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7-Aryl 1,5-dihydro-benzo[*e*][1,4]oxazepin-2-ones and analogs as non-steroidal progesterone receptor antagonists

Puwen Zhang[a,*], Jeffrey C. Kern[a], Eugene A. Terefenko[a], Andrew Fensome[a], Ray Unwalla[a], Zhiming Zhang[b], Jeffrey Cohen[b], Thomas J. Berrodin[b], Matthew R. Yudt[b], Richard C. Winneker[b], Jay Wrobel[a]

[a] *Chemical and Screening Sciences, Wyeth Research, 500 Arcola Road, Collegeville, PA 19426, USA*
[b] *Women's Health and Musculoskeletal Biology, Wyeth Research, 500 Arcola Road, Collegeville, PA 19426, USA*

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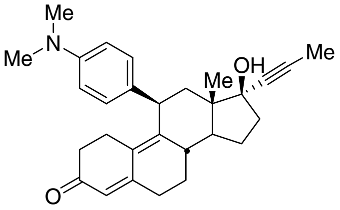
ABSTRACT

Novel 7-aryl benzo[1,4]oxazepin-2-ones were synthesized and evaluated as non-steroidal progesterone receptor (PR) modulators. The structure activity relationship of 7-aryl benzo[1,4]oxazepinones was examined using the T47D cell alkaline phosphatase assay. A number of 7-aryl benzo[1,4]oxazepinones such as **10j** and **10v** demonstrated good in vitro potency (IC_{50} of 10–30 nM) and selectivity (over 100-fold) at PR over other steroidal receptors such as glucocorticoid and androgen receptors (GR and AR). Several 7-aryl benzo[1,4]oxazepinones were active in the rat uterine decidualization model. In this in vivo model, compounds **10j** and **10u** were active at 3 mg/kg when dosed orally.

1. Introduction

The progesterone receptor (PR) is a member of the superfamily of ligand-dependent transcription factors[1] Progesterone, a natural PR agonist, plays an important role in female reproduction. PR agonists, both natural and synthetic, have been used extensively, often in combination with an estrogen, as oral contraceptives and in post-menopausal hormone therapy. In contrast, clinically successful PR antagonists remain scarce and their therapeutic potential has not yet been fully realized. Selective PR antagonists may be potentially used in female contraception[2] and for the treatment of various gynecological and obstetric diseases including hormone dependent cancers and non-malignant chronic conditions such as fibroids[3] and endometriosisp[4,5] Mifepristone (**1**), the only FDA approved steroidal PR antagonist that is in clinical use, demonstrated activity at other steroidal receptors such as glucocorticoid (GR) and androgen receptors (AR)[6] Mifepristone was nearly equipotent as an antagonist for both PR and GR and this potentially limits its chronic use. Clearly, the unmet need of selective PR antagonists presents a good opportunity for drug discovery in this area. To search for more selective PR antagonists, a number of non-steroidal PR antagonist templates have been investigated and reported[7–10] Recently, we have disclosed several series of novel PR antagonists including 5-aryl oxindoles (e.g., **2**), and 6-aryl benzoxazinones (e.g., **3**)[11–13] In an expansion of our SAR effort, we decided to examine 7-aryl benzo[1,4]oxazepin-2-ones as PR modulators. Herein, we report synthesis, in vitro SAR, and in vivo activity of novel 7-aryl benzoxazepin-2-ones and analogs (**10a–24**) as PR antagonists.



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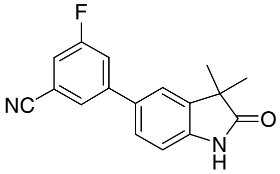

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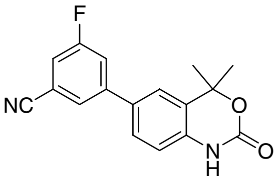

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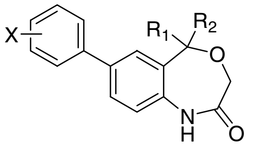

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2. Chemistry

The synthesis of 7-aryl benzoxazepin-2-ones and benzoxazepine-2-thiones **10a–10ad** is illustrated in Scheme 1. Treatment of

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[*] Corresponding author. Tel.: +1 484 865 3856; fax: +1 484 865 9398.
E-mail address: Zhangp@wyeth.com (P. Zhang).

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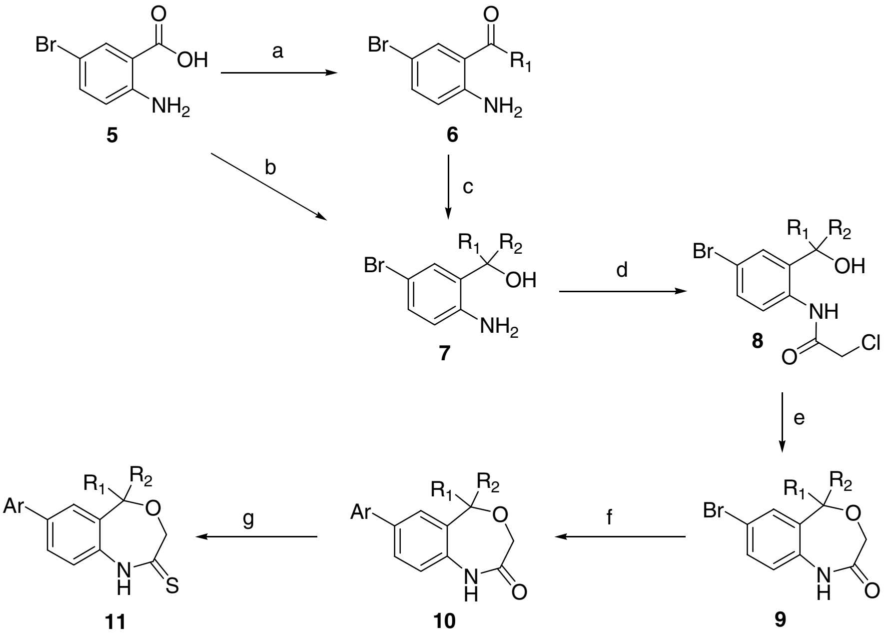
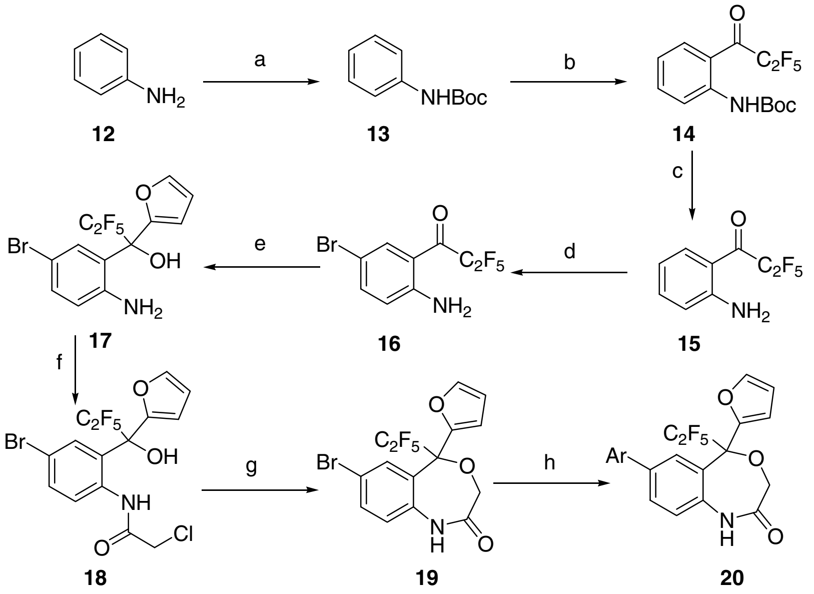


Scheme 1. Reagents and conditions: (a) R_1Li, THF, 0 °C, N_2, 30–70%; (b) when $R_1 = R_2$, R_1MgBr, diethyl ether, −78 °C–rt, N_2, 30–60%; (c) R_2MgBr or LiR_2, THF, 0 °C–rt, N_2, 25–90%; (d) chloroacetyl chloride, Et_3N, THF, 0 °C–rt, 50–70%; (e) NaH, THF, 0 °C to rt, N_2, 80–99%; (f) $ArB(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, Glyme/H_2O, 80–90 °C, 50–80%; (g) Lawesson's reagent, toluene, 110 °C.

anthranilic acid **5** with an appropriate organo-lithium agent afforded (2-amino-5-bromophenyl) ketones **6**. Conversion of ketones **6** to their corresponding carbinols **7** was readily furnished by the addition of a Grignard or organo-lithium reagent. Anthranilic acid **5** could also be directly converted to carbinols **7** ($R_1 = R_2$) by the addition of excess of an appropriate Grignard reagent. Acylation of **7** with chloroacetyl chloride led to the formation of **8**, which upon ring closure with sodium hydride provided the key intermediate benzoxazepinones **9**. The 7-aryl benzoxazepinones **10a–10ad** were obtained in good yields by coupling **9** and appropriate aryl boronic acids via a standard Suzuki cross-coupling protocol. 7-Aryl benzoxazepinones **10f** and **10p** were converted to their respective benzoxazepine-2-thiones **11a** and **11b** by refluxing with Lawesson's reagent in toluene.

Compounds **20a** and **20b** were prepared as shown in Scheme 2. Aniline **12** was first protected using di-*t*-butyl pyrocarbonate to give **13**. Ortho-directed lithiation of **13** followed by addition of ethyl pentafluoropropionate afforded ketone **14**. Removal of the Boc group under acidic conditions gave **15** and subsequent bromination using NBS provided compound **16**. The ring closure and arylation at the 7-position to deliver the desired target compounds **20a** and **20b** were carried in a similar fashion as illustrated in Scheme 1.

4,5-Dihydro-1*H*-benzo[1,4]diazepin-2-one **24** was furnished via the Scheme 3. Ring closure of 2-amino-5-bromoacetophenone **21**



Scheme 2. Reagents and conditions: (a) Di-*tert*-butyl pyrocarbonate, DMAP, THF, 70 °C, N_2, 81%; (b) ethyl pentafluoropropionate, *t*-BuLi, diethyl ether, −78 to −15 °C, N_2, 28%; (c) TFA, CH_2Cl_2, rt, 80%; (d) NBS, CH_2Cl_2, rt, 94%; (e) furan, *n*-BuLi, THF, −78 to 0 °C, N_2, >90%; (f) chloroacetyl chloride, Et_3N, THF, 0 °C–rt, 60%; (g) NaH, THF, 0 °C–rt, N_2, 50%; (h) $ArB(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, Glyme/H_2O, 80 °C, 52%.

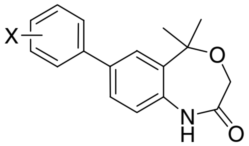
with glycine ethyl ester hydrochloride salt in refluxing pyridine formed 5-methyl-1*H*-benzo[*e*][1,4]diazepin-2(3*H*)-one **22**. Coupling **22** with 3-chloro-4-fluorophenyl boronic acid afforded compound **23** following the standard Suzuki cross-coupling protocol. Methylation of compound **23** at the 4-position followed by an addition of methylmagnesium bromide afforded benzodiazepin-2-one **24**.

