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Synthesis of substituted 2-heteroarylbenzazol-5-ol derivatives as potential ligands for estrogen receptors

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ABSTRACT

Exposure to estrogen is associated with increased risk of breast and other types of human cancer. One therapeutic goal would be the creation of new molecules that would retain hormonal potency while incorporating features to retard or prevent quinone toxicity. Hence, new structures closely related to ERB-041, a known ERβ selective agonist, were synthesized whereas the phenol ring is substituted with non-quinone forming rings such as pyrazole, 2-pyrimidine-2(1*H*)-one or pyridine-2(1*H*)-one. 2-Methyl-5-methoxy-1,3-benzoxazoles (or 1,3-benzothiazole) are key intermediates for the production of the pyrazole and pyrimidine-2(1*H*)-one analogs. The required 1,3-benzoxazoles were synthesized starting from reduction of 2-nitro-4-methoxyphenols, followed by condensation with trimethyl orthoacetate. Then, the diiminium perchlorate intermediates were prepared from the latter compounds by Vilsmeier–Haack reaction. The reaction of the resulting intermediates with hydrazine hydrate and guanidium chloride afforded the title pyrazole and pyrimidine-2(1*H*)-ones, respectively.

The pyridine analogs were synthesized starting from the reaction of 2-amino-4-methoxyphenols with 6-bromopyridine-3-carboxaldehyde followed by oxidation with DDQ to afford bromopyridines. These compounds were next treated with benzyl alcohol in the presence of potassium *tert*-butoxide to afford 2-benzyloxypyridine, which in subsequent dealkylation with boron tribromide produced the title pyridine-2-(1*H*)-ones.

1. Introduction

The safety of hormone therapies, particularly contraceptives and hormone replacement therapy (HRT), has been the subject of much controversy for many years now.[1] Epidemiological studies indicate increased risk of breast and uterine cancers associated with HRT usage, and contemporary medical practice suggests that women should minimize their usage of hormone supplements.[2] 'Women's Health Initiative' (WHI) was stopped in 2002 due to an increase in the reported cases of venous thromboembolism, myocardial infarction, stroke and breast cancer.[1] In recent years however, many investigations have focused primarily on the origin of cancer and the understanding of how sex steroid hormones are so closely related to breast cancer development.

Naturally occurring estrogens, estradiol and estrone, have the classic steroid structure containing the A, B, C, and D-rings (Fig. 1). The B, C, and D rings are saturated, but the A-ring is an aromatic phenol. Phenols are easily metabolized in the liver and elsewhere by the enzyme cytochrome P450 hydroxylase.[2,3] This leads to hydroxyl substitution at the positions adjacent to the first hydroxyl group (situated at position three in the A-ring), forming 2-OH estradiol and 4-OH estradiol. These metabolites, termed the 'catechol estrogens',[4]

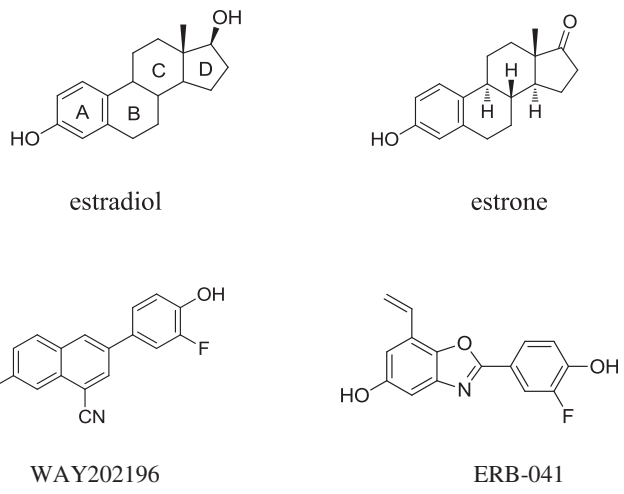

Fig. 1. Representative examples of estrogen receptor ligands.

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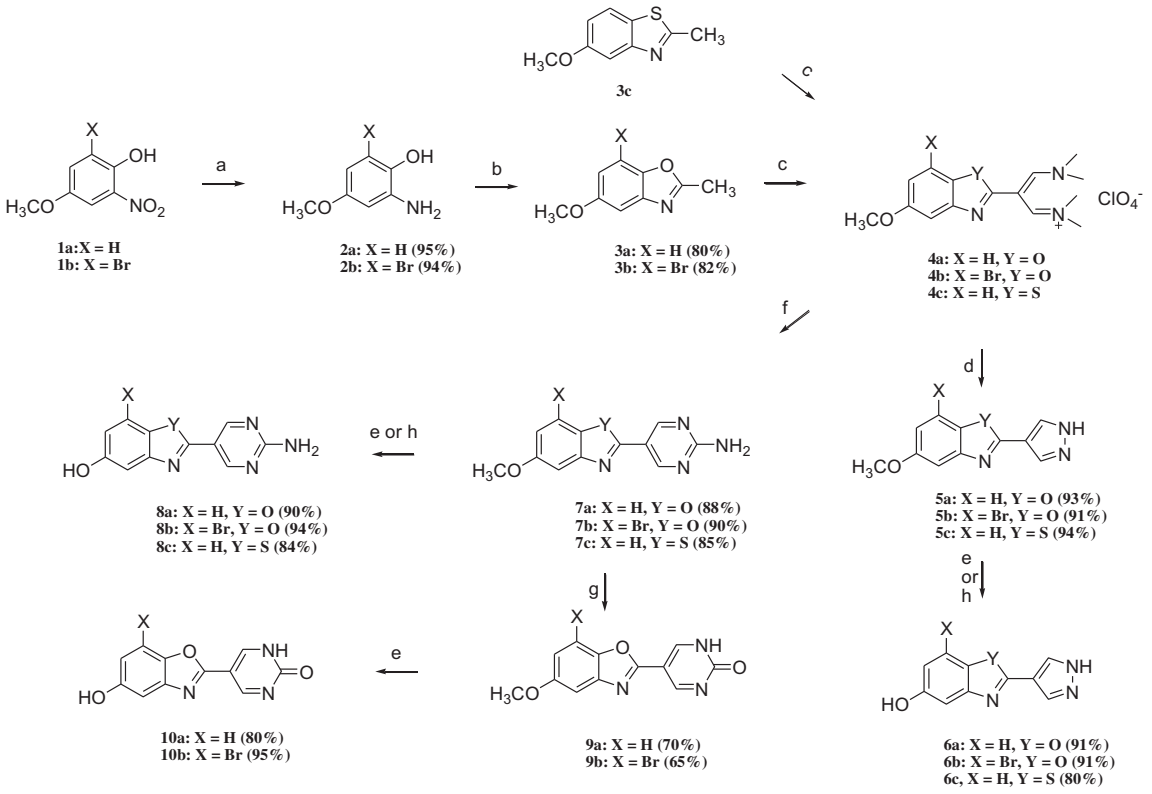
can be further metabolized by oxidizing substances present in the cell, e.g., peroxidase/P450 or tyrosinase/O_2,[5] or even in the presence of oxygen, to give the 2,3-quinone and 3,4-quinone.[6–15] Catechol estrogen quinones can react with DNA to form depurinating adducts. These adducts are released from DNA to generate apurinic sites. Error-prone base excision repair of this damage may lead to the mutations that can initiate breast, prostate and other types of cancer.

