3 (s, 1 C), 122.5 (s, 1 C), 145.5 (s, 1 C), 146.2 (s, 1 C), 156.8 (s, 1 C), 157.2 (s, 1 C), 160.1 (s, 1 C), 165.5 (s, 1 C), 171.8 (s, 1 C); (+ve)APCI-MS *m/z* =324.33; m/z calcd. for $C_{18}H_{16}N_2O_4$ [M]; found : 325.47[M+H]; Anal. Calcd. For $C_{18}H_{16}N_2O_4$: C, 66.66; H, 4.97; N, 8.64; Found: C, 66.89; H, 5.12; N, 8.41.

2,4 (Di-estrogen)) pyrimidine(8b):

General Procedure (GP) was followed by using 2,4 dichloropyrimidine (149 mg,1 mmol) and estrone (596 mg, 2.2 mmol, 2.2 eq.) provided desired (13S)-13-methyl-2-(2-((13R)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-2-yloxy)pyrimidin-4-yloxy)-7,8,9,11,12,13,15,16-octahydro-6H-cyclopenta[a]phenanthren-17(14H)-one (357 mg, 0.58 mmol, 58%) as a white amorphous solid. . Mp: 203-205°C,^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.86 - 0.93 (m, 6 H), 1.46 - 1.66 (m, 12 H), 1.94 - 2.15 (m, 8 H), 2.29 (br. s., 1 H), 2.33 - 2.56 (m, 5 H), 2.85 - 2.97 (m, 4 H), 6.52 (d, *J*=5.69 Hz, 1 H), 6.87 - 6.97 (m, 4 H), 7.21 - 7.40 (m, 2 H), 8.29 (d, *J*=5.59 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.2 (s, 1 C), 13.5 (s, 1 C), 20.9 (s, 1 C), 25.0 (s, 1 C), 25.1 (s, 1 C), 25.3 (s, 1 C), 25.7 (s, 1 C), 25.7 (s, 1 C), 25.9 (s, 1 C), 28.7 (s, 1 C), 28.8 (s, 1 C), 28.8 (s, 1 C), 29.0 (s, 1 C), 30.2 (s, 1 C), 30.9 (s, 1 C), 35.2 (s, 1 C), 37.3 (s, 1 C), 37.3 (s, 1 C), 37.7 (s, 1 C), 43.3 (s, 1 C), 43.5 (s, 1 C), 47.3 (s, 1 C), 47.3 (s, 1 C), 49.7 (s, 1 C), 101.9 (s, 1 C), 112.3 (s, 1 C), 114.7 (s, 1 C), 118.0 (s, 1 C), 118.2 (s, 1 C), 120.7 (s, 1 C), 120.9 (s, 1 C), 125.6 (s, 1 C), 125.7 (s, 1 C), 126.0 (s, 1 C), 130.5 (s, 1 C), 136.1 (s, 1 C), 136.7 (s, 1 C), 137.0 (s, 1 C), 137.3 (s, 1 C), 137.7 (s, 1 C), 149.4 (s, 1 C), 149.9 (s, 1 C), 153.8 (s, 1 C), 159.4 (s, 1 C), 164.7 (s, 1 C), 171.0 (s, 1 C), 206.5 (s, 1 C); (+ve)APCI-MS *m/z* =616.79; m/z calcd. for $C_{40}H_{44}N_2O_4$ [M]; found : 617.82[M+H]; Anal. Calcd. For $C_{40}H_{44}N_2O_4$: C, 77.89; H, 7.19; N, 4.54; Found: C, 77.92; H, 7.21; N, 4.34.