3. Results and discussion

We have recently reported several series of non-steroidal PR modulators. [11–16] Among the antagonist scaffolds examined, the 6-aryl benzoxazin-2-ones were the most promising and rendered the most potent and selective PR antagonists as demonstrated in a number of in vitro and in vivo models[12] In an expansion of our SAR efforts on the benzoxazin-2-one template, we have examined and disclosed the ring-contracted oxindole scaffold (e.g., **2**). The SAR effort led to several 5-aryl oxindoles that showed good in vitro and in vivo PR antagonist potency[11] To further exploit the SAR uncovered from benzene-fused 5-membered ring oxindole and 6-membered ring benzoxazin-2-one scaffolds, we decided to examine the benzoxazinone core ring expansion by inserting a methylene moiety between the 2-position carbonyl group and 3-position oxygen atom. This modification led to 7-aryl benzoxazepin-2-ones, a new class of PR modulators as demonstrated using the T47D cell alkaline phosphatase assay[17,18]

Using the 5,5-dimethylbenzoxazepinone as a core, a number of novel 7-phenyl based benzoxazepinones were prepared to probe the SAR of substitution on the 7-phenyl group (Table 1). 3-Fluorophenyl analog **10b** was more potent in the T47D alkaline phosphatase assay than its 2- and 4-fluoro congeners **10a** and **10c**. This finding was consistent with the SAR trend observed from the benzoxazinone and oxindole scaffolds in that an electron-withdrawing group was preferred at the 3-position of the pendant phenyl group[11,12] Disubstituted analogs **10d–k** had PR antagonist potency in the 30 nM or lower range that was comparable to that of their 3′-fluoro analog **10b**. Overall, the ring-expanded benzoxazepinones had similar in vitro potency compared to their benzoxazinone (**3**) and oxindole (**2**) analogs in the T47D alkaline phosphatase assay.[11,12]

Table 1
PR alkaline phosphatase activity of 7-aryl 5,5-dimethyl benzoxazepin-2-ones



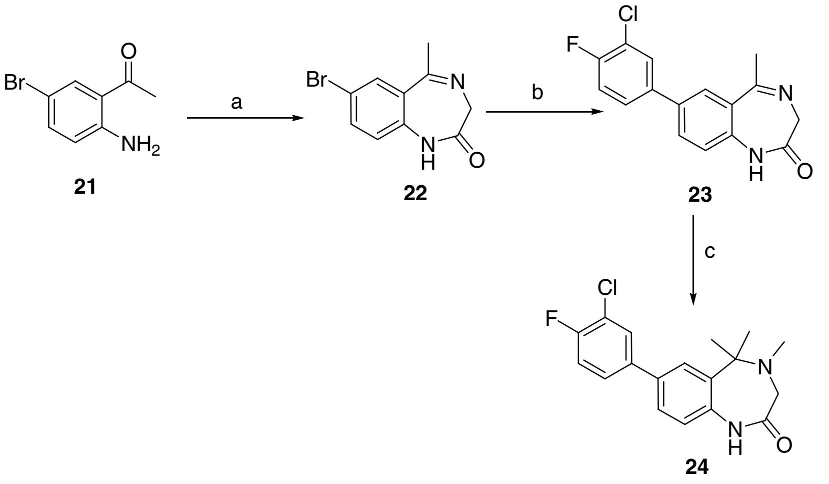
Compound	X	T47D alkaline phosphatase IC$_{50}$[a] (nM)
1		0.2
2		13.0
3		(90)[b]
10a	2-F	62.1
10b	3-F	14.9
10c	4-F	100.0
10d	2-F, 3-F	15.7
10e	3-F, 4-F	29.3
10f	3-F, 5-F	30.0
10g	3-Cl, 4-F	30.1
10h	3-Cl, 5-F	15.0
10i	3-Cl, 5-Cl	29.1
10j	3-CN, 5-F	25.0
10k	3-CN, 5-Cl	34.6

[a] Fifty percent inhibitory concentration of tested compounds on 1 nM progesterone induced alkaline phosphatase activity in the human T47D breast carcinoma cell line.

[b] The number in the parentheses is EC$_{50}$ value and represents 50% effective concentration of tested compounds on alkaline phosphatase activity in the human T47D breast carcinoma cell line. Values represent the average of at least duplicate determinations. The standard deviations for these assays were typically ±20% of the mean or less.

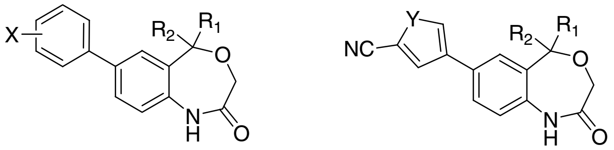
As previously disclosed,[11,12] 3-cyano-5-fluoro and 3-chloro-5-fluorophenyl substituted benzoxazinones showed weak to moderate PR agonist activity in T47D alkaline phosphatase assay while the corresponding ring-contracted oxindoles were PR antagonists in the same assay. Interestingly, both 3-cyano-5-fluoro and 3-chloro-5-fluorophenyl substituted benzoxazepinones (**10h**, **10j**) elicited PR antagonist activity suggesting the same SAR trend to their ring-contracted oxindole analogs.

Compounds **10l–ab** and **20a,b** (Table 2) were prepared to examine the SAR at the 5-position while maintaining the 7-(3-cyano-5-fluorophenyl) and 7-(3-chloro-4-fluorophenyl) group constant. Replacing one of methyl groups at the 5-position with a thien-2-yl moiety (**10l**, IC$_{50}$ = 65.5 nM) slightly decreased potency compared to 5,5-dimethyl analog **10g** (IC$_{50}$ = 30.1 nM). Increasing the size of alkyl group from methyl to propyl group (**10m–q**) caused reduction in PR antagonist potency. Substitution of fur-2-yl and thien-3-yl groups for thien-2-yl moiety (**10r–u** vs. **10m,n**) in-



Scheme 3. Reagents and conditions: (a) Glycine ethyl ester HCl salt, pyridine, reflux, 16%; (b) 3-Cl-4-F-phenyl boronic acid, Pd(PPh$_3$)$_4$, Na$_2$CO$_3$, Glyme/H$_2$O, 80 °C, 73%; (c) MeI, anhydrous acetonitrile, 50 °C; MeMgBr, ether, 5%.

Table 2
PR alkaline phosphatase activity of different 5,5-disubstituted benzoxazepin-2-ones



Compound	R_1	R_2	X	T47D alkaline phosphatase IC_{50}[a] (nM)
10l	CH_3	Thien-2-yl	3-Cl, 4-F	65.5
10m	C_2H_5	Thien-2-yl	3-Cl, 4-F	207.7
10n	C_2H_5	Thien-2-yl	3-CN, 5-F	100.0
10o	n-C_3H_7	Thien-2-yl	3-Cl, 4-F	349.4
10p	i-C_3H_7	Thien-2-yl	3-Cl, 4-F	365.7
10q	i-C_3H_7	Thien-2-yl	3-CN, 5-F	138.3
10r	C_2H_5	Thien-3-yl	3-Cl, 4-F	116.7
10s	C_2H_5	Thien-3-yl	3-CN, 5-F	59.2
10t	C_2H_5	Fur-2-yl	3-Cl, 4-F	62.5
10u	C_2H_5	Fur-2-yl	3-CN, 5-F	11.8
10v	Fur-2-yl	Fur-2-yl	3-CN, 5-F	13.3
10w	Fur-2-yl	Fur-2-yl	3-Cl, 4-F	22.5
10x	Thien-2-yl	Thien-2-yl	3-CN, 5-F	26.6
10y	Thien-2-yl	Thien-2-yl	3-Cl, 4-F	65.2
10z	Phenyl	Phenyl	3-Cl, 4-F	88.0
10aa	5′-Cl-thien-2-yl	5′-Cl-thien-2-yl	3-Cl, 4-F	1000.0
10ab	5′-Cl-thien-2-yl	5′-Cl-thien-2-yl	3-CN, 5-F	1000.0
10ac	C_2H_5	Fur-2-yl	Y = O	29.9
10ad	C_2H_5	Thien-2-yl	Y = S	107.6
20a	C_2F_5	Fur-2-yl	3-Cl, 4-F	82.4
20b	C_2F_5	Fur-2-yl	3-CN, 5-F	34.1

[a] % Inhibitory concentration of tested compounds on 1 nM progesterone induced alkaline phosphatase activity in the human T47D breast carcinoma cell line. Values represent the average of at least duplicate determinations. The standard deviations for these assays were typically ±20% of the mean or less.

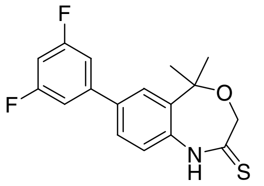
creased PR antagonist potency. Increasing the lipophilicity by replacing the ethyl group of compounds **10t,u** with a pentafluoroethyl group (**20a,b**) resulted in a slight reduction in potency. 5,5-Difuryl, 5,5-dithienyl, and 5,5-diphenyl analogs **10v–z** also showed good PR antagonist potency. However, replacing thien-2-yl group (**10x,y**) with 5′-chlorothien-2-yl group (**10aa,ab**) at the 5-position resulted in a greater than 15-fold loss in potency suggesting a size limitation at this position. Compounds **10ac,ad** also had good PR antagonist potency suggesting that the phenyl-based aryl groups at the 7-position can be replaced by an appropriate hetero aryl moiety without losing PR antagonist potency.

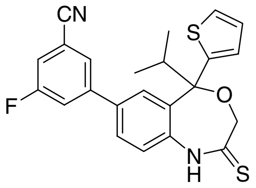
As shown in Table 3, benzoxazepine-2-thione **11a** became a PR agonist with moderate potency when the 2-carbonyl group was replaced by a 2-thiocarbonyl moiety. However, **11a** was over 20-fold less potent than its corresponding benzoxazine-2-thione congener[16] Interestingly, benzoxazepine-2-thione **11b** with larger 5-substituents remained as a PR antagonist with a similar potency as that of its parent compound **10p**. Replacing the 4-oxygen by *N*-methyl group led to 4,5-dihydrobenzodiazepin-2-one **24**, which was 3-fold less potent compared to **10g**. In addition, benzodiazepin-2-one **23**, a precursor of **24**, was PR antagonist with the moderate potency.

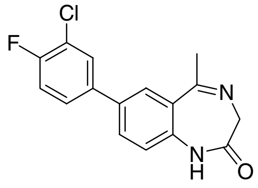
Clearly, there appeared different SAR trends between 6-aryl benzoxazinones and 7-aryl benzoxazepinones. In contrast to 6-aryl benzoxazinones that showed both PR agonist and antagonist activities dependent on the nature of 6-aryl substitution, 7-aryl benzoxazepinones demonstrated more consistent PR antagonist activity regardless of 7-aryl substitutions. Furthermore, 7-aryl benzoxazepine-2-thiones **11a** and **11b** were either less potent PR agonist or remained a PR antagonist in contrast to the consistent agonism of similar substituted 6-aryl benzoxazine-2-thiones.[16] To understand the binding mode of these 7-aryl benzoxazepinones within the progesterone receptor, docking studies were carried out on compound **10u** using the recently published X-ray structure of PR LBD with asoprisnil, a steroidal selective progesterone modulator (SPRM). The PR/asoprisnil crystal structure showed helix-12 in an antagonist conformation, which is different than the typical agonist conformations seen in the PR/progesterone complex and the non-steroidal PR agonist ligand tanaproget. Inspection of the docked structure of **10u** revealed that the nitrile group of the A-ring makes a network of hydrogen bond interactions with Arg766 and Gln725 residues that are held in position by a water molecule. The benzoxazepin-2-one ring lied in a similar orientation as seen in the benzoxazine-2-thione ring of tanaproget and the NH group of the ligand made hydrogen bond interaction with the carbonyl group of the Asn719 residue within helix-3. The larger substituents on the 5-position, that is, ethyl and furan, were accommodated in the pocket occupied by the Phe794 and Leu797 residues. An overlay of the PR/asoprisnil complex structure onto the PR/tanaproget structure showed backbone deviations of 0.7 Å in this region, which allowed residues Phe794, Leu797, and Tyr890 to swing away from the ligand in the asoporisnil structure and created more room for these groups to be accommodated. This also explained why our earlier attempts to dock **10u** into the tanaproget binding site did not yield any reasonable low energy bound pose for this ligand. Clearly the steric interactions with the rotamers of these residues present in the tanaproget structure did not allow these bulky groups to be accommodated. Taken together, docking studies suggested that the more bulky benzoxazepin-2-ones preferred an antagonist conformation in the PR binding pocket thus leading to more consistent PR antagonism (Fig. 1).

