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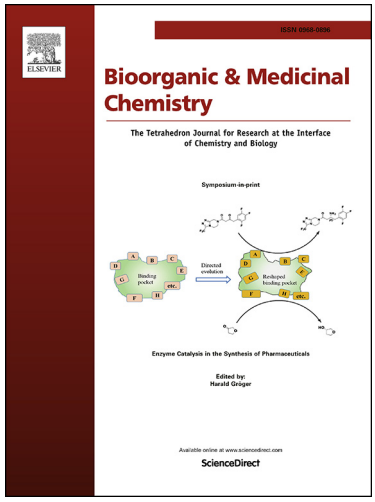

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Optimization of diarylpentadienones as chemotherapeutics for prostate cancer

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ABSTRACT: Our earlier studies indicate that (1*E*,4*E*)-1,5-bis(1-alkyl-1*H*-imidazol-2-yl)penta-1,4-diene-3-ones and (1*E*,4*E*)-1,5-bis(1-alkyl-1*H*-benzo[*d*] imidazol-2-yl)penta-1,4-diene-3-ones exhibit up to 121-fold greater antiproliferative potency than curcumin in human prostate cancer cell models, but only 2-10 fold increase in mouse plasma concentrations. The present study aims to further optimize them as anti-prostate cancer agents with both good potency and bioavailability. (1*E*,4*E*)-1,5-Bis(1*H*-imidazol-2-yl)penta-1,4-diene-3-one, the potential metabolic product of (1*E*,4*E*)-1,5-bis(1-alkyl-1*H*-imidazol-2-yl)penta-1,4-diene-3-ones, was synthesized and evaluated for its anti-proliferative activity. The promising potency of 1,5-bis(1-alkyl-1*H*-imidazol-2-yl)penta-1,4-diene-3-ones was completely abolished by removing the 1-alkyl group, suggesting the critical role of an appropriate group on the N1 position. We then envisioned that *N*-aryl substitution to exclude the C-H bond on the carbon adjacent to the *N*1 position (α-H) may increase the metabolic stability. Consequently, seven (1*E*,4*E*)-1,5-bis(1-aryl-1*H*-imidazol-2-yl)penta-1,4-dien-3-ones and three (1*E*,4*E*)-1,5-bis(1-aryl-1*H*-benzo[*d*]imidazol-2-yl)penta-1,4-dien-3-ones, as well as three (1*E*,4*E*)-1,5-bis(1-aryl-1*H*-pyrrolo[3,2-*b*]pyridine-2-yl)penta-1,4-dien-3-ones, were synthesized through a three-step transformation, including *N*-arylation via Ullmann condensation, formylation, and Horner-Wadsworth-Emmons reaction. Six optimal (1*E*,4*E*)-

1,5-bis(1-aryl-1*H*-imidazol-2-yl)penta-1,4-dien-3-ones exhibit 24- to 375-fold improved potency as compared with curcumin. Replacement of the imidazole with bulkier benzoimidazole and 4-azaindole results in a substantial decrease in the potency. (1*E*,4*E*)-1,5-Bis(1-(2-methoxyphenyl)-1*H*-imidazol-2-yl)penta-1,4-dien-3-one (**17d**) was established as an optimal compound with both superior potency and good bioavailability that is sufficient to provide the therapeutic efficacy necessary to suppress *in vivo* tumor growth.

Key words: diarylpentadienone, prostate cancer, antiproliferative activity, pharmacokinetic study