2.3 Synthesis of 6-alkoxy functionalized purine

2-(6-(8-Bromonaphthalen-1-yloxy)-9H-purin-9-yl)-5-(hydroxymethyl)-tetrahydrofuran-3,4-diol (10a):

General Procedure (GP) was followed by using 6-chloro purine riboside(287 mg,1 mmol) and 1-bromo napthol (268 mg, 1.2 mmol, 1.2 eq.) provided desired 2-(6-(8-bromonaphthalen-1-yloxy)-9H-purin-9-yl)-5-(hydroxymethyl)-tetrahydrofuran-3,4-diol (302 mg, 0.64 mmol, 64%) as a colorless solid. . Mp: >261ºC (decomposes),^{1}H NMR (300 MHz, DMSO-d_6) δ: 3.55 - 3.67 (m, 1 H), 3.67 - 3.79 (m, 1 H), 4.02 (q, *J*=3.67 Hz, 1 H), 4.18 - 4.26 (m, 1 H), 4.68 (q, *J*=5.65 Hz, 1 H), 5.15 (t, *J*=5.50 Hz, 1 H), 5.28 (d, *J*=4.95 Hz, 1 H), 5.58 (d, *J*=5.96 Hz, 1 H), 6.08 (d, *J*=5.78 Hz, 1 H), 7.58 - 7.65 (m, 1 H), 7.65 - 7.71 (m, 1 H), 7.71 - 7.79 (m, 1 H), 8.06 - 8.14 (m, 2 H), 8.20 (d, *J*=8.34 Hz, 1 H), 8.46 (s, 1 H) 8.84 (s, 1 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 61.0 (s, 1 C) 70.1 (s, 1 C) 73.5 (s, 1 C) 78.8 (s, 1 C) 85.5 (s, 1 C) 87.6 (s, 1 C) 114.0 (s, 1 C) 120.8 (s, 1 C) 122.5 (s, 1 C) 125.8 (s, 1 C) 126.4 (s, 1 C) 128.1 (s, 1 C) 128.3 (s, 1 C) 129.1 (s, 1 C) 131.7 (s, 1 C) 131.8 (s, 1 C) 143.5 (s, 1 C) 147.5 (s, 1 C) 151.1 (s, 1 C) 152.8 (s, 1 C) 158.4 (s, 1 C); (+ve)APCI-MS m/z = 472.04 m/z calcd. for $C_{20}H_{17}BrN_4O_5$ [M]; found : 473.12 [M+H]. Anal.Calcd. For $C_{20}H_{17}BrN_4O_5$: C, 50.76; H, 3.62; N, 11.84; Found: C, 51.02; H, 3.88; N, 11.94.

2-(Hydroxymethyl)-5-(6-(4-methoxyphenoxy)-9H-purin-9-yl)-tetrahydrofuran-3,4-diol (10b):

General Procedure (GP) was followed by using 6-chloro purine riboside(287 mg,1 mmol) and 4-methoxy phenol (149 mg, 1.2 mmol, 1.2 eq.) provided desired 2-(hydroxymethyl)-5-(6-(4-methoxyphenoxy)-9H-purin-9-yl)-tetrahydrofuran-3,4-diol (231.9 mg, 0.62 mmol, 62%) as a

colorless solid. Mp: >253°C (decomposes),[1]H NMR (300 MHz, $CDCl_3$) δ: 3.66 - 3.81 (m, 5 H), 3.86 - 3.97 (m, 1 H), 4.28 (s, 1 H), 4.40 (br. s., 1 H), 4.50 (d, *J*=4.95 Hz, 1 H), 5.10 (br. s., 1 H), 5.87 - 6.13 (m, 3 H), 6.89 (m, *J*=9.08 Hz, 2 H), 7.12 (m, *J*=8.99 Hz, 2 H), 8.16 (s, 1 H), 8.32 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 55.4 (s, 1 C), 62.8 (s, 1 C), 72.2 (s, 1 C), 73.6 (s, 1 C), 87.5 (s, 1 C), 91.3 (s, 1 C), 114.6 (s, 1 C), 115.8 (s, 1 C), 121.8 (s, 1 C), 122.2 (s, 1 C), 143.4 (s, 1 C), 144.9 (s, 1 C), 150.8 (s, 1 C), 151.7 (s, 1 C), 157.2 (s, 1 C), 160.1 (s, 1 C); The compound exhibited identical ^{1}H and ^{13}C NMR data to previous reported.[36]