There are two subtypes of estrogen receptor, ERα and ERβ, which are members of nuclear receptor. It is hypothesized that selectivity for ERβ can be a desirable therapeutic feature.[16–18] Several groups have investigated a variety of nonsteroidal scaffols mimicking either the dihydroxy arrangement of the nonselective estradiol or the moderately ERβ-selective phytoestrogen as potential ERβ ligands. Diarylpropylnitriles (DPN),[19,20] biphenyl compounds,[21,22] and benzothiazoles/benzoxazoles[23,24] exhibited as much as ~70-fold selectivity for ERβ. ERB-041 and WAY 202196 (phenolic) and the 17-position (17β-OH) in estradiol.[3] In estradiol the O–O interatomic distance is 11.0 Å, and in general it is thought that for optimum hydrogen bonding this distance should be 11.0±05 Å.[27] Aiming to design new non-quinone forming estrogen analogs, it is thought that fluorination at both *ortho*-positions on the A-ring would suppress quinone formation. Hence, to find new ERβ non-quinone forming ligands, the substitution of phenol ring in a selective agonist with hetrocycles (or substituted heterocycles) providing two hydrogen bonding donor and acceptor in neighboring positions interacting with Glu and Arg on the active site of the receptor has been investigated. Herein, the synthesis of ERB-041 analogs, whereas the phenol ring is substituted with pyrazole, 2-hydroxypyrimidine or 2-hydroxypyridine with different substitutions on 7-position, is reported.

The synthetic reactions used for the synthesis of pyrazole, pyrimidine and pyridine-substituted 1,3-benzoxazol-5-ols or 1,3-benzothiazol-5-ols are outlined in Schemes 1–3.



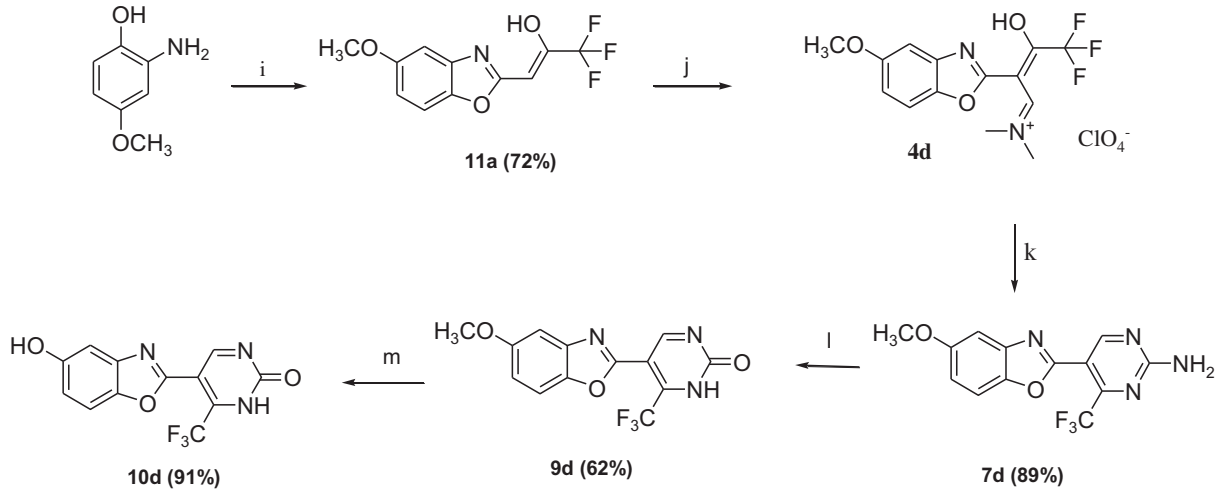
Scheme 1. Reagents and conditions: (a) Sn, HCl, EtOH, reflux, overnight; (b) $CH_3C(OCH_3)_3$, reflux, 12 h; (c) $POCl_3$, DMF, 0 °C to rt, overnight; (d) $NH_2NH_2{\cdot}H_2O$, H_2O, reflux, 5 min; (e) BBr_3, CH_2Cl_2, −78 °C to rt, 24 h; (f) $(NH_2)_2C{=}N{\cdot}HCl$, $(CH_3)_3COK$, $(CH_3)_3COH$, 60 °C, overnight; (g) $NaNO_2$, HCl, H_2O, AcOH, 0–70 °C, 3 h; (h) $AlCl_3$, dichloroethane, reflux, 3 h.

are two known examples of ERβ selective agonists (Fig. 1).[25] Considering the above approach and as a continuation of our ongoing study,[26] we synthesized new molecules resembling ERB-041 that would retain hormonal potency while conferring some features to retard or prevent quinine toxicity. The focus here is on synthetic structures closely related to ERB-041 wherein the phenol ring is substituted with non-quinone forming rings such as pyrazole, 2-hydroxypyrimidine or 2-hydroxypyridine. Further studies are required to investigate a suitable substitution for 5-hydroxybenzoxazole moiety.