Compounds **10j, 10u**, and **10v** were evaluated for their selectivity against other steroidal receptors by using a Gal4-DNA binding domain (DBD)-hormone receptor ligand binding domain (LBD) one-hybrid assay for each receptor[19] (Table 4). Compared to steroidal PR antagonist mifepristone (**1**), these compounds are more selective at PR over other hormone receptors. Both **10j** and **10v** have 100-fold or greater selectivity at PR over other steroid recep-

Table 3
PR alkaline phosphatase activity of 7-aryl benzoxazepine-2-thiones and benzodiazepine-2-one


11a


11b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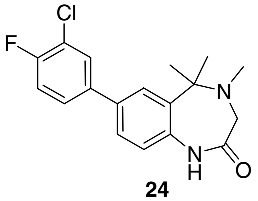
24

Compound	X	Y	T47D alkaline phosphatase EC_{50}[a] (nM)	T47D alkaline phosphatase IC_{50}[b] (nM)
11a			35.8	
11b				78.2
23				676.7
24				104.7

[a] Fifty percent effective concentration of tested compounds on alkaline phosphatase activity in the human T47D breast carcinoma cell line.
[b] Fifty percent inhibitory concentration of tested compounds on 1 nM progesterone induced alkaline phosphatase activity in the human T47D breast carcinoma cell line. Values represent the average of at least duplicate determinations. The standard deviations for these assays were typically ±20% of the mean or less.

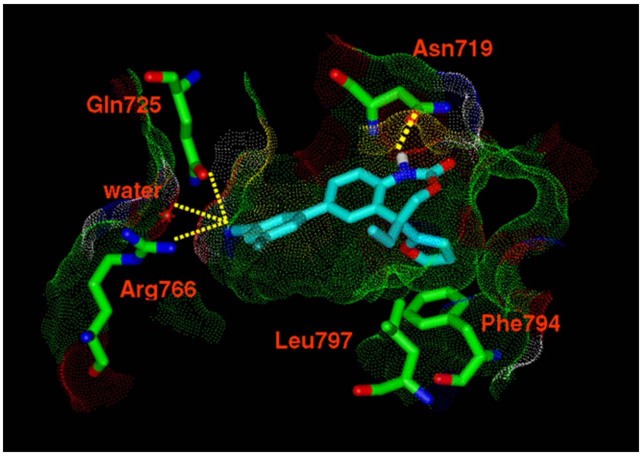

Figure 1. Proposed binding mode of compound **10j** (cyan) in PR/asoprisinil LBD binding site. (Only key residues and a Connolly surface of the binding site are shown for simplicity. Hydrogen bonds are shown as yellow dotted lines.)

tors suggesting that these novel PR ligands might have less potential AR- or GR-related side effects. Several 7-aryl benzoxazepinones were also evaluated for their oral activity in the ovariectomized mature female rat decidualization model.[20] Both **10j** and **10u** were PR antagonists in this in vivo model inhibiting progesterone induced decidualization by ~50% when dosed orally at 3 mg/kg.

In summary, a novel series of non-steroidal 7-aryl benzo[1,4]oxazepin-2-ones and analogs were evaluated as progesterone receptor (PR) modulators. The structure activity relationship of 7-aryl benzo[1,4]oxazepinones was examined using the T47D cell alkaline phosphatase assay. A number of 7-aryl benzo[1,4]oxazepinones such as **10j** and **10u** demonstrated good in vitro potency and selectivity at PR over other steroidal receptors such as GR and AR. In addition, several 7-aryl benzo[1,4]oxazepinones were active PR antagonists in the rat uterine decidualization model.

4. Experimental

4.1. General

^{1}H NMR spectra were recorded on a Bruker DPX300, Varian INOVA 400, or Varian INOVA 500 instrument. Chemical shifts are reported in δ values (parts per million, ppm) relative to an internal standard of tetramethylsilane in $CDCl_3$ or DMSO-d_6. Electrospray (ESI) mass spectra were recorded using a Hewlett-Packard 5989B MS engine or Waters Alliance-ZMD mass spectrometer. Electron Impact ionization (EI, EE = 70 eV) mass spectra were recorded on a Finnigan Trace mass spectrometer. Elemental analyses were carried out on a modified Perkin-Elmer model 2400 series II CHN analyzer or sent to Robertson Microlit. Analytical thin-layer chromatography (TLC) was carried out on precoated plates (silica gel, 60 F-254), and spots were visualized with UV light and stained in iodine. Preparative HPLC purifications were performed on a preparative Gilson HPLC system using a CombiPrep Pro C18 column with acetonitrile (0.1% TFA) and water (0.1% TFA) as solvents at a flow rate of 20 mL/min. Solvents were purchased as anhydrous grade and were used without further purification.

4.1.1. 2-(2-Amino-5-bromophenyl)propan-2-ol (7a)

A solution of 2-amino-5-bromobenzoic acid (10.0 g, 46 mmol) in dry THF (200 mL) was treated at −78 °C under nitrogen with a solution of methylmagnesium bromide in ether (3.0 M, 90 mL, 270 mmol). The reaction mixture was slowly warmed to ambient temperature, kept stirring for 48 h under nitrogen and then poured into a cold 0.5 N aqueous hydrochloride solution (300 mL). The mixture was neutralized with aqueous 1N sodium hydroxide solution and ethyl acetate (300 mL) was added. The organic layer was separated and aqueous layer was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with brine and dried ($MgSO_4$). After removal of solvent in vacuo, the residue was purified by a silica gel flash chromatography (hexane–ethyl acetate, 3:2) to give 2-(2-amino-5-bromophenyl)propan-2-ol as off-white solid (6.0 g, 57%): mp 62–63 °C; MS (ESI) *m/z* 230 ($[M+H]^+$); ^{1}H NMR ($CDCl_3$): δ 7.19 (d, 1H, $J = 2.3$ Hz), 7.12 (dd, 1H, $J = 8.4, 2.3$ Hz), 6.51 (d, 1H, $J = 8.4$ Hz), 4.70 (s, 2H), 1.82 (s, 1H), 1.65 (s, 6H).

4.1.2. *N*-[4-Bromo-2-(1-hydroxy-1-methyl-ethyl)-phenyl]-2-chloro-acetamide (8a)

To a solution of 2-(2-amino-5-bromophenyl)propan-2-ol (4.6 g, 20 mmol) in a mixture of anhydrous diethyl ether (100 mL) at 0 °C under nitrogen was added triethyl amine (6.3 mL, 45 mmol) and chloroacetyl chloride (1.8 mL, 22.6 mmol). After addition, the reaction mixture was slowly warmed to rt, stirred for 3 h, and treated with a cold 1N hydrogen chloride aqueous solution (70 mL). Ethyl acetate (100 mL) was added and organic layer separated, dried (Mg_2SO_4), concentrated to yield the title compound as an off-white solid (4.5 g, 74%): mp 133–134 °C. MS (ESI) *m/z* 304 ($[M-H]^-$); ^{1}H NMR (DMSO-d_6): δ 1.21 (s, 1H), 8.12 (d, $J = 8.6$ Hz, 1H), 7.46 (dd,

Table 4
Antagonist cross-activities of **1**, **10j**, **10u**, and **10v**

Compound	PR IC$_{50}$[a] (nM)	ER IC$_{50}$[b] (nM)	AR IC$_{50}$[b] (nM)	GR IC$_{50}$[b] (nM)	MR IC$_{50}$[b] (nM)
1	0.2	5000 (50)	6.9 (95)	0.6 (97)	590 (96)
10j	25.0	NA[c]	>3000 (57)	>3000 (23)	>3000 (32)
10u	11.8	NA	690 (82)	190 (91)	>3000 (82)
10v	13.3	NA	>3000 (62)	1300 (82)	>3000 (60)

[a] Fifty percent inhibitory concentration of tested compounds on 1 nM progesterone induced alkaline phosphatase activity in the human T47D breast carcinoma cell line. Values represent the average of at least duplicate determinations. The standard deviations for these assays were typically ±20% of the mean or less.

[b] Experimental values represented the average of at least duplicate determinations and values in the parentheses represented percentage of inhibition. The standard deviation for these assays was typically ±30% of mean or less. See Section 4 for details.

[c] Not active up to 10 μM concentration.

J = 8.6, 2.3 Hz, 1H), 7.44 (d, *J* = 2.3 Hz, 1H), 6.28 (s, 1H), 4.43 (s, 2H), 1.53 (s, 6H).

4.1.3. 7-Bromo-5,5-dimethyl-1,5-dihydro-4,1-benzoxazepin-2(3H)-one (9a)

To a solution of *N*-[4-bromo-2-(1-hydroxy-1-methyl-ethyl)-phenyl]-2-chloro-acetamide (3.0 g, 9.9 mmol) in anhydrous THF (30 mL) was added sodium hydride (60% in mineral oil, 0.85 g, 21 mmol) at 0 °C under nitrogen. After addition, the reaction mixture was stirred for 3 h, treated with an aqueous saturated ammonium chloride solution (30 mL). Ethyl acetate (50 mL) was added and organic layer separated, dried (Mg$_2$SO$_4$), and concentrated to yield the title compound as an off-white solid (2.7 g, 99%): mp 120–121 °C. MS (ESI) *m/z* 270 ([M+H]$^+$); ^{1}H NMR (DMSO-d_6): δ 10.01 (s, 1H), 7.46 (d, *J* = 2.3 Hz, 1H), 7.37 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.04 (d, *J* = 8.6 Hz, 1H), 4.23 (s, 2H), 1.53 (s, 6H).

4.1.4. 7-(3-Fluorophenyl)-5,5-dimethyl-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one (10b)

A mixture of 7-bromo-5,5-dimethyl-1,5-dihydro-4,1-benzoxazepin-2(3H)-one (1.0 g, 3.7 mmol), 3-fluorophenyl boronic acid (0.8 g, 5.7 mmol), tetrakis(triphenylphosphine) palladium (0) (0.25 g, 0.22 mmol), sodium carbonate (1.2 g, 11.3 mmol) in a mixture of DME and water (20 mL and 5 mL) was degassed to remove air and then heated at 90 °C under nitrogen for 4 h. The mixture was allowed to cool to rt, treated with a saturated aqueous ammonium sulfate solution (50 mL). Ethyl acetate (80 mL) was added and organic layer separated, dried (Mg$_2$SO$_4$), and concentrated. The residue was purified by a flash chromatography on a silica gel column (hexane–ethyl acetate, 3:1) to give the title compound as an off-white solid: mp 196–197 °C; ^{1}H NMR (DMSO-d_6): δ 9.98 (s, 1H), 7.43–7.58 (m, 5H), 7.12–7.20 (m, 2H), 4.23 (s, 2H), 1.63 (s, 6H). MS (ESI) *m/z* 286 ([M+H]$^+$); Anal. Calcd for $C_{17}H_{16}FNO_2$: C, 71.56; H, 5.65; N:4.91. Found: C, 71.54; H, 5.77; N, 4.82.

4.1.5. 7-(2-Fluorophenyl)-5,5-dimethyl-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one (10a)

Prepared from **9a** and 2-fluorophenyl boronic acid according to the coupling procedure described in example **10b**. ^{1}H NMR (DMSO-d_6): δ 10.01 (s, 1H), 7.63 (m, 1H), 7.51–7.57 (m, 1H), 7.36–7.43 (m, 2H), 7.25–7.30 (m, 2H), 7.19 (d, *J* = 8.32 Hz, 1H), 4.27 (s, 2H), 1.59 (s, 6H); MS (ESI) *m/z* 286 ([M+H]$^+$); MS (ESI) *m/z* 284 ([M−H]$^-$).

4.1.6. 7-(4-Fluorophenyl)-5,5-dimethyl-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one (10c)

Prepared from **9a** and 4-fluorophenyl boronic acid according to the coupling procedure described in example **10b**. ^{1}H NMR (DMSO-d_6): δ 9.92 (s, 1H), 7.64–7.67 (m, 2H), 7.41–7.46 (m, 2H), 7.17–7.25 (m, 2H), 7.12 (s, *J* = 2.26 Hz, 1H), 4.21 (s, 2H), 1.57 (s, 6H); MS (ESI) *m/z* 286 ([M+H]$^+$); MS (ESI) *m/z* 284 ([M−H]$^-$).