9-ethyl-6-(2-isopropyl-5-methylphenoxy)-9H-purine (10c):

General Procedure (GP) was followed by using 6-chloro-9-ethyl-9H-purine (164 mg, 1 mmol) and Thymol (180 mg, 1.2 mmol, 1.2 eq.) provided desired 9-ethyl-6-(2-isopropyl-4-methylphenoxy)-9H-purine (213 mg, 0.719 mmol, 72%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.24 (s, 6 H), 1.66 (t, J=7.24 Hz, 3 H), 2.38 (s, 3 H), 2.98 - 3.11 (m, 1 H), 4.55 (q, J=7.24 Hz, 2 H), 6.95 - 7.01 (m, 1 H), 7.12 - 7.20 (m, 1 H), 7.35 (d, J=7.98 Hz, 1 H), 8.24 (s, 1 H), 8.64 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 17.2 (s, 1 C), 21.1 (s, 1 C), 23.0 (s, 1 C), 23.3 (s, 1 C), 27.3 (s, 1 C), 43.3 (s, 1 C), 120.8 (s, 1 C), 122.8 (s, 1 C), 126.1 (s, 1 C), 127.1 (s, 1 C), 132.1 (s, 1 C), 137.3 (s, 1 C), 137.6 (s, 1 C), 149.0 (s, 1 C), 152.6 (s, 1 C), 154.0 (s, 1 C), 162.7 (s, 1 C); (+ve)APCI-MS m/z = 296.37 calcd. for $C_{17}H_{20}N_4O$ [M], found : 297.42 [M+H].

2.4 Tandem catalytic processes using the Pd/TPABS system

2-(4-(Phenylethynyl)phenoxy)benzo[d]thiazole (11a):

General Procedure (GPT) was followed by using 2-Chlorobenzthiazole (84.82mg, 0.065ml, 0.50 mmol) and 4-Bromo phenol (104.3mg, 0.60 mmol, 1.2 eq.) and Phenyl acetylene (76.5mg, 0.09 ml, 0.75 mmol, 1.5 eq) yielded the desired product(134 mg, 0.41 mmol, 82%) as a yellow

powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 7.6, 0.5 Hz, 1H), 7.68 (dd, *J* = 7.7, 0.4 Hz, 1H), 7.60 (d, *J* = 8.6 Hz, 2H), 7.53 (dd, *J* = 6.0, 2.6 Hz, 2H), 7.42 – 7.31 (m, 6H), 7.29 (d, *J* = 7.0 Hz, 1H).^{13}C NMR (400 MHz, $CDCl_3$) δ 156.9(s), 154.2(s), 133.2(s), 131.6(s), 131.5(s), 128.3(s), 128.3(s), 126.3(s), 124.2(s), 121.8(s), 121.2(s), 120.5(s), 89.7(s), 88.7(s).Anal. Calcd. For $C_{21}H_{13}NOS$: C, 77.04; H, 4.00; N, 4.28; O: 4.89; S, 9.79; Found: C, 76.75; H, 3.97; N, 3.97; S, 9.94.

2-(4-((4-Methoxyphenyl)ethynyl)phenoxy)benzo[d]thiazole (11b):

General Procedure (GPT) was followed by using 2-Chlorobenzthiazole (84.82mg, 0.065ml, 0.50 mmol) and 4-Bromo phenol (104.3mg, 0.60 mmol, 1.2 eq.) and 4-Methoxyphenyl acetylene (132.2mg, 0.1 ml, 0.75 mmol, 1.5 eq) yielded the desired product(149 mg, 0.42 mmol, 84%) as a white powder.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 – 7.72 (m, 1H), 7.68 (d, *J* = 8.7 Hz, 1H), 7.60 – 7.53 (m, 2H), 7.47 (d, *J* = 8.9 Hz, 2H), 7.41 – 7.31 (m, 3H), 7.29 (d, *J* = 6.7 Hz, 1H), 6.88 (d, *J* = 8.5 Hz, 2H), 3.82 (s, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.0(s), 133.0(s), 126.2(s), 124.1(s), 121.8(s), 121.2(s), 120.5(s), 114.0(s), 114.01(s), 89.8(s), 55.2(s).; Anal. Calcd. For $C_{22}H_{15}NO_2S$: C, 73.93; H, 4.23; N, 3.92; S, 8.97; Found: C, 73.67; H, 4.19; N, 3.70; S, 8.85.