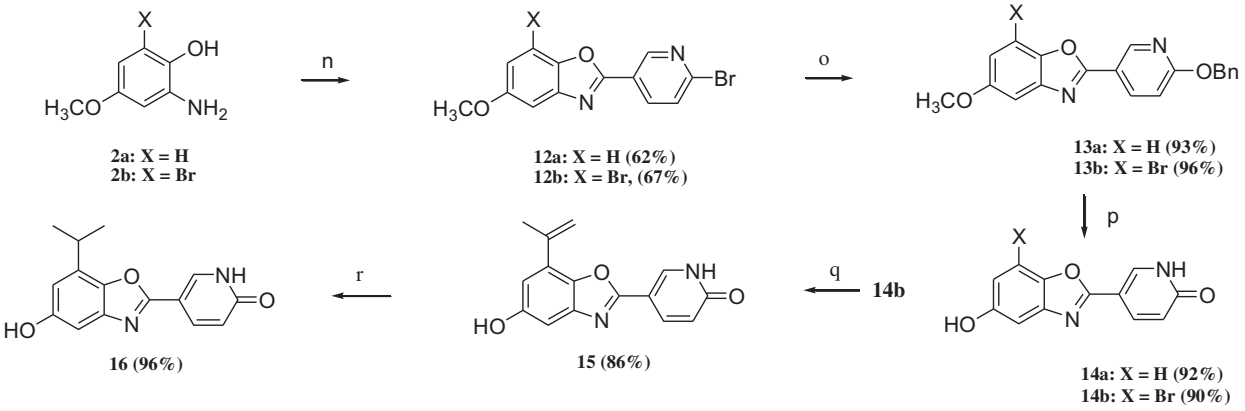
2. Results and discussion

The basic requirements for an estrogen receptor-active pharmacophore are two H-bonding anchors located near the 3-position

In Scheme 1, two synthetic routes were used to produce pyrazole and pyrimidine analogs using a common intermediate (**4a**–**c**). The 2-(1*H*-pyrazol-3-yl)-1,3-benzoxazol-5-ols (**6a**,**b**) were synthesized starting from 2-nitro-4-methoxy phenols (**1a**,**b**). The reduction of **1a**,**b** with tin in acidic media[28] followed by condensation with trimethyl orthoacetate[29] produced 2-methyl-5-methoxy-1,3-benzoxazoles (**3a**,**b**). Pyrazole analogs (**5a**–**c**) were prepared via diiminium perchlorate intermediate (**4a**–**c**) starting from **3a**,**b** and commercially available **3c** by Vilsmeier–Haack reaction. The reaction of **3a**–**c** with the cold mixture of phosphorus oxychloride and DMF followed by treatment with the solution of $NaClO_4$ produced the latter intermediate.[30] The reaction of the resulting intermediate with hydrazine hydrate in aqueous media afforded **5a**–**c**.[30–35] Demethylation of **5a**–**c** with boron tribromide resulted in title compounds **6a**–**c**.[25]



Scheme 2. Reagents and conditions: (i) $CF_3C(O)=C(OCH_3)_2$, toluene, rt, 0.5 h then 95 °C, 3 h; (j) $POCl_3$, DMF, 0 °C to rt, overnight; (k) $(NH_2)_2C=N\cdot HCl$, $(CH_3)_3COK$, $(CH_3)_3COH$, 60 °C, overnight; (l) $NaNO_2$, HCl, H_2O, AcOH, 0–70 °C, 3 h; (m) BBr_3, CH_2Cl_2, −78 °C to rt, 24 h.



Scheme 3. Reagents and conditions: (n) 6-bromopyridine-3-carbaldehyde, MeOH, rt, overnight then DDQ, CH_2Cl_2, rt, 1 h; (o) BnOH, $(CH_3)_3COK$, THF, rt, overnight; (p) BBr_3, CH_2Cl_2, −78 °C to rt, 24 h; (q) $CH_2=C(CH_3)B(OH)_2$, $Pd[Ph_3P]_4$, Cs_2CO_3, DME, 110 °C, 24 h; (r) H_2, Pd/C, rt, 24 h.

The 2-aminopyrimidine (**8a**–**c**) and pyrimidin-2(1*H*)-one analogs (**10a**–**c**) were prepared according to Scheme 1 via the common intermediates (**4a**–**c**). Treatment of the intermediates (**4a**–**c**) with guanidinium chloride in the presence of potassium *tert*-butoxide furnished 2-aminipyrimidine analogs (**7a**–**c**). Demethylation of **7a**–**c** with boron tribromide produced the title 2-(2-aminopyrimidin-5-yl)-1,3-benzoxazol-5-ols (**8a**,**b**) and 1,3-benzothiazol-5-ol (**8c**). Diazotization of **7a**–**c** followed by heating in acidic media afforded the 2-pyrimidones **9a**–**c**. Demethylation of the latter with boron tribromide resulted in title 5-(5-hydroxy-1,3-benzoxazol (or 1,3-benzothiazol)-2-yl)pyrimidin-2(1*H*)-one (**10a**–**c**).

Moreover, it is reported that meta-substitution in the phenol ring can strongly increase the receptor binding affinity.[3] Therefore, the 4-CF_3 substituted pyrimidin-2(1*H*)-one (**10d**) was synthesized starting from 2-aminophenol **2a** as shown in Scheme 2. The reaction of **2a** with 1,1,1,-trifluoro-4,4-dimethoxy-but-3-en-2-one produced substituted 1,3-benzoxazole **11a**[36,37], which subsequently was reacted with cold mixture of phosphorus oxychloride and DMF, then treated with guanidium chloride to afford **7d**. Diazotization followed by demethylation with boron tribromide resulted in title compound **10d**.

The pyridin-2(1*H*)-one analogs (**14a**,**b**, **15**, **16**) were prepared according to Scheme 3. The reaction of 2-amino-4-methoxyphenols (**2a**,**b**) with 6-bromopyridine-3-carboxaldehyde followed by oxidation with DDQ afforded bromopyridines (**12a**,**b**).[38] Compounds **12a**,**b** were next treated with benzyl alcohol in the presence of potassium *tert*-butoxide to afford 2-benzyloxypyridine **13a**,**b**, which in subsequent dealkylation with boron tribromide produced the title compound **14a**,**b**. The Suzuki coupling of **14b** with isopropenylboronic acid resulted in **15**. Hydrogenation of the latter afforded the title compound **16**.