4.1.7. 7-(2,3-Difluorophenyl)-5,5-dimethyl-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one (10d)

Prepared from **9a** and 2,3-difluorophenyl boronic acid according to the coupling procedure described in example **10b**. ^{1}H NMR (DMSO-d_6): δ 10.04 (s, 1H), 7.2–7.45 (m, 6H), 4.28 (s, 2H), 1.59 (s, 6H); MS (ESI) *m/z* 304 ([M+H]$^+$); MS (ESI) *m/z* 302 ([M−H]$^-$).

4.1.8. 7-(3,4-Difluorophenyl)-5-ethyl-5-(2-furyl)-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one (10e)

Prepared from **9a** and 3,4-difluorophenyl boronic acid using the coupling procedure described in example **10b**. ^{1}H NMR (DMSO-d_6): δ 9.98 (s, 1H), 7.76–7.83 (m, 1H), 7.60–7.67 (m, 1H), 7.49–7.56 (m, 3H), 7.17 (d, *J* = 8.32 Hz, 1H), 4.26 (s, 2H), 1.61 (s, 6H); MS (ESI) *m/z* 304 ([M+H]$^+$); MS (ESI) *m/z* 302 ([M−H]$^-$).

4.1.9. 7-(3,5-Difluorophenyl)-5,5-dimethyl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one (10f)

Prepared from **9a** and 3,5-difluorophenyl boronic acid according to the coupling procedure described in example **10b**. ^{1}H NMR (DMSO-d_6): δ 10.04 (s, 1H), 7.61–7.57 (m, 2H), 7.52–7.45 (m, 2H), 7.23–7.17 (m, 2H), 4.72 (s, 2H), 1.60 (s, 6H); MS (FI) *m/z* 304 [M+H]$^+$.

4.1.10. 7-(3-Chloro-4-fluorophenyl)-5,5-dimethyl-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one (10g)

Prepared from **9a** and 3-chloro-4-fluorophenyl boronic acid according to the coupling procedure described in example **10b**. A white solid: mp 170–171 °C; ^{1}H NMR (DMSO-d_6): δ 10.01 (s, 1H), 7.93 (dd, *J* = 8.1, 2.3 Hz, 1H), 7.68 (m, 1H), 7.44–7.59 (m, 3H), 7.18 (d, *J* = 8.4 Hz, 1H), 4.25 (s, 2H), 1.63 (s, 6H). MS (ESI) *m/z* 318 ([M−H]$^-$); Anal. Calcd for $C_{17}H_{15}ClFNO_2$: C, 63.86; H, 4.73; N, 4.38. Found: C, 63.54; H, 4.72; N, 4.11.

4.1.11. 7-(3-Chloro-5-fluorophenyl)-5,5-dimethyl-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one (10h)

Prepared from **10b** and 5-chloro-3-fluoro phenyl boronic acid according to the coupling procedure described in example **10b**. ^{1}H NMR (DMSO-d_6): δ 10.01 (s, 1H), 7.61–7.65 (m, 4H), 7.36–7.39 (m, 1H), 7.18 (d, *J* = 8.54 Hz, 1H), 4.26 (s, 2H), 1.62 (s, 6H); MS (ESI) *m/z* 320/322 ([M+H]$^+$); MS (ESI) *m/z* 318/320 ([M−H]$^-$).

4.1.12. 7-(3,5-Dichlorophenyl)-5,5-dimethyl-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one (10i)

Prepared from **9a** and 3,5-dichlorophenyl boronic acid according to the coupling procedure described in example **10b**. ^{1}H NMR (DMSO-d_6): δ 10.02 (s, 1H), 7.76 (s, 2H), 7.55–7.64 (m, 3H), 7.18 (d, *J* = 8.45 Hz, 1H), 4.26 (s, 2H), 1.62 (s 6H); MS (ESI) *m/z* 336/338 ([M+H]$^+$); MS (ESI) *m/z* 334/336 ([M−H]$^-$).

4.1.13. 3-(5,5-Dimethyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-5-fluorobenzonitrile (10j)

Prepared from **9a** and 3-cyano-5-fluorophenyl boronic acid according to the coupling procedure described in example **10b**. A white solid: mp 238–239 °C; ^{1}H NMR (DMSO-d_6): δ 10.1 (s, 1H), 8.14 (t, *J* = 1.5 Hz, 1H), 7.98 (m, 1H), 7.80 (m, 1H), 7.69 (d, *J* = 1.9 Hz, 1H), 7.64 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.19 (d, *J* = 8.3 Hz, 1H), 4.27 (s, 2H), 1.63 (s, 6H). MS *m/z* 309 ([M−H]$^-$); Anal. Calcd for $C_{18}H_{15}FN_2O_2$: C, 69.67; H, 4.87; N, 9.03. Found: C, 69.51; H, 4.63; N, 9.07.

4.1.14. 3-Chloro-5-(5,5-dimethyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)benzonitrile (10k)

Prepared from **9a** and 3-chloro-5-cyano phenyl boronic acid according to example **10b**. ^{1}H NMR (DMSO-d_6): δ 10.03 (s, 1H), 8.22 (m, 1H), 8.14 (m, 1H), 7.97 (m, 1H), 7.69 (m, 1H), 7.64 (dd, *J* = 8.54, 2.44 Hz, 1H), 7.20 (d, *J* = 8.54 Hz, 1H), 4.27 (s, 2H), 1.63 (s, 6H); MS (ESI) *m/z* 327/329 ([M+H]$^+$); MS (ESI) *m/z* 325/327 ([M−H]$^-$).

4.1.15. 1-(2-Amino-5-bromo-phenyl)-ethanone (6a)

To a solution of 5-bromo anthranilic acid (50.0 g, 0.23 mol) in anhydrous THF (500 mL) at 0 °C was added methyllithium (1.4 M in diethyl ether, 661 mL, 0.93 mol) under nitrogen in a dropwise manner. After addition, the reaction mixture was allowed to slowly warm to rt, stirred overnight, and treated with a saturated aqueous ammonium chloride solution (1000 mL). Ethyl acetate (400 mL) was added and organic layer was separated. The aqueous layer was extracted with ethyl acetate (3 × 200 mL). The combined organic layers were dried (Mg_2SO_4) and concentrated. The residue was purified by a flash chromatography on silica gel (hexane:ethyl acetate/9:1) to afford the title compound as a brown solid (29.3 g, 59%). MS (ES) *m/z* 214/216 ([M+H]$^+$).

4.1.16. 1-(2-Amino-5-bromo-phenyl)-1-thiophen-2-yl-ethanol (7b)

To a solution of 1-(2-amino-5-bromo-phenyl)-ethanone (3.0 g, 14 mmol) in anhydrous THF (50 mL) was added 2-thienyllithium (1.0 M in THF, 28 mL, 28 mmol) at −78 °C under nitrogen. The reaction mixture was allowed to slowly warm to −20 °C, treated with a saturated aqueous ammonium chloride solution (50 mL). Ethyl acetate (50 mL) was added and organic layer was separated, dried (Mg_2SO_4), and concentrated to afford the title compound as clear oil (3.9, 95%). ^{1}H NMR (DMSO-d_6): δ 7.4 (d, *J* = 4.9 Hz, 1H), 7.07–7.11 (m, 2H), 6.94 (m, 1H), 6.84 (dd, *J* = 3.5, 0.5 Hz, 1H), 6.55 (d, *J* = 8.2 Hz, 1H), 6.36 (s, 1H), 5.31 (s, 2H), 1.85 (s, 3H).

4.1.17. *N*-[4-Bromo-2-(1-hydroxy-1-thien-2-ylethyl)phenyl]-2-chloroacetamide (8b)

Prepared from **7b** and chloroacetyl chloride according to the procedure described in example **8a**. A white solid: ^{1}H NMR (DMSO-d_6): δ 10.78 (s, 1H), 8.05 (d, *J* = 8.7 Hz, 1H), 7.51 (dd, *J* = 8.7, 2.2 Hz, 1H), 7.43 (d, *J* = 5.0 Hz, 1H), 7.37 (m, 2H), 6.95 (m, 1H), 6.88 (dd, *J* = 3.4, 0.8 Hz, 1H), 4.26 (d, *J* = 6.9 Hz, 2H), 1.94 (s, 3H).

4.1.18. 7-Bromo-5-methyl-5-thien-2-yl-1,5-dihydro-4,1-benzoxazepin-2(3H)-one (9b)

Prepared from **8b** according to the procedure described in example **9a**. A white solid: ^{1}H NMR (DMSO-d_6): δ 10.13 (s, 1H), 7.57 (dd, *J* = 5.0, 1.0 Hz, 1H), 7.47 (dd, *J* = 8.6, 1.4 Hz, 1H), 7.39 (d, *J* = 1.67 Hz, 1H), 7.11 (d, *J* = 8.4 Hz, 1H), 7.00 (m, 1H), 6.88 (dd, *J* = 2.6, 0.9 Hz, 1H), 4.18 (d, *J* = 15.8 Hz, 1H), 4.03 (d, *J* = 16.3 Hz, 1H), 1.99 (s, 3H). MS (ES) *m/z* 338/340 ([M+H]$^+$).

4.1.19. 7-(3-Chloro-4-fluorophenyl)-5-methyl-5-thien-2-yl-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one (10l)

Prepared from **9b** and 3-chloro-4-fluorophenyl boronic acid according to the coupling procedure described in example **10b**. ^{1}H NMR (DMSO-d_6): δ 10.13 (s, 1H), 7.86 (dd, *J* = 6.8, 2.0 Hz, 1H), 7.64 (m, 2H), 7.55 (m, 2H), 7.48 (t, *J* = 8.8 Hz, 1H), 7.25 (d, *J* = 8.3 Hz, 1H), 6.99 (dd, *J* = 4.9, 3.4 Hz, 1H), 6.91 (dd, *J* = 3.4, 1.0 Hz, 1H), 4.16 (d, *J* = 16.1 Hz, 1H), 4.06 (d, *J* = 16.1 Hz, 1H), 2.08 (s, 3H); MS (ES) *m/z* 388 ([M+H]$^+$); Anal. Calcd for $C_{20}H_{15}ClFNO_2S$: C, 61.93; H, 3.90; N, 3.61. Found: C, 61.88; H, 3.99; N, 3.35.

4.1.20. (2-Amino-5-bromophenyl)(2-thienyl)methanone (6b)

Prepared from 5-bromo anthranilic acid and 2-thenyllithium using the procedure described in example **6a**. ^{1}H NMR ($CDCl_3$): δ 7.86 (d, *J* = 2.3 Hz, 1H), 7.71 (dd, *J* = 5.0, 1.0 Hz, 1H), 7.59 (dd, *J* = 3.8, 1.0 Hz, 1H), 7.39 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.19 (m, 1H), 6.66 (d, *J* = 8.8 Hz, 1H), 5.71 (s, 2H); MS (ES) *m/z* 280 ([M−H]$^-$).

4.1.21. *N*-[4-Bromo-2-(1-hydroxy-1-thien-2-ylpropyl)phenyl]-2-chloroacetamide (8c)

Prepared from **6b** using the procedures described in examples **7b** and **8a**. ^{1}H NMR ($CDCl_3$): δ 10.23 (s, 1H), 8.11 (d, *J* = 8.7 Hz, 1H), 7.46 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.37 (d, *J* = 2.3 Hz, 1H), 7.29 (dd, *J* = 5.1, 1.0 Hz, 1H), 6.97 (m, 1H), 6.90 (dd, *J* = 3.5, 1.0 Hz, 1H), 4.09 (m, 2H), 2.80 (s, 1H), 2.43 (m, 2H), 1.03 (t, *J* = 7.3 Hz, 3H); MS (ES) *m/z* 386 ([M−H]$^-$); Anal. Calcd for $C_{15}H_{15}BrClNO_2S$: C, 46.35; H, 3.89; N, 3.60. Found: C, 46.67; H, 3.80; N, 3.52.