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1. Introduction

Diferuloylmethane (**1**, Figure 1), commonly known as curcumin, is a naturally occurring diarylheptanoid from the rhizomes of *Curcuma longa* L (turmeric) of the Zingiberaceae family. Turmeric, with curcumin as its major and active chemical component, has long been used as curry ingredient and as traditional medicines in China and India.[1] Curcumin was first revealed by Dorai and co-workers to have the capability of suppressing human prostate cancer proliferation and inducing prostate cancer apoptosis.[2-4] Additionally, the safety profile of curcumin in humans has been validated by the Food and Drug Administration (FDA) in the USA.[4-5] However, the low bioavailability of curcumin together with its moderate potency has hindered its clinical advancement.[6-7] The reported IC_{50} values of curcumin in suppressing cell proliferation against three prostate cancer cell lines (LNCaP, DU145, and PC-3) range from 2.0 μM to 39.6 μM.[2] A phase I trial indicates that curcumin concentration in plasma falls below the detection limit after oral administration of 450-3600 mg of curcumin daily.[7] One way to address these weaknesses is to develop analogs with improved potency and/or bioavailability.[2,8] For example, replacement of the unstable diketone moiety with monokeone leads to a 10-20 fold increase in *in vitro* potency.[2,8] Our earlier studies have identified (1*E*,4*E*)-1,5-diheteroarylpenta-1,4-diene-3-ones (**2**-**6**, Fig. 1) as the most impressive and promising class of curcumin-based anti-prostate cancer agents due to their superior *in vitro* potency in prostate cancer cell models.[9-10] The 1-alkyl-1*H*-imidazol-2-yl group in compounds **2**-**4** (Fig. 1) and the 1-alkyl-1*H*-benzo[*d*]imidazole-2-yl group in compounds **5**-**6** (Fig. 1) have been demonstrated to be significantly beneficial to the *in vitro* antiproliferative potency in three prostate cancer cell models.[10] The most potent compounds showed up to 121-fold improved anti-proliferative potency toward both androgen-dependent and androgen-independent prostate cancer cells. However, their bioavailability is only slightly increased, as evidenced by the 2-10 fold increase in mouse plasma concentration.[9-10]

The present study aims to further optimize (1*E*,4*E*)-1,5-bis(1-alkyl-1*H*)-imidzaole-2-yl)penta-1,4-diene-3-ones (e.g. **2**-**4**) and (1*E*,4*E*)-1,5-bis(1-alkyl-1*H*-benzo[d]imidazole-2-yl)penta-1,4-diene-3-ones

(e.g. **5**-**6**). New groups of 1,5-diheretoarylpenta-1,4-dien-3-ones (**7**) with the hope of integrating optimal potency and pharmacokinetic profile were thus designed by incorporating a metabolically stable group to the *N*1 position of imidazole and benzoimidazole moiety.

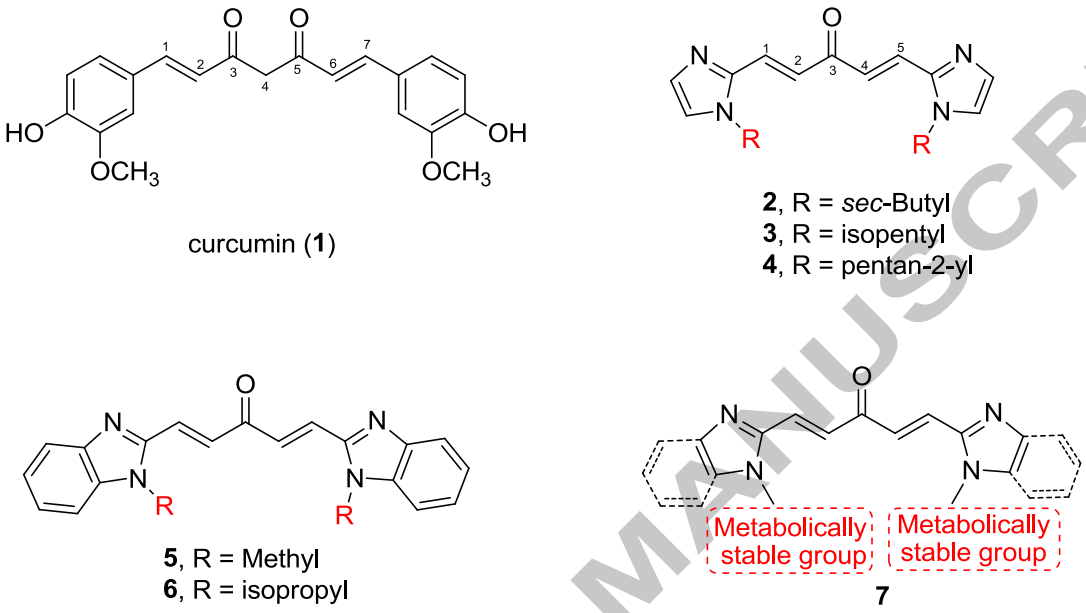


Fig. 1. Structures of curcumin and its mimics

2. Results and Discussion

2.1 Design, Synthesis, and Antiproliferative Activity of (1*E*,4*E*)-1,5-bis(1*H*-imidazol-2-yl)penta-1,4-diene-3-one (14):