In conclusion, aiming at synthesizing non-quinone forming estrogen analogs, new structures closely related to ERB-041, a known ERβ selective agonist, were prepared, whereas, the phenol ring is substituted with heteroaryl rings, such as pyrazole, 2-hydroxypyrimidine or 2-hydroxypyridine.

3. Experimental

3.1. General

Chemicals were obtained from commercial sources. Melting points were measured on a Kofler hot stage apparatus. ^1H NMR spectra were recorded on a Bruker FT-500 MHz or Varian FT-400 MHz spectrometer in $CDCl_3$ or DMSO-d_6, and TMS was used as an internal standard. Infrared (IR) spectra were acquired on a Nicollet Magna 550-FT spectrometer. The Elemental analyses were carried out with a Perkin–Elmer model 240-C apparatus. The results of elemental analyses (C, H, N) were within ±0.4% of the calculated values.

*3.1.1. 7-Bromo-5-methoxy-2-methyl-1,3-benzoxazole (**3b**).* 2-Amino-6-bromo-4-methoxyphenol (2.2 g, 10 mmol) was added to trimethyl orthoacetate (20 mL) and the mixture was refluxed for 12 h. The

remaining volatiles were evaporated under reduced pressure. Purification by flash chromatography (CH_2Cl_2) gave **3b** (1.96 g) as a light pink solid.

Yield, 82%; mp 106–109 °C; IR (KBr) ν 1133, 1193 cm^{-1} (C–O); ^1H NMR ($CDCl_3$) δ 7.08 (d, J=2.0 Hz, 1H), 7.05 (d, J=2.0 Hz, 1H), 3.85 (s, 3H) 2.64 (s, 3H).

Anal. Calcd for $C_9H_8BrNO_2$: C, 44.66; H, 3.33; N, 5.79. Found: C, 44.73; H, 3.20; N, 5.64.

3.2. General procedure for the synthesis of 5-methoxy-2-(1*H*-pyrazol-4-yl)-1,3-benzoxazole (or 1,3-benzothiazole) (5a–c)

To dry DMF (5 mL) was added dropwise phosphorus oxychloride (2.0 mL, 21 mmol) at 5–10 °C with constant stirring. The mixture was stirred for an additional hour at room temperature. Then, it was added dropwise to a cooled solution (at 0 °C) of **3a**–**c** (6 mmol) in DMF (5 mL) and the solution was stirred overnight at room temperature. The resulting mixture was poured on crushed ice. After decomposition of the excess Vilsmeier reagent, a saturated solution of $NaClO_4$ (4.0 g) was added with stirring. The resulting nearly yellow precipitate of the diiminium perchlorate intermediate (**4a**–**c**) was filtered and washed with two 15 mL portions of water. The compound was used in the next step without further purification.

Then, the iminium perchlorate intermediate (**4a**–**c**, 1 mmol) was poured into water (30 mL) and heated until complete dissolution. Then, hydrazine hydrate (0.3 mL, 3 mmol) was added to the mixture, it was heated for 5 min, and the resulting precipitate was filtered, washed with water, and recrystallized from EtOAc/hexane to give **5a**–**c**.

*3.2.1. 5-Methoxy-2-(1H-pyrazol-4-yl)-1,3-benzoxazole (**5a**).* Yield, 93% (200 mg, light cream crystal); mp 257–260 °C; IR (KBr) ν 3175 cm^{-1} (N–H); ^1H NMR (DMSO-d_6) δ 13.53 (br s, 1H, NH), 8.54 (br s, 1H), 8.12 (br s, 1H), 7.45 (d, J=8.8 Hz, 1H), 6.99 (d, J=2.5 Hz, 1H), 6.75 (dd, J=8.8, 2.5 Hz, 1H), 3.75 (s, 3H).

Anal. Calcd for $C_{11}H_9N_3O_2$: C, 61.39; H, 4.22; N, 19.53. Found: C, 61.12; H, 4.43; N, 19.76.

*3.2.2. 7-Bromo-5-methoxy-2-(1H-pyrazol-4-yl)-1,3-benzoxazole (**5b**).* Yield, 91% (266 mg, light cream crystal); mp >300 °C; IR (KBr) ν 3150 cm^{-1} (N–H); ^1H NMR (DMSO-d_6) δ 13.54 (br s, 1H), 8.38 (br s, 2H), 7.25 (d, J=1.5 Hz, 1H), 7.16 (d, J=1.5 Hz, 1H), 3.81 (s, 3H).

Anal. Calcd for $C_{11}H_8BrN_3O_2$: C, 44.92; H, 2.74; N, 14.29. Found: C, 44.74; H, 2.96; N, 14.20.

*3.2.3. 5-Methoxy-2-(1H-pyrazol-4-yl)-1,3-benzothiazole (**5c**).* Yield, 94% (216 mg, cream crystal); mp 201–203 °C; IR (KBr) ν 3163 cm^{-1} (N–H); ^1H NMR (DMSO-d_6) δ 13.44 (br s, 1H), 8.50 (br s, 1H), 8.07 (br s, 1H), 7.91 (d, J=8.8 Hz, 1H), 7.49 (d, J=2.5 Hz, 1H), 7.00 (dd, J=8.8, 2.5 Hz, 1H), 3.97 (s, 3H).

Anal. Calcd for $C_{11}H_9N_3OS$: C, 57.13; H, 3.92; N, 18.17. Found: C, 56.98; H, 4.05; N, 18.35.

3.3. General procedures for the demethylation

*3.3.1. Method A. Demethylation of 5-methoxy-1,3-benzoxazoles (**5a**,**b**,**7a**,**b**, **9a**,**b** or **9d**).* Boron tribromide (1 M in dichloromethane, 3 equiv) was added dropwise at −78 °C to a suspension of **5a**,**b**, **7a**,**b**, **9a**,**b** or **9d** (1 mmol) in CH_2Cl_2 (5 mL). The mixture was allowed to warm to room temperature and was stirred overnight. Then it was poured into cold water (50 mL) and the resulting mixture was neutralized with $NaHCO_3$, extracted three times with EtOAc and dried over Na_2SO_4. The solvent was evaporated and the residue was purified by preparative TLC (EtOAc) to give **6a**,**b**, **8a**,**b**, **10a**,**b** or **10d**.