4.1.22. 7-Bromo-5-ethyl-5-thien-2-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one (9c)

Prepared from *N*-[4-bromo-2-(1-hydroxy-1-thien-2-ylpropyl)phenyl]-2-chloroacetamide **8c** using the procedure described in example **9a**. ^{1}H NMR ($CDCl_3$): δ 7.80 (br s, 1H), 7.39 (m, 3H), 6.97 (m, 1H), 6.81 (m, 2H), 4.19 (d, *J* = 16.0 Hz, 1H), 4.05 (d, *J* = 16.0 Hz, 1H), 2.58 (m, 1H), 2.31 (m, 1H), 0.87 (t, *J* = 7.2 Hz, 3H); MS (ES) *m/z* 350 ([M−H]$^-$).

4.1.23. 7-(3-Chloro-4-fluoro-phenyl)-5-ethyl-5-thiophen-2-yl-1,5-dihydro-benzo[*e*][1,4]oxazepin-2-one (10m)

Prepared from **9c** and 3-chloro-4-fluorophenyl boronic acid using the coupling procedure described in example **10a**. ^{1}H NMR (DMSO-d_6): δ 10.08 (s, 1H), 7.85 (dd, *J* = 7.1, 2.2 Hz, 1H), 7.65 (m, 2H), 7.57 (dd, *J* = 5.0, 1.0 Hz, 1H), 7.52 (m, 2H), 7.26 (d, *J* = 8.5 Hz, 1H), 7.01 (m, 2H), 4.11 (d, *J* = 15.4 Hz, 1H), 3.95 (d, *J* = 15.4 Hz, 1H), 2.41 (m, 2H), 0.78 (t, *J* = 7.0 Hz, 3H); MS (ES) *m/z* 400 ([M−H]$^-$).

4.1.24. 3-(5-Ethyl-2-oxo-5-thiophen-2-yl-1,2,3,5-tetrahydro-benzo[*e*][1,4]oxazepin-7-yl)-5-fluoro-benzonitrile (10n)

Prepared from **9c** and 5-fluoro-3-cyanophenyl boronic acid using the coupling procedure described in example **10a**. ^{1}H NMR (DMSO-d_6): δ 10.12 (s, 1H), 8.07 (s, 1H), 7.95 (dt, *J* = 10.3, 2.0 Hz, 1H), 7.81 (m, 2H), 7.69 (d, *J* = 2.0 Hz, 1H), 7.57 (dd, *J* = 5.0, 0.9 Hz, 1H), 7.29 (d, *J* = 8.5 Hz, 1H), 7.01 (m, 1H), 6.95 (m, 1H), 4.10 (d, *J* = 15.5 Hz, 1H), 4.01 (d, *J* = 15.5 Hz, 1H), 2.65 (m, 2H), 0.78 (t, *J* = 7.0 Hz, 3H); MS (ES) *m/z* 391 ([M−H]$^-$).

4.1.25. *N*-[4-Bromo-2-(1-hydroxy-1-thien-2-ylbutyl)phenyl]-2-chloroacetamide (8d)

Prepared from the 5-bromoanthranilic acid according to the procedures described in examples **6a**, **7b**, and **8a**. ^{1}H NMR (DMSO-d_6): δ 10.93 (s, 1H), 8.06 (d, *J* = 8.5 Hz, 1H), 7.47 (dd, *J* = 8.8, 2.3 Hz, 1H), 7.41 (m, 2H), 7.15 (s, 1H), 6.94 (m, 2H), 4.28 (m, 2H), 2.15–2.40 (m, 2H), 1.25–1.40 (m, 2H), 0.88 (t, *J* = 7.3 Hz, 3H). MS (ESI) *m/z* 400/402 ([M−H]$^-$). Anal. Calcd for

$C_{16}H_{17}BrClNO_2S$: C, 47.72; H, 4.25; N, 3.48. Found: C, 47.76; H, 4.39; N, 3.46.

4.1.26. 7-Bromo-5-propyl-5-thien-2-yl-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one (9d)

Prepared from **8d** according to the procedure described in example **9a**. A white solid: ^{1}H NMR (DMSO-d_6): δ 10.06 (s, 1H), 7.58 (dd, *J* = 5.1, 1.1 Hz, 1H), 7.45 (dd, *J* = 8.7, 2.2 Hz, 1H), 7.36 (d, *J* = 2.3 Hz, 1H), 7.12 (d, *J* = 8.7 Hz, 1H), 7.03 (dd, *J* = 5.1, 3.6 Hz, 1H), 6.92 (dd, *J* = 3.6, 1.1 Hz, 1H), 4.08 (d, *J* = 15.4 Hz, 1H), 3.91 (d, *J* = 15.3 Hz, 1H), 2.32 (m, 2H), 1.43 (m, 1H), 0.92 (m, 1H), 08.84 (t, *J* = 7.2 Hz, 3H); MS (ESI) *m/z* 366/368 ([M+H]$^+$); MS (ESI) *m/z* 364/366 ([M−H]$^-$); Anal. Calcd for $C_{16}H_{16}BrNO_2S$: C, 52.47; H, 4.40; N, 3.82. Found: C, 52.37; H, 4.21; N, 3.77.

4.1.27. 7-(3-Chloro-4-fluorophenyl)-5-propyl-5-thien-2-yl-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one (10o)

Prepared from **9d** and 3-chloro-4-fluorophenyl boronic acid using the procedure described in example **10a**. A white solid: mp 183–184 °C; ^{1}H NMR (DMSO-d_6): δ 10.07 (s, 1H), 7.83 (dd, *J* = 7.1, 2.2 Hz, 1H), 7.51–7.68 (m, 4H), 7.47 (t, *J* = 9.0 Hz, 1H), 7.24 (d, *J* = 8.5 Hz, 1H), 7.02 (t, *J* = 5.0 Hz, 1H), 6.96 (dd, *J* = 3.5, 1.0 Hz, 1H), 4.09 (d, *J* = 15.3 Hz, 1H), 3.90 (d, *J* = 15.3 Hz, 1H), 2.45 (m, 2H), 1.48 (m, 1H), 0.98 (m, 1H), 0.86 (t, *J* = 7.2 Hz, 3H). MS (ESI) *m/z* 415/417 ([M−H]$^-$).

4.1.28. *N*-[4-Bromo-2-(1-hydroxy-2-methyl-1-thien-2-ylpropyl)phenyl]-2-chloroacetamide (8e)

Prepared from (2-amino-5-bromophenyl)(2-thienyl)methanone (6b) in two steps using the procedures described in examples **7b** and **8a**. ^{1}H NMR (DMSO-d_6): δ 11.25 (s, 1H), 8.14 (d, *J* = 8.8 Hz, 1H), 7.50 (d, *J* = 2.3 Hz, 1H), 7.46 (dd, *J* = 8.8, 2.3 Hz, 1H), 7.40 (dd, *J* = 5.0, 1.1 Hz, 1H), 7.02 (d, *J* = 3.5, 1.1 Hz, 1H), 6.96 (m, 2H), 4.36 (d, *J* = 15.0 Hz, 1H), 4.30 (d, *J* = 15.0 Hz, 1H), 2.86 (m, 1H), 0.94 (dd, *J* = 22.0, 6.6 Hz, 6H); MS (ES) *m/z* 400 ([M−H]$^-$); Anal. Calcd for $C_{16}H_{17}BrClNO_2S$: C, 47.72; H, 4.25; N, 3.48. Found: C, 47.89; H, 4.14; N, 3.37.

4.1.29. 7-Bromo-5-isopropyl-5-thien-2-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one (9e)

Prepared from *N*-[4-bromo-2-(1-hydroxy-2-methyl-1-thien-2-ylpropyl)phenyl]-2-chloroacetamide using the procedure described in example **9a**. ^{1}H NMR (DMSO-d_6): δ 10.01 (s, 1H), 7.56 (dd, *J* = 4.9, 1.0 Hz, 1H), 7.52 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.44 (d, *J* = 2.2 Hz, 1H), 7.10 (d, *J* = 8.6 Hz, 1H), 7.03 (m, 2H), 4.22 (d, *J* = 14.4 Hz, 1H), 3.87 (d, *J* = 14.4 Hz, 1H), 2.69 (m, 1H), 0.93 (dd, *J* = 17.8, 6.8 Hz, 6H); MS (ES) *m/z* 364 ([M−H]$^-$).

4.1.30. 7-(3-Chloro-4-fluorophenyl)-5-isopropyl-5-thien-2-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one (10p)

Prepared from **9e** and 3-chloro-4-fluorophenyl boronic acid using the coupling procedure described in example **10a**. ^{1}H NMR (DMSO-d_6): δ 10.02 (s, 1H), 7.83 (dd, *J* = 7.1, 2.2 Hz, 1H), 7.67 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.60 (m, 2H), 7.53 (m, 1H), 7.52 (m, 1H), 7.23 (d, *J* = 8.5 Hz, 1H), 7.05 (dd, *J* = 3.6, 1.3 Hz, 1H), 7.02 (dd, *J* = 5.0, 3.7 Hz, 1H), 4.21 (d, *J* = 14.4 Hz, 1H), 3.90 (d, *J* = 14.4 Hz, 1H), 2.81 (m, 1H), 0.91 (m, 6H); Anal. Calcd for $C_{22}H_{19}ClFNO_2S$: C, 63.53; H, 4.60; N, 3.37. Found: C, 63.34; H, 4.92; N, 2.97.

4.1.31. 3-Fluoro-5-(5-isopropyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)benzonitrile (10q)

Prepared from **9e** and 3-cyano-5-fluorophenyl boronic acid using the coupling procedure described in example **10a**. ^{1}H NMR (DMSO-d_6): δ 10.07 (s, 1H), 8.03 (s, 1H), 7.90 (m, 1H), 7.84 (m, 1H), 7.77 (m, 2H), 7.51 (dd, *J* = 5.0, 1.2 Hz, 1H), 7.24 (d, *J* = 8.5 Hz, 1H), 7.04 (m, 2H), 4.20 (d, *J* = 14.4 Hz, 1H), 3.96 (d, *J* = 14.4 Hz, 1H), 2.90 (m, 1H), 0.92 (t, *J* = 6.4 Hz, 6H); MS (ES) *m/z* 407 ([M+H]$^+$).

4.1.32. *N*-[4-Bromo-2-(1-hydroxy-1-thien-3-ylpropyl)phenyl]-2-chloroacetamide (8f)

Prepared from 1-(2-amino-5-bromophenyl)-propan-1-one using the procedure described in examples **7b** and **8a**. ^{1}H NMR (DMSO-d_6): δ 10.95 (s, 1H), 8.05 (dd, *J* = 6.8, 2.9 Hz, 1H), 7.47 (m, 2H), 7.42 (m, 1H), 7.40 (m, 1H), 6.88 (dd, *J* = 4.9, 1.0 Hz, 1H), 6.74 (s, 1H), 4.32 (d, *J* = 31.7, 1H), 4.25 (d, *J* = 31.7 Hz, 1H), 2.30 (m, 2H), 0.82 (t, *J* = 7.3 Hz, 3H); MS (ES) *m/z* 386 ([M+H]$^+$); Anal. Calcd for $C_{15}H_{15}BrClNO_2S$: C, 46.35, H, 3.89, N, 3.60. Found: C, 46.03, H, 3.73, N, 3.55.

4.1.33. 7-Bromo-5-ethyl-5-thien-3-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one (9f)

Prepared from **8f** using the procedure described in example **9a**. ^{1}H NMR (DMSO-d_6): δ 10.03 (s, 1H), 7.57 (dd, *J* = 4.9, 3.0 Hz, 1H), 7.45 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.28 (d, *J* = 2.2 Hz, 1H), 7.26 (dd, *J* = 2.7, 1.4 Hz, 1H), 7.12 (dd, *J* = 5.2, 1.4 Hz, 1H), 7.10 (d, *J* = 8.5 Hz, 1H), 4.05 (d, *J* = 15.4 Hz, 1 H), 3.93 (d, *J* = 15.4 Hz, 1H), 2.51 (m, 1H), 2.20 (m, 1H), 0.73 (t, *J* = 7.1 Hz, 3H); MS (ES) *m/z* 352 ([M+H]$^+$); Anal. Calcd for $C_{15}H_{14}BrNO_2S$: C, 51.15, H, 4.01, N, 3.98. Found: C, 51.38, H, 4.09, N, 3.82.