2-(4-(p-Tolylethynyl)phenoxy)benzo[d]thiazole (11c):

General Procedure (GPT) was followed by using 2-Chlorobenzthiazole (84.82mg, 0.065ml, 0.50 mmol) and 4-Bromo phenol (104.3mg, 0.60 mmol, 1.2 eq.) and 4-Tolylphenyl acetylene (87 mg, 0.09 ml, 0.75 mmol, 1.5 eq) yielded the desired product(141 mg, 0.41 mmol, 83%) as a white powder.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 7.1 Hz, 1H), 7.68 (d, *J* = 7.6 Hz, 1H), 7.58 (dd, *J* = 6.9, 1.8 Hz, 2H), 7.41 (t, *J* = 7.0 Hz, 3H), 7.35 (d, *J* = 8.8 Hz, 2H), 7.28 (d, *J* = 8.6 Hz, 1H), 7.15 (d, *J* = 7.5 Hz, 2H), 2.36 (s, 3H).; ^{13}C NMR (400 MHz, $CDCl_3$) δ 154.2(s), 152.9(s), 148.9(s), 138.5(s), 133.1(s), 131.4(s), 129.1(s), 126.2(s), 124.2(s), 121.8(s), 121.5(s), 121.2(s),

120.5(s), 89.9(s), 21.4(s).; Anal. Calcd. For $C_{22}H_{15}NOS$: C, 77.39; H, 4.43; N, 4.10; S, 9.39; Found: C, 77.09; H, 4.37; N, 4.04; S, 9.04.

6-(4-(Benzo[d]thiazol-2-yloxy)phenyl)-3-(4-hydroxy-5(hydroxymethyl)tetrahydrofuran-2-yl)furo[2,3-d]pyrimidin-2(3H)-one (13):

A 25 mL of oven dried schlenk tube was charged with 1 mol % of $Pd(OAc)_2$, 2 mol % of PTABS (ligand) and 2-Chlorobenzthiazole (84.82mg, 0.065ml, 0.50 mmol) derivative under N_2 atmosphere and the resultant mixture dissolved in 1.5 mL of dry DMF. The reaction mixture stirred for 5 minutes and was added 2.5 equiv of Potassium phosphate, 4-Bromo phenol (104.3mg, 0.60 mmol, 1.2 eq.) and 1.5 ml dry DMF. The resultant mixture was stirred at 60 ^oC for 2 h. After consumption of starting material (monitored by TLC-MS), in the reaction mixture was added 1 mol % of $Pd(OAc)_2$, 2 mol% of XPhos, 5-Ethynyl deoxy uridine - EDU (113 mg, , 0.49 mmol, 0.98 eq), 0.5 mol % of Copper iodide and lastly 2.1 equiv of Triethyl amine and was stirred at 80 ^oC for 24 h. This was followed by addition of 3.7mL of Methanol, 1.7 mL of Triethylammine and 6.0 mol% of Copper Iodide and continued to stir for another 24 h at 80 ^oC. Then the solvent was removed in vacuum and the resultant residue obtained was purified by column chromatography in Dichloromethane: Methanol (3.0% to 4.0%) solvent system to afford the desiredproduct(174 mg, 0.36 mmol, **73%**) as a white powder.^{1}H NMR (400 MHz, DMSO-d_6) δ 8.87 (s, 1H), 7.99 – 7.85 (m, 3H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.45 – 7.36 (m, 1H), 7.32 (d, *J* = 10.1 Hz, 2H), 6.16 (t, *J* = 6.0 Hz, 1H), 5.29 (d, *J* = 3.1 Hz, 1H), 5.17 (t, *J* = 5.0 Hz, 1H), 4.23 (d, *J* = 4.2 Hz, 1H), 3.92 (d, *J* = 2.6 Hz, 1H), 3.65 (dd, *J* = 30.1, 12.8 Hz, 2H), 2.38 (dd, *J* = 5.9, 4.4 Hz, 1H), 2.09 (dt, *J* = 8.5, 4.7 Hz, 1H).^{13}C NMR (400 MHz, DMSO-d_6) δ 171.6(s), 171.4(s), 155.0(s), 154.1(s), 153.1(s), 148.8(s), 138.9(s), 132.3(s), 127.0(s), 126.8(s), 124.8(s), 122.7(s), 122.0(s), 121.7(s), 107.1(s), 100.5(s), 88.6(s), 88.1(s), 69.9(s),