*3.3.2. 2-(1H-Pyrazol-4-yl)-1,3-benzoxazol-5-ol (**6a**).* Yield, 91% (167 mg, cream solid); mp 298–301 °C; IR (KBr): 3462 (O–H), 3150 cm^{-1} (N–H); ^1H NMR (DMSO-d_6) δ 13.53 (br s, 1H, NH), 9.44 (br, 1H, OH), 8.53 (br s, 1H), 8.12 (br s, 1H), 7.45 (d, J=8.5 Hz, 1H), 6.99 (d, J=2.0 Hz, 1H), 6.75 (dd, J=8.5, 2.0 Hz).

Anal. Calcd for $C_{10}H_7N_3O_2$: C, 59.70; H, 3.51; N, 20.89. Found: C, 59.76; H, 3.53; N, 20.81.

*3.3.3. 7-Bromo-2-(1H-pyrazol-4-yl)-1,3-benzoxazol-5-ol (**6b**).* Yield, 91% (293 mg, cream solid); mp 268–270 °C; IR (KBr) ν 3476 (O–H), 3158 cm^{-1} (N–H); ^1H NMR (DMSO-d_6) δ 13.58 (br s, 1H), 9.85 (br s, 1H), 8.37 (br s, 2H), 6.99 (d, J=1.5 Hz, 1H), 6.96 (d, J=1.5 Hz, 1H).

Anal. Calcd for $C_{10}H_7N_3O_2$: C, 59.70; H, 3.51; N, 20.89. Found: C, 59.58, H, 3.77, N, 21.05.

*3.3.3.1. Method B. Demethylation of 5-methoxy1,3-benzothiazoles (**5c**, **7c** or **9c**).* To a solution of **5c**, **7c** or **9c** (0.35 mmol) in 1,2-dichloroethane (20 mL) was added $AlCl_3$ (0.465 g, 3.5 mmol). The mixture was heated at reflux for 3 h. Then the solvent was evaporated under reduced pressure, and cold water was added to the residue. The resulting mixture was extracted with EtOAc. The organic phase was dried, evaporated, and purified by preparative TLC (EtOAc) to give **6c**, **8c** or **10c**.

*3.3.4. 2-(1H-Pyrazol-4-yl)-1,3-benzothiazol-5-ol (**6c**).* Yield, 80% (170 mg, light cream solid); mp 263–265 °C; IR (KBr) ν 3476 (O–H), 3121 cm^{-1} (N–H); ^1H NMR (DMSO-d_6) δ 9.62 (br s, 1H, OH), 8.47 (br s, 1H), 8.05 (br s, 1H), 7.79 (d, J=8.8 Hz, 1H), 7.27 (d, J=2.5 Hz, 1H), 6.87 (dd, J=8.8, 2.5 Hz, 1H).

Anal. Calcd for $C_{10}H_7N_3O_2$: C, 59.70; H, 3.51; N, 20.89. Found: C, 59.51; H, 3.66, N, 21.02.

3.4. Synthesis of 3,3,3-trifluoro-1-(5-methoxy-1,3-benzoxazol-2-yl)prop-1-en-2-ol (11a)

2-Amino-4-methoxyphenol (**2a**, 556 mg, 4 mmol) was added to a solution of 1,1,1-trifluoro-4,4-dimethoxybut-3-en-2-one (735 mg, 4 mmol) in toluene (30 mL). The mixture was stirred for 3 h at 90–95 °C and was then allowed to cool to room temperature. The solvent was evaporated to dryness under reduced pressure and the crude product was then purified by flash chromatography (EtOAc/hexane; 1:9) to give the desired compound (747 mg) as a white solid. Yield, 72%; mp 154–157 °C; IR (KBr): 3480 (OH), 1183, 1132 cm^{-1} (CF_3); ^1H NMR ($CDCl_3$) δ 7.38 (d, J=9.0 Hz, 1H), 7.06 (d, J=2.5 Hz, 1H), 6.91 (dd, J=9.0, 2.5 Hz, 1H), 6.02 (s, 1H), 3.86 (s, 3H).

Anal. Calcd for $C_{11}H_8F_3NO_3$: C, 50.98; H, 3.11; N, 5.40. Found: C, 50.88; H, 2.96; N, 5.32.

3.5. General procedure for the synthesis of 2-(2-aminopyrimidin-5-yl)-5-methoxy-1,3-benzoxazoles (or 1,3-benzothiazole) (7a–d)

Compounds **4a**–**d** (1 mmol) were added to a mixture of guanidinium chloride (190 mg, 2 mmol), potassium *tert*-butoxide (200 mg, 1.8 mmol), and *tert*-butanol (15 mL), and it was heated at 60 °C for 15 h. Then it was cooled to room temperature and added to cold water. The resulting precipitate was filtered and recrystallized from EtOAc/hexane to give **7a**–**d**.

*3.5.1. 2-(2-Aminopyrimidin-5-yl)-5-methoxy-1,3-benzoxazole (**7a**).* Yield, 88% (212 mg, white crystal); mp 275–276 °C; IR (KBr) ν 3368, 3320 cm^{-1} (NH_2); ^1H NMR (DMSO-d_6) δ 8.92 (s, 2H), 7.60 (d, J=8.8 Hz, 1H), 7.52 (br s, 2H), 7.27 (d, J=2.5 Hz, 1H), 6.94 (dd, J=8.8, 2.5 Hz, 1H), 3.82 (s, 3H).

Anal. Calcd for $C_{12}H_{10}N_4O_2$: C, 59.50; H, 4.16; N, 23.13. Found: C, 59.67; H, 4.03; N, 22.96.

*3.5.2. 2-(2-Aminopyrimidin-5-yl)-7-bromo-5-methoxy-1,3-benzoxazole (**7b**).* Yield, 90% (290 mg, yellowish-white crystal); mp 269–270 °C; IR (KBr) ν 3432, 3380 cm^{-1} (NH_2); ^1H NMR (DMSO-d_6) δ 8.90 (s, 2H), 7.61 (br s, 2H), 7.29 (d, J=2.0 Hz, 1H), 7.19 (d, J=2.0 Hz, 1H), 3.82 (s, 3H).