4.1.34. 7-(3-Chloro-4-fluorophenyl)-5-ethyl-5-thien-3-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one (10r)

Prepared from **9f** and 3-chloro-4-fluorophenyl boronic acid using the coupling procedure described in example **10a**. ^{1}H NMR (DMSO-d_6): δ 10.03 (s, 1H), 7.84 (dd, *J* = 6.9, 2.2 Hz, 1H), 7.62 (m, 2H), 7.56 (dd, *J* = 5.2, 3.0 Hz, 1H), 7.48 (m, 2H), 7.27 (m, 1H), 7.24 (d, *J* = 8.5 Hz, 1H), 7.16 (dd, *J* = 5.2, 1.4 Hz, 1H), 4.04 (d, *J* = 15.4 Hz, 1H), 3.94 (d, *J* = 15.4 Hz, 1H), 2.53 (m, 1H), 2.35 (m, 1H), 0.75 (t, *J* = 7.1 Hz, 3H); MS (ES) *m/z* 402 ([M+H]$^+$).

4.1.35. 3-(5-Ethyl-2-oxo-5-thien-3-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-5-fluorobenzonitrile (10s)

Prepared from **9f** and 3-cyano-5-fluorophenyl boronic acid using the coupling procedure described in example **10a**. ^{1}H NMR (DMSO-d_6): δ 10.07 (s, 1H), 8.07 (t, *J* = 1.5 Hz, 1H), 7.94 (dt, *J* = 10.3, 2.0 Hz, 1H), 7.80 (m, 1H), 7.73 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.63 (d, *J* = 2.4 Hz, 1H), 7.57 (dd, *J* = 4.9, 2.9 Hz, 1H), 7.27 (m, 2H), 7.17 (dd, *J* = 4.9, 1.5 Hz, 1H), 4.02 (d, *J* = 15.6 Hz, 1H), 3.96 (d, *J* = 15.6 Hz, 1H), 2.54 (m, 1H), 2.49 (m, 1H), 0.74 (t, *J* = 7.3 Hz, 3H); MS (ES) *m/z* 393 ([M+H]$^+$).

4.1.36. *N*-{4-Bromo-2-[1-(2-furyl)-1-hydroxypropyl]phenyl}-2-chloroacetamide (8g)

Prepared from 1-(2-amino-5-bromophenyl)-propan-1-one in two steps using the procedure described in examples 7b and **8a**. ^{1}H NMR (DMSO-d_6): δ 10.96 (s, 1H), 8.11 (d, *J* = 8.8 Hz, 1H), 7.60 (d, *J* = 1.0 Hz, 1H), 7.49 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.11 (d, *J* = 2.0 Hz, 1H), 6.95 (s, 1H), 6.47 (m, 2H), 4.35 (s, 2H), 2.23 (q, 7.3 Hz, 2H), 0.82 (t, *J* = 7.3 Hz, 3H); MS (ES) *m/z* 372 ([M−H]$^-$).

4.1.37. 7-Bromo-5-ethyl-5-(2-furyl)-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one (9g)

Prepared from **8g** using the procedure described in example **9a**. ^{1}H NMR (DMSO-d_6): δ 10.08 (s, 1H), 7.72 (t, *J* = 1.0 Hz, 1H), 7.47 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.17 (d, *J* = 2.4 Hz, 1H), 7.12 (d, *J* = 8.8 Hz, 1H), 6.48 (dd, *J* = 2.4, 1.0 Hz, 1H), 6.34 (d, *J* = 2.4 Hz, 1H), 4.21 (d, *J* = 15.1 Hz, 1H), 3.95 (d, *J* = 15.1 Hz, 1H), 2.45 (m, 1H), 2.10 (m, 1H), 0.73 (t, *J* = 7.3 Hz, 3H); MS (ES) *m/z* 336 ([M+H]$^+$).

4.1.38. 7-(3-Chloro-4-fluorophenyl)-5-ethyl-5-(2-furyl)-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one (10t)

Prepared from **9g** and 3-chloro-4-fluorophenyl boronic acid using the procedure described in example **10a**. ^{1}H NMR (DMSO-d_6): δ 10.08 (s, 1H), 8.32 (s, 1H), 7.81 (dd, J = 7.1, 2.5 Hz, 1H), 7.72 (s, 1H), 7.63 (dd, J = 8.5, 2.2 Hz, 1H), 7.47 (t, J = 9.0 Hz, 1H), 7.33 (d, J = 2.2 Hz, 1H), 7.25 (d, J = 8.5 Hz, 1H), 6.47 (m, 1H), 6.32 (d, J = 3.3 Hz, 1H), 4.19 (d, J = 15.4 Hz, 1H), 3.95 (d, J = 15.4 Hz, 1H), 2.52 (m, 1H), 2.26 (m, 1H), 0.75 (t, J = 7.1 Hz, 3H); MS (ES) *m/z* 386 ([M+H]$^+$).

4.1.39. 3-[5-Ethyl-5-(2-furyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-5-fluorobenzonitrile (10u)

Prepared from **9g** and 3-cyano-5-fluorophenyl boronic acid according to the coupling procedure described in example **10a**. ^{1}H NMR (DMSO-d_6): δ 10.13 (s, 1H), 8.03 (s, 1H), 7.90 (dt, J = 10.5, 2.2 Hz, 1H), 7.80 (m, 1H), 7.74 (m, 2H), 7.52 (d, J = 2.2 Hz, 1H), 7.28 (d, J = 8.5 Hz, 1H), 6.46 (m, 1H), 6.29 (d, J = 3.3 Hz, 1H), 4.14 (d, J = 15.6 Hz, 1H), 3.96 (d, J = 15.6 Hz, 1H), 2.54 (m, 1H), 2.49 (m, 1H), 0.75 (t, J = 7.4 Hz, 3H); MS (ES) *m/z* 753 (2M+H)$^+$.

4.1.40. *N*-[4-Bromo-2-[di(2-furyl)(hydroxy)methyl]phenyl]-2-chloroacetamide (8h)

To a solution of furan (369.6 g, 5.4 mol) in anhydrous THF (250 mL) was added at 0 °C *n*-butyllithium (2.5 M in hexane, 217 mL, 543 mmol) under nitrogen. The mixture was stirred for 30 min and treated with a solution of methyl 2-amino-5-bromobenzoate (25.0 g, 108.7 mmol) in THF (150 mL). The mixture was stirred for overnight and treated with an ice-cold saturated aqueous ammonium chloride solution (200 mL). Ethyl acetate (500 mL) was added and organic layer was separated, dried ($MgSO_4$) and concentrated. The residue was triturated in a mixture of hexane and ethyl acetate to afford (2-amino-5-bromophenyl)[di(2-furyl)]methanol as an orange solid (32.7 g, 90%). The title compound was prepared according to the procedure described in example **8a**. ^{1}H NMR (DMSO-d_6): δ 10.4 (s, 1H), 8.06 (d, J = 8.79 Hz, 1H), 8.04 (s, 1H), 7.70–7.71 (m, 2H), 7.55 (dd, J = 8.79, 2.44 Hz, 1H), 6.67 (d, J = 2.44 Hz, 1H), 6.49–6.50 (m, 2H), 6.23–6.24 (m, 2H), 4.23 (s, 2H); MS (ES) *m/z* 408/410 ([M−H]$^-$).

4.1.41. 7-Bromo-5,5-di(2-furyl)-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one (9h)

Prepared from **8h** using the procedure described in example **9a**. ^{1}H NMR (DMSO-d_6): δ 10.27 (s, 1H), 7.78 (d, J = 0.98 Hz, 2H), 7.52 (dd, J = 8.79, 2.44 Hz, 1H), 7.18 (d, J = 8.79 Hz, 1 H), 6.73 (d, J = 2.44 Hz, 1H), 6.51 (dd, J = 3.42, 1.95 Hz, 2H), 6.24 (dd, J = 3.42, 0.98 Hz, 2H), 4.1 (s, 2H); MS (ES) *m/z* 372/374 ([M−H]$^-$); MS (ES) *m/z* 374/376 ([M+H]$^+$).

4.1.42. 3-[5,5-Di(2-furyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-5-fluorobenzonitrile (10v)

Prepared from **9h** and 3-cyano-5-fluorobenzeneboronic acid according to the coupling procedure of example **10a**. ^{1}H NMR (DMSO-d_6): δ 10.34 (s, 1H), 7.73–7.87 (m, 5H), 7.59 (dt, J = 10.25, 1.95 Hz, 1H), 7.35 (d, J = 8.3 Hz, 1H), 6.98 (d, J = 1.95 Hz, 1H), 1H, 6.52 (dd, J = 3.42, 1.95 Hz, 2H), 6.29 (dd, J = 3.42, 0.98 Hz, 2H), 4.16 (s, 2H); MS (ESI) *m/z* 415 ([M+H]$^+$); MS (ESI) *m/z* 413 ([M−H]$^-$).

4.1.43. 7-(3-Chloro-4-fluorophenyl)-5,5-di(2-furyl)-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one (10w)

Prepared from **9h** and 3-chloro-4-fluorophenyl boronic acid according to the coupling procedure of example **10a**. ^{1}H NMR (DMSO-d_6): δ 10.28 (s, 1H), 7.77 (dd, J = 1.95, 0.98 Hz, 2H), 7.66 (dd, J = 8.3, 1.95 Hz, 1H), 7.59 (dd, J = 7.32, 2.44 Hz, 1H), 7.45 (dd, $J_{HF} = J_{HH}$ = 8.79 Hz, 1H), 7.33–7.36 (m, 1H), 7.32 (d, J = 8.79 Hz, 1H), 6.89 (d, J = 2.44 Hz, 1H), 6.51 (dd, J = 3.42, 1.95 Hz, 2H), 6.27 (dd, J = 3.42, 0.98 Hz, 2H), 4.17 (s, 2H); MS (ESI) *m/z* 422/424 ([M−H]$^-$).

4.1.44. (2-Amino-5-bromophenyl)(dithien-2-yl)methanol (7c)

Prepared from methyl 2-amino-5-bromobenzoate and 2-thienyllithium using the procedure similar to example **8h**. ^{1}H NMR ($CDCl_3$): δ 7.35 (dd, J = 5.3, 1.1 Hz, 2H), 7.26 (dd, J = 8.4, 2.3 Hz, 1H), 6.98 (m, 2H), 6.82 (d, J = 2.3 Hz, 1H), 6.79 (m, 2H), 6.62 (d, J = 8.4 Hz, 1H), 5.45 (br s, 1H), 3.86 (br s, 2H).

4.1.45. 2-Bromo-*N*-{4-bromo-2-[hydroxy(dithien-2-yl)methyl]phenyl}acetamide (8i)

Prepared from **7c** and bromoacetyl chloride using the procedure described in example **8a**. ^{1}H NMR (DMSO-d_6): δ 10.22 (s, 1H), 8.42 (s, 1H), 8.05 (d, J = 9.0 Hz, 1H) 7.59 (m, 3H), 7.05 (m, 2H), 6.87 (m, 2H), 6.78 (d, J = 3 Hz, 1H), 3.92 (s, 2H); MS (ES) *m/z* 484 ([M−H]$^-$).

4.1.46. 7-Bromo-5,5-dithien-2-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one (9i)

Prepared from **8i** using the similar procedure described in example **9a**. ^{1}H NMR ($CDCl_3$): δ 8.08 (br s, 1H), 7.40 (d, J = 4.0 Hz, 2H), 7.37 (d, J = 2.1 Hz, 1H), 7.14 (d, J = 2.2 Hz, 1H), 6.99 (m, 2H), 6.89 (d, J = 3.6 Hz, 2H), 6.83 (d, J = 8.5 Hz, 1H), 4.35 (s, 1H); MS (ES) *m/z* 404 ([M−H]$^-$); Anal. Calcd for $C_{17}H_{12}BrNO_2S_2$: C, 50.25; H, 2.98; N, 3.45. Found: C, 50.57; H, 3.01; N, 3.25.