61.0(s), 41.7(s); Anal. Calcd. For $C_{24}H_{19}N_3O_6S$: C, 60.37; H, 4.01; N, 8.80; S, 6.72; Found: C, 60.45; H, 4.02; N, 8.93; S, 6.50.

2.5 Palladium-catalyzed etherification for the synthesis of XK469 (anti-tumor agent)

Methyl (S)-2-(4-((7-chloroquinoxalin-2-yl)oxy)phenoxy)propanoate (15):

General Procedure (GP) was followed by using 2,7-dichloroquinoxaline (1 mmol, 1 equiv.) and methyl (R)-2-(4-methoxyphenoxy)propanoate (1.1 mmol, 1.1 eq.) yielded a desired product (232 mg, 65**%**) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (s, 1H), 7.95 (d, *J* = 8.8 Hz, 1H), 7.74 (s, 1H), 7.56 – 7.49 (m, 1H), 7.20 – 7.11 (m, 2H), 6.97 – 6.90 (m, 2H), 4.77 (dd, *J* = 13.1, 6.4 Hz, 1H), 3.78 (s, 3H), 1.64 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.5 (s), 157.6 (s), 155.0 (s), 146.5 (s), 140.5 (s), 139.2 (s), 138.0 (s), 136.1 (s), 129.9 (s), 128.1 (s), 126.7 (s), 122.4 (s), 116.0 (s), 73.1 (s), 52.3 (s), 18.6 (s); Anal. Calcd. For $C_{18}H_{15}ClN_2O_4$: C, 60.26; H, 4.21; N, 7.81. Found: C, 60.21; H, 4.19; N, 7.72.

Methyl (S)-2-(4-(benzo[d]thiazol-2-yloxy)phenoxy)propanoate (16):

General Procedure (GP) was followed by using 2-chlorobenzothiazole (1 mmol, 1 equiv.) and methyl (R)-2-(4-methoxyphenoxy)propanoate (1.1 mmol, 1.1 eq.) yielded a desired product (293 mg, 89**%**) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 7.9 Hz, 1H), 7.64 (d, *J* = 7.9 Hz, 1H), 7.40 – 7.34 (m, 1H), 7.29 – 7.23 (m, 3H), 6.95 – 6.89 (m, 2H), 4.75 (dd, *J* = 13.5, 6.7 Hz, 1H), 3.77 (s, 3H), 1.62 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.4 (d), 155.5 (s), 149.0 (d), 132.1 (s), 126.2 (s), 123.9 (s), 121.8 (s), 121.6 (s), 121.2 (s), 116.2 (s), 73.1 (s), 52.3 (s), 18.5 (s). Anal.Calcd. For $C_{17}H_{15}NO_4S$: C, 61.99; H, 4.59; N, 4.25; S, 9.73. Found: C, 62.01; H, 4.39; N, 4.21; S, 9.71.

Supporting information: ^{1}H, ^{13}C and ^{19}F NMR spectras as well as x-ray crystallographical data for all the characterized compounds have been provided in the supporting information file.

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