Anal. Calcd for $C_{12}H_9BrN_4O_2$: C, 44.88; H, 2.82; N, 17.45. Found: C, 45.04; H, 2.73; N, 17.31.

*3.5.3. 2-(2-Aminopyrimidin-5-yl)-5-methoxy-1,3-benzothiazole (**7c**).* Yield, 85% (220 mg, yellow crystal); mp 258–260 °C; IR (KBr) ν 3477, 3420 cm^{-1} (NH_2); ^1H NMR (DMSO-d_6) δ 8.85 (s, 2H), 7.95 (d, J=8.8 Hz, 1H), 7.53 (d, J=2.5 Hz, 1H), 7.41 (br s, 2H), 7.04 (dd, J=8.8, 2.5 Hz, 1H), 3.84 (s, 3H).

Anal. Calcd for $C_{12}H_{10}N_4O_2S$: C, 55.80; H, 3.90; N, 21.69. Found: C, 55.97; H, 3.93; N, 21.61.

*3.5.4. 2-(2-Amino-4-trifluoromethylpyrimidin-5-yl)-5-methoxy-1,3-benzoxazole (**7d**).* Yield, 89% (275 mg, brown solid); mp 243–245 °C; IR (KBr) ν 3455, 3367 (NH_2), 1190, 1124 cm^{-1} (CF_3); ^1H NMR (DMSO-d_6) δ 9.04 (s, 1H), 8.03 (2br s, 2H), 7.67 (d, J=9.0 Hz, 1H), 7.37 (d, J=2.0 Hz, 1H), 7.01 (dd, J=9.0, 2.0 Hz, 1H), 3.82 (s, 3H).

Anal. Calcd for $C_{13}H_9F_3N_4O_2$: C, 50.33; H, 2.92; N, 18.06. Found: C, 50.45; H, 3.11; N, 17.97.

*3.5.5. 2-(2-Aminopyrimidin-5-yl)-1,3-benzoxazol-5-ol (**8a**).* Yield, 90% (203 mg, cream solid); mp >300 °C; IR (KBr) ν 3475, 3430, 3402 cm^{-1} (NH_2, OH); ^1H NMR (DMSO-d_6) δ 9.49 (br s, 1H), 8.90 (s, 2H), 7.50 (br s, 2H), 7.47 (d, J=8.75 Hz, 1H), 7.01 (d, J=2.35 Hz, 1H), 6.77 (dd, J=8.75, 2.35 Hz, 1H).

Anal. Calcd for $C_{11}H_8N_4O_2$: C, 57.89; H, 3.53; N, 24.55. Found: C, 58.10; H, 3.69; N, 24.36.

*3.5.6. 2-(2-Aminopyrimidin-5-yl)-7-bromo-1,3-benzoxazol-5-ol (**8b**).* Yield, 94% (290 mg, cream solid); mp >300 °C; IR (KBr) ν 3415, 3487, 3327 cm^{-1} (NH_2, OH); ^1H NMR (DMSO-d_6) δ 9.88 (br s, 1H), 8.89 (s, 2H), 7.59 (br s, 2H), 7.03 (d, J=1.9 Hz, 1H), 6.99 (d, J=1.9 Hz, 1H).

Anal. Calcd for $C_{11}H_7BrN_4O_2$: C, 43.02; H, 2.30; N, 18.24. Found: C, 43.21; H, 2.06; N, 18.13.

*3.5.7. 2-(2-Aminopyrimidin-5-yl)-1,3-benzothiazol-5-ol (**8c**).* Yield, 84% (203 mg, cream solid); mp >300; IR (KBr) ν 3475, 3452, 3416 cm^{-1} (NH_2, OH); ^1H NMR (DMSO-d_6) δ 9.75 (br s, 1H, OH), 8.83 (s, 2H), 7.84 (d, J=9.0 Hz, 1H), 7.39 (br s, 2H, NH_2), 7.30 (d, J=2.0 Hz, 1H), 6.9 (dd, J=9.0, 2.0 Hz, 1H).

Anal. Calcd for $C_{11}H_8N_4OS$: C, 54.09; H, 3.30; N, 22.94. Found: C, 53.90; H, 3.46; N, 23.10.

3.6. General procedure for the synthesis of 5-(5-methoxy-1,3-benzoxazol-2-yl)pyrimidin-2(1*H*)-one (9a,b or 9d)

To an ice cooled suspension of **7a**,**b** or **7d** (1 mmol) in acetic acid/water (30 mL, 1:1) was added hydrochloric acid (37 percent, 2 mL) and then a solution of $NaNO_2$ (5 equiv) in water over 10 min. The mixture was heated to 70 °C for 3 h. It was cooled to room temperature, neutralized with $NaHCO_3$, extracted with EtOAc, dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. The residue was recrystallized from EtOAc/hexane to give **9a**,**b** or **9d**.

*3.6.1. 5-(5-Methoxy-1,3-benzoxazol-2-yl)pyrimidin-2(1H)-one (**9a**).* Yield, 61% (148 mg, cream crystal); mp 270 °C (dec); IR (KBr) ν 3416 (N–H), 1619 cm^{-1} (C=O); ^1H NMR (DMSO-d_6) δ 9.48 (br s, 1H, OH), 8.93 (s, 2H), 7.61 (d, J=9.0 Hz, 1H), 7.29 (d, J=2.5 Hz, 1H), 6.96 (dd, J=9.0, 2.5 Hz, 1H), 3.80 (s, 3H).

Anal. Calcd for $C_{12}H_{10}N_3O_3$: C, 59.26; H, 3.73; N, 17.28. Found: C, 59.43; H, 3.90; N, 17.41.

*3.6.2. 5-(7-Bromo-5-methoxy-1,3-benzoxazol-2-yl)pyrimidin-2(1H)-one (**9b**).* Yield, 65% (210 mg, cream crystal); mp 202–204 °C; IR (KBr) ν 3423 (N–H), 1645 cm^{-1} (C=O); ^1H NMR (DMSO-d_6) δ 12.76 (br, 1H, OH), 8.94 (s, 2H), 7.33 (d, J=2.0 Hz, 1H), 7.22 (d, J=2.0 Hz, 1H), 3.84 (s, 3H).