4.1.47. 3-Fluoro-5-(2-oxo-5,5-dithien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)benzonitrile (10x)

Prepared from **9i** and 3-cyano-5-fluorophenyl boronic acid using the coupling procedure described in example **10a**. ^{1}H NMR (DMSO-d_6): δ 10.32 (s, 1H), 7.81 (m, 3H), 7.63 (m, 3H), 7.30 (m, 2H), 7.05 (m, 4H), 4.21 (s, 2H); MS (ES) *m/z* 445 ([M−H]$^-$).

4.1.48. 7-(3-Chloro-4-fluorophenyl)-5,5-dithien-2-yl-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one (10y)

Prepared from **9i** and 3-chloro-4-fluorophenyl boronic acid using the coupling procedure described in example **10a**. ^{1}H NMR (DMSO-d_6): δ 10.27 (s, 1H), 7.68 (m, 4H), 7.48 (t, J = 8.8 Hz, 1H), 7.38 (m, 1H), 7.27 (d, J = 8.5 Hz, 1H), 7.16 (d, J = 2.1 Hz, 1H), 7.04 (dd, J = 5.0, 3.6 Hz, 2H), 6.93 (dd, J = 3.6, 1.2 Hz, 2H), 4.22 (s, 2H); MS (ES) *m/z* 456 ([M+H]$^+$); Anal. Calcd for $C_{23}H_{15}ClFNO_2S_2$: C, 60.59; H, 3.32; N, 3.07. Found: C, 60.35; H, 3.28; N, 2.91.

4.1.49. 7-(3-Chloro-4-fluorophenyl)-5,5-diphenyl-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one (10z)

Prepared from 7-bromo-5,5-diphenyl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one (**9j**, prepared in a similar manner as that for compound **9i**) and 3-chloro-4-fluoro benzeneboronic acid according to the coupling procedure described in example **10a**. ^{1}H NMR (DMSO-d_6): δ 10.17 (s, 1H), 7.65 (dd, J = 8.3, 2.44 Hz, 1H), 7.50 (dd, J = 7.32, 2.44 Hz, 1H), 7.34–7.43 (m, 7H), 7.25 (d, J = 8.3 Hz, 1H), 7.22–7.24 (m, 1H), 7.16–7.19 (m, 4H), 6.75 (d, 1.95 Hz, 1 H), 4.26 (s, 2H); MS (ESI) *m/z* 442/444 ([M−H]$^-$); Anal. Calcd for $C_{27}H_{19}ClFNO_2$: C, 73.06; H, 4.31; N, 3.16. Found: C, 72.67; H, 4.36; N, 2.89.

4.1.50. 7-(3-Chloro-4-fluorophenyl)-5,5-bis(4-chlorophenyl)-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one (10aa)

Prepared from 7-bromo-5,5-bis(4-chlorophenyl)-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one (**9k**, prepared in a similar manner as that for compound **9i**) and 3-chloro-4-fluorobenzeneboronic acid according to the coupling procedure described in example **10a**. ^{1}H NMR (DMSO-d_6): δ 10.17 (s, 1H), 7.69 (dd, J = 8.3, 2.4 Hz, 1H), 7.58 (dd, J = 6.8, 2.4 Hz, 1H), 7.46 (m, 5H), 7.31 (m, 1H), 7.24 (d, J = 8.3 Hz, 1H), 7.22 (m, 4H), 6.78 (d, J = 2.0 Hz, 1H), 4.23 (s, 2H);

MS (ES) *m/z* 510 ([M−H]$^-$); Anal. Calcd for $C_{27}H_{17}Cl_3FNO_2$: C, 63.24; H, 3.34; N, 2.73. Found: C, 62.75; H, 3.58; N, 2.72.

4.1.51. 3-[5,5-Bis(4-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-5-fluorobenzonitrile (10ab)

Prepared from 7-bromo-5,5-bis(4-chlorophenyl)-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one (**9k**) and 5-fluoro-3-cyanobenzeneboronic acid according to the coupling procedure described in example **10a**. ^{1}H NMR (DMSO-d_6): δ 10.24 (s, 1H), 7.79 (m, 3H), 7.59 (dt, *J* = 9.8, 2.0 Hz, 1H), 7.46 (m, 4H), 7.28 (d, *J* = 8.3 Hz, 1H), 7.26 (m, 4H), 6.93 (d, *J* = 2.0 Hz, 1H), 4.20 (s, 2H); MS (ES) *m/z* 501 ([M−H]$^-$); Anal. Calcd for $C_{28}H_{17}Cl_2FN_2O_2$: C, 66.81; H, 3.40; N, 5.57. Found: C, 66.46; H, 3.43; N, 5.48.

4.1.52. 3-[5,5-Bis(4-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-5-fluorobenzonitrile (10ac)

To a stirred solution of 7-bromo-5-ethyl-5-(2-furyl)-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one (**9g**, 5.0 g, 14.8 mmol) in DMF (100 mL) were added potassium acetate (4.5 g, 44.4 mmol), bis(pinacolato)diboron (7.5 g, 29.6 mmol), and [1,1′-bis(diphenylphosphino)-ferrocene]dichloropalladium (II) (0.6 g, 0.8 mmol) at rt under nitrogen. The mixture was heated at reflux under nitrogen overnight. The solution was allowed to cool to room temperature and partitioned between ammonium chloride solution (sat.) (100 mL) and ethyl acetate (150 mL). The aqueous layer was extracted with ethyl acetate (3 × 50 mL). The organic layers were combined, dried over magnesium sulfate, filtered through silica gel and triturated with ether to give 5-ethyl-5-(2-furyl)-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one as a white solid (2.9 g, 50%). ^{1}H NMR (DMSO-d_6): δ 10.08 (s, 1H), 7.71 (s, 1H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.33 (s, 1H), 7.16 (d, *J* = 8.1 Hz, 1 H), 6.48 (d, *J* = 3.2 Hz, 1H), 6.30 (d, *J* = 3.2 Hz, 1H), 4.21 (d, *J* = 15.4 Hz, 1H), 4.04 (d, *J* = 15.4 Hz, 1H), 2.45 (m, 1H), 2.00 (m, 1H), 1.25 (s, 8H), 0.71 (t, *J* = 7.1 Hz, 3H); MS (ES) *m/z* 384 ([M+H]$^+$).

The title compound **10ac** was prepared from 5-ethyl-5-(2-furyl)-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one and 4-bromo-furan-2-carbonitrile using the coupling procedure described in example **10a**. ^{1}H NMR (DMSO-d_6): δ 10.02 (s, 1H), 8.55 (d, *J* = 2.2 Hz, 1H), 8.10 (d, *J* = 2.0 Hz, 1H), 7.71 (d, *J* = 1.9 Hz, 1H), 7.58 (m, 1H), 7.41 (s, 1H), 7.24 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.45 (s, 1H), 6.25 (d, *J* = 2.7 Hz, 1H), 4.11 (d, *J* = 15.6 Hz, 1H), 3.96 (d, *J* = 15.6 Hz, 1H), 2.50 (m, 1H), 2.33 (m, 1H), 0.75 (m, 3H); MS (ES) *m/z* 349 ([M+H]$^+$); Anal. Calcd for $C_{20}H_{16}N_2O_4$: C, 68.96; H, 4.63; N, 8.04. Found: C, 68.38; H, 4.73; N, 7.84.

4.1.53. 4-(5-Ethyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)thiophene-2-carbonitrile (10ad)

Prepared from 7-bromo-5-ethyl-5-thien-2-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one (**9c**) and 4-bromo-2-cyanothiophene according to the procedures described in example **10ac**. A yellowish solid: mp 202–204 °C; ^{1}H NMR (DMSO-d_6): *δ* 10.06 (s, 1H), 8.48 (s, 1H), 8.33 (s, 1H), 7.64–7.7 (m, 2H), 7.55 (d, *J* = 5.0 Hz, 1H), 7.23 (d, *J* = 8.48 Hz, 1H), 6.92–7.03 (m, 2H), 4.06 (d, *J* = 15.52 Hz, 1H), 3.94 (d, *J* = 15.44 Hz, 1H), 3.37 (m, 1H), 2.5 (m, 1H), 0.76 (t, *J* = 6.79 Hz, 1H); MS (ESI) *m/z* 381 ([M+H]$^+$); MS (ESI) *m/z* 379 ([M−H]$^-$); Anal. Calcd for $C_{20}H_{16}N_2O_2S_2$: C, 63.14; H, 4.24; N, 7.36. Found: C, 62.53; H, 4.25; N, 7.12.

4.1.54. 7-(3,5-Difluorophenyl)-5,5-dimethyl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-thione (11a)

To a solution of 7-(3,5-difluorophenyl)-5,5-dimethyl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one (**10f**) (0.4 g, 1.3 mmol) in a mixture of toluene (20 mL) and THF (10 mL, help to dissolve the starting material) was added the Lawesson's reagent (0.3 g, 0.71 mmol) at rt under nitrogen. The mixture was heated at 100 °C for 10 min, cooled to rt, and concentrated. The residue was purified by a flash chromatography on silica gel column (hexane:THF/4:1) to give the title compound as a yellowish solid (0.25 g, 59%). ^{1}H NMR (DMSO-d_6): δ 12.01 (s, 1H), 7.70–7.63 (m, 2H), 7.59–7.48 (m, 2H), 7.41 (d, *J* = 8.82 Hz, 1H), 7.28–7.18 (m, 1H), 4.51 (s, 2H), 1.62 (s, 6H); MS (FI) *m/z* 318 ([M−H]$^-$).

4.1.55. 3-Fluoro-5-(5-isopropyl-5-thien-2-yl-2-thioxo-1,2,3,5-tetrahydo-4,1-benzoxazepin-7-yl)benzonitrile (11b)

Prepared by heating a mixture of 3-fluoro-5-(5-isopropyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1- benzoxazepin-7-yl)benzonitrile (**10q**) and Lawesson's reagent at reflux in toluene according to example **11a**. ^{1}H NMR (DMSO-d_6): δ 12.09 (s, 1H), 8.1 (s, 1H), 7.96 (d, *J* = 10.1 Hz, 1H), 7.88 (m, 2H), 7.83 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.48 (dd, *J* = 4.9, 0.66 Hz, 1H), 7.40 (d, *J* = 8.5 Hz, 1H), 7.03 (d, *J* = 2.6 Hz, 1H), 7.00 (m, 1H), 4.48 (d, *J* = 14.1 Hz, 1H), 4.37 (d, *J* = 14.1 Hz, 1H), 2.96 (m, 1H), 0.93 (d, *J* = 6.7 Hz, 3H), 0.87 (d, *J* = 6.5 Hz, 3H); MS (ES) *m/z* 421 ([M−H]$^-$).

4.1.56. 1-(2-Amino-5-bromophenyl)-2,2,3,3,3-pentafluoropropan-1-one (16)

A solution of BOC protected aniline (14.0 g, 72 mmol) in anhydrous ether (150 mL) at −15 °C under nitrogen was treated with a solution of *tert*-butyllithium (1.7 M in pentane, 106 mL, 183 mmol). The reaction mixture was stirred at −15 °C for 4 h, cooled to −78 °C, and treated with ethyl pentafluoropropionate (13 mL, 88 mmol). The mixture was allowed to slowly warm to rt and brine (500 mL) was added. The organic layer was separated, dried ($MgSO_4$), and concentrated. The residue was taken up in methylene chloride (100 mL) and treated with TFA (5 mL) at 0 °C under nitrogen. After 1.5 h, the solution was treated with a cold sodium bicarbonate solution (3 N, 100 mL) and organic layer was separated, dried ($MgSO_4$), and concentrated. The crude residue (5.0 g, 21 mmol) was then taken up in methylene chloride (80 mL) and treated with NBS (3.6 g, 20 mmol) in portions at rt under nitrogen. After 1 h, the solution was washed with aqueous 3 N sodium bicarbonate solution (3 × 20 mL), dried ($MgSO_4$), and concentrated to give 1-(2-amino-5-bromophenyl)-2,2,3,3,3-pentafluoropropan-1-one as a yellow solid (6.0 g, 25% in three steps). ^{1}H NMR (DMSO-d_6): *δ* 7.97 (s, 2H), 7.67 (d, *J* = 2.3 Hz, 1H), 7.56 (dd, *J* = 9.2, 2.2 Hz, 1H), 6.94 (d, *J* = 9.3 Hz, 1H); MS (ESI) *m/z* 318/320 ([M+H]$^+$); MS (ESI) *m/z* 316/318 ([M−H]$^-$).