Anal. Calcd for $C_{12}H_8BrN_3O_3$: C, 44.74; H, 2.50; N, 13.05. Found: C, 44.65; H, 2.53; N, 12.98.

*3.6.3. 5-(5-Methoxy-1,3-benzoxazol-2-yl)-6-trifluoromethylpyrimidin-2(1H)-one (**9d**).* Yield, 62% (240 mg, cream crystal); mp 185–188 °C; IR (KBr) ν 3414 (N–H), 1711 (C=O), 1186, 1126 cm^{-1} (CF_3); ^1H NMR (DMSO-d_6+D_2O) δ 7.62 (s, 1H), 7.49 (d, J=8.5 Hz, 1H), 7.16 (s, 1H), 6.88 (d, J=8.5 Hz, 1H), 3.78 (s, 3H).

Anal. Calcd for $C_{13}H_8F_3N_3O_3$: C, 50.17; H, 2.59; N, 13.50. Found: C, 49.97; H, 2.83; N, 13.34.

*3.6.4. 5-(5-Hydroxy-1,3-benzoxazol-2-yl)pyrimidin-2(1H)-one (**10a**).* Yield, 80% (277 mg, cream solid); mp >300 °C; IR (KBr) ν 3492, 3406 (N–H, O–H), 1650 cm^{-1} (C=O); ^1H NMR (DMSO-d_6+D_2O) δ 9.05 (s, 2H), 7.55 (d, J=8.8 Hz, 1H), 7.33 (d, J=2.5 Hz, 1H), 6.90 (dd, J=8.8, 2.5 Hz, 1H).

Anal. Calcd for $C_{11}H_7N_3O_3$: C, 57.65; H, 3.08; N, 18.33. Found: C, 57.82; H, 2.90; N, 18.57.

*3.6.5. 5-(5-Hydroxy-7-bromo-1,3-benzoxazol-2-yl)pyrimidin-2(1H)-one (**10b**).* Yield, 95% (290 mg, light cream solid); mp >300 °C; IR (KBr) ν 3475, 3623 (N–H, O–H), 1645 cm^{-1} (C=O); ^1H NMR (DMSO-d_6) δ 12.76 (br s, 1H, NH), 10.08 (br s, 0.65H, OH), 9.92 (br s, 0.35H, OH), 9.39 (s, 0.65H), 9.31 (s, 0.65H), 8.90 (br s, 0.7H), 7.15 (s, 0.65H), 7.14 (s, 0.65H), 7.03 (s, 0.35H), 7.00 (s, 0.35H).

Anal. Calcd for $C_{11}H_6BrN_3O_3$: C, 42.88; H, 1.96; N, 13.64. Found: C, 43.12; H, 2.12; N, 13.50.

*3.6.6. 5-(5-Hydroxy-1,3-benzoxazol-2-yl)-6-trifluoromethylpyrimidin-2(1H)-one (**10d**).* Yield, 91% (270 mg, light cream solid); mp 183–186 °C; IR (KBr) ν 3487, 3376 (N–H, O–H), 1717 (C=O) 1183, 1132 cm^{-1} (CF_3); ^1H NMR (DMSO-d_6+D_2O) δ 7.60 (s, 1H), 7.39 (d, J=8.5 Hz, 1H), 6.94 (s, 1H), 6.73 (d, J=8.5 Hz, 1H).

Anal. Calcd for $C_{12}H_5BrF_3N_3O_3$: C, 38.32; H, 1.34; N, 11.17. Found: C, 38.48; H, 1.11; N, 11.29.

3.7. General procedure for the synthesis of 2-(6-bromopyridin-3-yl)-5-methoxy-1,3-benzoxazoles (12a,b)

To a solution of 2-amino-4-methoxyphenol derivative (**2a**,**b**, 2.15 mmol) in dry methanol was added 6-bromo-3-pyridinecarboxaldehyde (400 mg, 2.15 mmol). The resulting mixture was stirred at room temperature overnight and then solvent was evaporated to dryness under reduced pressure. The residue was taken up in CH_2Cl_2 (10 mL) and DDQ (550 mg, 1.1 equiv) was added. After stirring at room temperature for 45 min, the resulting mixture was diluted with CH_2Cl_2 (10 mL) and washed sequentially with saturated Na_2CO_3 (2×10 mL) and brine (10 mL). The organic layer was dried over Na_2SO_4 and evaporated to give a brown solid. The crude was purified by flash chromatography (CH_2Cl_2/hexane; 1:1) to give **12a**,**b**.

*3.7.1. 2-(6-Bromopyridin-3-yl)-5-methoxy-1,3-benzoxazole (**12a**).* The physical and spectral data of **12a** was similar to those reported.[38]

*3.7.2. 7-Bromo-2-(6-bromopyridin-3-yl)-5-methoxy-1,3-benzoxazole (**12b**).* Yield, 67% (555 mg, light cream solid); mp 210–212 °C; ^1H NMR ($CDCl_3$) δ 9.22 (d, J=2.5 Hz, 1H), 8.36 (dd, J=8.0, 2.5 Hz, 1H), 7.69 (d, J=8.5 Hz, 1H), 7.21 (d, J=2.0 Hz, 1H), 7.19 (d, J=2.0 Hz, 1H), 3.88 (s, 3H).

Anal. Calcd for $C_{13}H_8Br_2N_2O_2$: C, 40.66; H, 2.10; N, 7.29. Found: C, 40.79; H, 2.26; N, 7.15.

3.8. General procedure for the synthesis of 2-(6-benzyloxypyridin-3-yl)-5-methoxy-1,3-benzoxazole (13a,b)

To a mixture of benzyl alcohol (130 mg, 1.2 mmol), potassium *tert*-butoxide (130 mg, 1.16 mmol) in dry THF (10 mL) was added **12a**,**b** (1 mmol). The resulting mixture was stirred at room temperature for 12 h and then poured into cold water. The precipitated solid was filtered and recrystallized from CH_2Cl_2/hexane to give **13a**,**b**.

*3.8.1. 2-(6-Benzyloxypyridin-3-yl)-5-methoxy-1,3-benzoxazole (**13a**).* Yield, 93% (283 mg, light cream crystal); mp 178–180 °C; ^{1}H NMR (DMSO-d_6) δ 8.96 (d, J=2.2 Hz, 1H), 8.40 (dd, J=8.7, 2.2 Hz, 1H), 7.67 (d, J=8.9 Hz, 1H), 7.34–7.49 (m, 6H), 7.10 (d, J=8.7 Hz, 1H), 6.99 (dd, J=8.9, 2.5 Hz, 1H), 5.46 (s, 2H), 3.82 (s, 3H).

Anal. Calcd for $C_{20}H_{16}N_2O_3$: C, 72.28; H, 4.85; N, 8.43. Found: C, 72.11; H, 4.99; N, 8.24.

*3.8.2. 7-Bromo-2-(6-benzyloxypyridin-3-yl)-5-methoxy-1,3-benzoxazole (**13b**).* Yield, 96% (394 mg, light cream crystal); mp 160–163 °C; ^{1}H NMR (DMSO-d_6) δ 8.94 (s, 1H), 8.37 (d, J=7.8 Hz, 1H), 7.24–7.48 (m, 6H), 7.10 (s, 1H), 7.09 (s, 1H), 5.46 (s, 2H), 3.83 (s, 3H).

Anal. Calcd for $C_{20}H_{15}BrN_2O_3$: C, 58.41; H, 3.68; N, 6.81. Found: C, 58.18; H, 3.83; N, 19.45.

*3.8.3. 5-(5-Hydroxy-1,3-benzoxazol-2-yl)pyridin-2(1H)-one (**14a**).* It was prepared starting from **13a** and according to method A. Yield, 92% (210 mg, light cream solid); mp >300 °C; IR (KBr) ν 3476 (OH), 1638 cm^{-1} (C=O); ^{1}H NMR (DMSO-d_6) δ 12.22 (br s, 1H), 9.48 (br s, 1H), 8.18 (d, J=2.5 Hz, 1H), 8.04 (dd, J=9.6, 2.5 Hz, 1H), 7.47 (d, J=8.7 Hz, 1H), 7.00 (d, J=2.2 Hz, 1H), 6.77 (dd, J=8.7, 2.2 Hz, 1H), 6.50 (d, 1H, J=9.6 Hz).

Anal. Calcd for $C_{12}H_8N_2O_3$: C, 63.16; H, 3.53; N, 12.28. Found: C, 62.92; H, 3.69; N, 12.42.

*3.8.4. 5-(7-Bromo-5-hydroxy-1,3-benzoxazol-2-yl)pyridin-2(1H)-one (**14b**).* It was prepared starting from **13b** and according to method A. Yield, 90% (277 mg, light cream solid); mp 276–280 °C; IR (KBr) ν 3422 (OH), 1669 cm^{-1} (C=O); ^{1}H NMR (DMSO-d_6) δ 10.11 (br s, 0.5H), 9.54 (br s, 0.5H), 9.07 (d, J=1.5 Hz, 0.5H), 8.38 (dd, J=8.3, 1.5 Hz, 0.5H), 8.18 (d, J=1.5 Hz, 0.5H), 8.00 (dd, J=9.5, 1.5 Hz, 0.5H), 7.89 (d, J=8.3 Hz, 0.5H), 7.14 (s, 0.5H), 7.13 (s, 0.5H), 7.02 (s, 0.5H), 7.00 (s, 0.5H), 6.51 (d, J=9.5 Hz, 0.5H).

Anal. Calcd for $C_{12}H_7BrN_2O_3$: C, 46.93; H, 2.30; N, 9.12. Found: C, 50.12; H, 2.14; N, 9.01.

3.9. Synthesis of 5-(7-isopropenyl-5-hydroxy-1,3-benzoxazol-2-yl)pyridin-2(1*H*)-one (15)

To a stirred suspension of **14b** (92 mg, 0.3 mmol), isopropenylboronic acid (77 mg, 0.9 mmol) and Pd[Ph_3P]$_4$ (20 mg) in dimethoxyethane (2 mL) was added a solution of Cs_2CO_3 (1 mL, 2 M) and the resulting mixture was heated at 110 °C for 24 h under argon. It was cooled, diluted with water, extracted with EtOAc and dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was purified by preparative TLC to give **15** (69 mg, light brown solid). Yield, 86%; mp 152–155 °C; IR (KBr) ν 3467, 3414 (N–H, O–H), 1664 cm^{-1} (C=O); ^{1}H NMR (CD_3OD) δ 8.30 (dd, J=8.5, 1.5 Hz, 1H), 8.22 (d, J=1.5 Hz, 1H), 6.99 (s, 1H), 6.88 (s, 1H), 6.68 (d, J=8.5 Hz, 1H), 5.85 (s, 1H), 5.44 (s, 1H), 2.27 (s, 3H).

Anal. Calcd for $C_{15}H_{12}N_2O_3$: C, 67.16; H, 4.51; N, 10.44. Found: C, 67.02, H, 4.73, N, 10.27.

3.10. Synthesis of 5-(7-isopropyl-5-hydroxy-1,3-benzoxazol-2-yl)pyridin-2(1*H*)-one (16)

Compound **15** (40 mg, 0.15 mmol) in methanol (5 mL) was hydrogenated over Pd/C (10%, 8 mg) under atmospheric pressure overnight. The resulting mixture was filtered through Celite and concentrated under reduced pressure, purified by preparative TLC (EtOAc) to give **16** (38 mg) as a brown solid. Yield, 96%; mp 246–249 °C; IR (KBr) ν 3506, 3405 (N–H, O–H), 1657 (C=O), 1387 cm^{-1} (doublet, –CH(CH_3)$_2$); ^{1}H NMR (CD_3OD) δ 8.30 (s, 0.5H), 8.25 (d, J=8.5 Hz, 0.5H), 7.67–7.55 (m, 1.5 H), 6.87 (s, 1H), 6.73 (s, 1H), 6.65 (d, J=8.5 Hz, 0.5H), 3.50–3.47 (m, 1H), 1.39 (d, J=7.0 Hz, 6H).

Anal. Calcd for $C_{15}H_{14}N_2O_3$: C, 66.66; H, 5.22; N, 10.36. Found: C, 66.80, H, 5.37, N, 10.22.

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