4.1.57. *N*-{4-Bromo-2-[2,2,3,3,3-pentafluoro-1-(2-furyl)-1-hydroxypropyl]phenyl}-2-chloroacetamide (18)

To a solution of furan (13.0 g, 190 mmol) in anhydrous THF (150 mL) was added *n*-butyllithium (2.5 M in hexane, 40 mL, 100 mmol) at 0 °C under nitrogen. The solution was stirred at 0 °C for 30 min, cooled to −78 °C, and treated with a solution of 1-(2-amino-5-bromophenyl)-2,2,3,3,3-pentafluoropropan-1-one. The mixture was allowed to warm to −30 °C, a saturated ammonium chloride solution (100 mL) was added and mixture was warmed to rt. Ethyl acetate (300 mL) was added and organic layer separated, dried ($MgSO_4$), and concentrated. The residue was dissolved in anhydrous THF. The resultant solution was cooled to 0 °C, treated with triethylamine followed by addition of chloroacetyl chloride following the procedure described in example **8a** to give *N*-{4-bromo-2-[2,2,3,3,3-pentafluoro-1-(2-furyl)-1-hydroxypropyl]phenyl}-2-chloroacetamide as a white solid. ^{1}H NMR (DMSO-d_6): *δ* 10.54 (s, 1H), 9.11 (s, 1H), 8.18 (d, *J* = 9.0 Hz, 1H), 7.79 (m, 1H), 7.64 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.21 (d, *J* = 1.7 Hz, 1H), 6.71 (s, 1H), 6.58 (m, 1H), 4.35 (d, *J* = 1.5 Hz, 2H). MS (ESI) *m/z* 462/464 ([M+H]$^+$); MS (ESI) *m/z* 460/462 ([M−H]$^-$).

4.1.58. 7-Bromo-5-(2-furyl)-5-(pentafluoroethyl)-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one (19)

Prepared from *N*-{4-bromo-2-[2,2,3,3,3-pentafluoro-1-(2-furyl)-1-hydroxypropyl]phenyl}-2-chloroacetamide using the procedure described in example **9a**. ^{1}H NMR (DMSO-d_6): δ 10.33 (s, 1H), 7.93 (s, 1H), 7.68 (dd, *J* = 8.6, 2.0 Hz, 1H), 7.49 (s, 1H), 7.20 (d, *J* = 8.7 Hz, 1H), 6.75 (d, *J* = 2.9 Hz, 1H), 6.64 (m, 1H), 4.49 (d, *J* = 14.8 Hz, 1H), 4.14 (d, *J* = 14.9 hz, 1H); MS (ESI) *m/z* 426/428 ($[M+H]^+$); MS (ESI) *m/z* 424/426 ($[M-H]^-$).

4.1.59. 7-(3-Chloro-4-fluorophenyl)-5-(2-furyl)-5-(pentafluoroethyl)-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one (20a)

Prepared from 7-bromo-5-(2-furyl)-5-(pentafluoroethyl)-1,5-dihydro-4,1-benzoxazepin- 2(*H*)-one and 3-chloro-4-fluorophenyl boronic acid according to the coupling procedure described in example **10a**. ^{1}H NMR (DMSO-d_6): δ 10.36 (s, 1H), 7.93 (d, *J* = 1.3 Hz, 1H), 7.82 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.72 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.45–7.58 (m, 3H), 7.36 (d, *J* = 8.6 Hz, 1H), 6.78 (d, *J* = 3.4 Hz, 1H), 6.63 (dd, *J* = 3.5, 1.8 Hz, 1H), 4.49 (d, *J* = 14.8 Hz, 1H), 4.12 (d, *J* = 14.8 Hz, 1H); MS (ESI) *m/z* 474/476 ($[M-H]^-$).

4.1.60. 7-(3-Chloro-4-fluorophenyl)-5-(2-furyl)-5-(pentafluoroethyl)-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one (20b)

Prepared from 7-bromo-5-(2-furyl)-5-(pentafluoroethyl)-1,5-dihydro-4,1-benzoxazepin- 2(*H*)-one and 3-cyano-5-fluorophenyl boronic acid according to the coupling procedure described in example 1. ^{1}H NMR (DMSO-d_6): δ 10.41 (s, 1H), 7.84–7.94 (m, 4H), 7.76 (td, *J* = 10.1, 2.1 Hz, 1H), 7.68 (d, *J* = 1.7 Hz, 1H), 7.36 (d, J= 8.6 Hz, 1H), 6.84 (d, *J* = 3.4 Hz, 1H), 6.64 (dd, *J* = 3.4, 1.8 Hz, 1H), 4.45 (d, *J* = 14.9 Hz, 1H), 4.14 (d, J= 14.8 Hz, 1H); MS (ESI) *m/z* 467 ($[M+H]^+$); MS (ESI) *m/z* 465 ($[M-H]^-$); Anal. Calcd for $C_{22}H_{12}F_6N_2O_3$: C, 56.66; H, 2.59; N, 6.01. Found: C, 56.64; H, 2.85; N, 5.61.

4.1.61. 7-Bromo-5-methyl-1,3-dihydro-benzo[*e*][1,4]diazepin-2-one (22)

A mixture of 1-(2-amino-5-bromo-phenyl)-ethanone (8.0 g, 37 mmol) and glycine ethyl ester hydrogen chloride (6.7 g, 48 mmol) in pyridine was heated at reflux for 24 h under nitrogen. The reaction mixture was cooled, solvent removed, and residue was treated with a saturated aqueous ammonium chloride solution (200 mL). Ethyl acetate (300 mL) was added and organic layer was separated, dried ($MgSO_4$), concentrated, and the residue purified on silica gel column (hexane–ethyl acetate, 1:1) to give 7-bromo-5-methyl-1,3-dihydro-benzo[*e*][1,4]diazepin-2-one as a brown solid (1.5 g, 16%). ^{1}H NMR (DMSO-d_6): δ 10.49 (s, 1H), 7.92 (d, *J* = 2.0 Hz, 1 H), 7.66 (dd, *J* = 8.7, 2.1 Hz, 1 H), 7.08 (d, *J* = 8.7 Hz, 1H), 3.91 (s, 2H), 2.39 (s, 3H). MS (ESI) *m/z* 253/255 ($[M+H]^+$).

4.1.62. 7-(3-Chloro-4-fluorophenyl)-5-methyl-1,3-dihydro-*H*-1,4-benzodiazepin-2-one (23)

Prepared from 7-bromo-5-methyl-1,3-dihydro-benzo[*e*][1,4]-diazepin-2-one and 3-chloro-4-fluorophenyl boronic acid using the coupling procedure described in example **10a**. ^{1}H NMR (DMSO-d_6): δ 10.52 (s, 1H), 8.02 (d, *J* = 2.2 Hz, 1H), 7.99 (d, *J* = 2.1 Hz, 1H), 7.83 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.76 (m, 1H), 7.52 (t, *J* = 8.76 Hz, 1H), 7.20 (d, *J* = 8.5 Hz, 1H), 3.91 (s, 2H), 2.48 (s, 3H); MS (ESI) *m/z* 303/305 ($[M+H]^+$); MS (ESI) *m/z* 301/303 ($[M-H]^-$); Anal. Calcd for $C_{16}H_{12}ClFN_2O$: C, 63.48; H, 4.00; N, 9.25. Found: C, 63.16; H, 4.02; N, 8.85.

4.1.63. 7-(3-Chloro-4-fluorophenyl)-4,5,5-trimethyl-1,3,4,5-tetrahydro-*H*-1,4-benzodiazepin-2-one (24)

A mixture of 7-(3-chloro-4-fluorophenyl)-5-methyl-1,3-dihydro-*H*-1,4-benzodiazepin-2-one (0.4 g, 1.32 mmol) and iodomethane (0.13 mL, 2 mmol) in anhydrous acetonitrile (20 mL) was heated at 50 °C under nitrogen for 24 h. The solvent was removed and residue triturated in ethyl acetate to give 7-(3-chloro-4-fluorophenyl)-4,5-dimethyl-2-oxo-2,3-dihydro-*H*-1,4-benzodiazepin-4-ium as greenish solid (60 mg, 14%). ^{1}H NMR (DMSO-d_6): δ 11.52 (s, 1H), 8.24 (d, *J* = 2.0 Hz, 1H), 8.13 (dd, *J* = 5.2, 2.2 Hz, 1H), 8.06 (dd, *J* = 7.0, 2.3 Hz, 1 H), 7.81 (m, 1H), 7.58 (t, *J* = 9.0 Hz, 1H), 7.39 (d, *J* = 8.7 Hz, 1H), 4.48 (bs, 2H), 3.84 (s, 3H), 2.98 (s, 3H). MS (ESI) *m/z* 317/319 ($[M]^+$).

A mixture of 7-(3-chloro-4-fluorophenyl)-4,5-dimethyl-2-oxo-2,3-dihydro-*H*-1,4-benzodiazepin-4-ium (0.2 g, 0.63 mmol) and methyl magnesium bromide (1 mL in diethyl ether, 3 M, 3 mmol) in anhydrous diethyl ether (20 mL) was heated at reflux under nitrogen for 3 h. The reaction mixture was treated with a saturated aqueous ammonium chloride solution (30 mL). The organic layer was separated and aqueous layer was extracted with ethyl acetate (3 × 30 mL). The organic extracts were combined, dried ($MgSO_4$), concentrated, and residue purified on a silica gel column (hexane–ethyl acetate 3:1) to give the title compound as a white solid (11 mg, 5.2%). ^{1}H NMR (DMSO-d_6): δ 10.06 (s, 1H), 7.92 (dd, *J* = 7.1, 2.2 Hz, 1H), 7.68 (m, 1H), 7.45–7.53 (m, 3H), 7.26 (d, *J* = 8.2 Hz, 1H), 3.78 (s, 2H), 2.18 (s, 3H), 1.52 (s, 6H). MS (ESI) *m/z* 333/335 ($[M+H]^+$).

4.2. Steroid receptor (GAL-4) cross reactivity assays

Plasmids and cells: The ligand binding domains (LBD) of the GR (aa 485–777), MR (aa 669–984), ERα (aa 303–595), and AR (aa 644–920) were cloned into the pM GAL4-DBD vector (Clontech). For the AR two-hybrid assay, SRC-2 (aa 620–1121) was cloned into the pVP16 vector (Clontech). For the $GAL4_{UAS}$-luciferase reporter, 5 copies of the 17bp GAL_{UAS} sequence along with the E1b minimal TATA promoter were cloned into the pG5basic luciferase vector (Promega). Experiments were performed in COS-7 African green monkey kidney fibroblast-like cells (ATCC #CRL-1651) grown in phenol red-free Dulbecco's Modified Minimum Essential Medium (Gibco) supplemented with 10% charcoal/dextran-treated fetal bovine serum (Hyclone). GAL4 fusion assays.[20] The GAL4-steroid receptor LBD fusion plamid and $GAL4_{UAS}$-luciferase reporter plasmid (50 ng/well each) were transfected for 16 h into COS-7 cells using Fugene6 (0.5 μL/well) according to the manufacturer's protocol (Roche). In the AR assay the addition of VP16-SRC-2 was necessary for optimal response. Cells were treated with compounds for 20 h and luciferase activity was measured using Cell Culture Lysis Buffer and Luciferase Reagent (Promega) on a Victor2 luminometer (Perkin-Elmer).

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