To optimize the potency and bioavailability of 1,5-bis(1*H*-imidazol-2-yl)penta-1,4-dien-3-ones (**2**-**4**), we first evaluated the *in vitro* anti-proliferative potency of (1*E*,4*E*)-1,5-bis(1*H*-imidazol-2-yl)penta-1,4-diene-3-one (**14**). Compound **14** was first studied because it may be the metabolic product of 1,5-bis(1*H*-imidazol-2-yl)penta-1,4-dien-3-ones through *N*-dealkylation catalyzed by cytochrome P450[11] and it can be used to test the necessity of an 1-alkyl group for the *in vitro* potency. Consequently, we

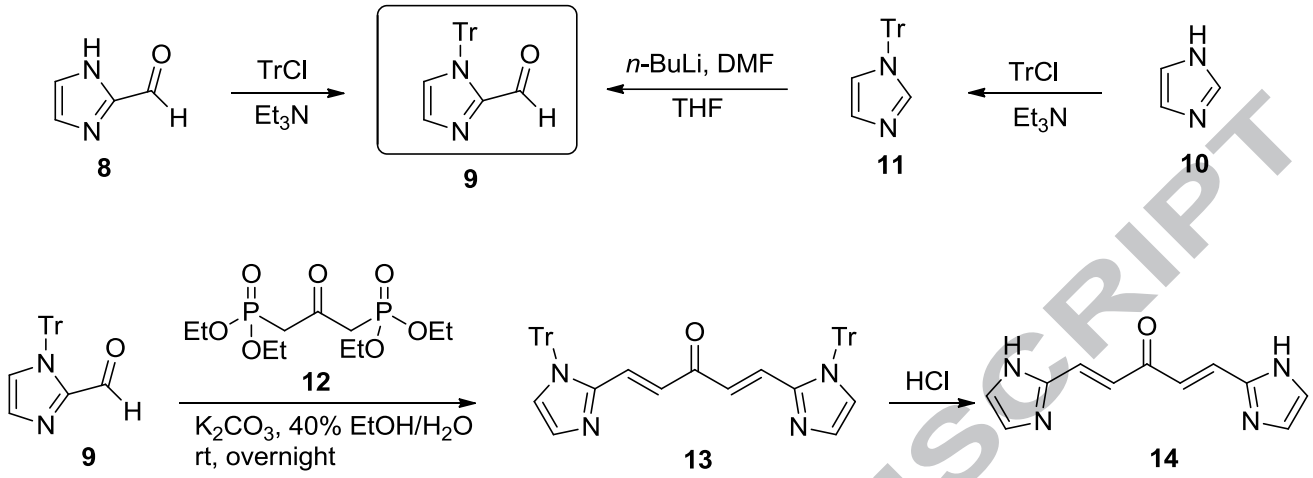
started our optimization with the synthesis and anti-proliferative evaluation of (1*E*, 4*E*)-1,5-bis(1*H*-imidazol-2-yl)penta-1,4-diene-3-one (**14**). As shown in Scheme 1, potential metabolic product (**14**) of (1*E*,4*E*)-1,5-bis(1-alkyl-1*H*-imidazol-2-yl)penta-1,4-diene-3-ones (**2**-**4**) was synthesized through the Horner-Wadsworth-Emmons reaction of 1-trityl-1*H*-imidazole-2-carbaldehyde (**9**) with 1,3-bis(diethylphosphonato)acetone (**12**) followed by removal of the trityl protecting group of **13** in the presence of hydrochloric acid. 1-Trityl-1*H*-imidazole-2-carbaldehyde (**9**) was initially synthesized by tritylation of 2-imidazolecarboxaldehyde (**8**) with trityl chloride using triethylamine as base in 20% yield. Replacement of triethylamine with potassium carbonate did not improve the yield. Alternately, aldehyde **9** was achieved in 60% yield by formylation of 1-trityl-1*H*-imidazole (**11**) that was derived from tritylation of imidazole (**10**).

The anti-proliferative activity of (1*E*,4*E*)-1,5-bis(1*H*-imidazol-2-yl)penta-1,4-diene-3-one (**14**) against androgen-insensitive prostate cancer cell lines (PC-3 and DU145) and androgen-sensitive prostate cancer cell line (LNCaP) has been evaluated by WST-1 cell proliferation assay following the procedure as described in the experimental section. The IC_{50} values for (1*E*,4*E*)-1,5-bis(1*H*-imidazol-2-yl)penta-1,4-diene-3-one (**14**) towards three prostate cancer cell lines range from 73 μM to 305 μM, which indicates that (1*E*,4*E*)-1,5-bis(1*H*-imidazol-2-yl)penta-1,4-diene-3-one (**14**) is even less potent than curcumin (IC_{50}, 14-26 μM) and that removal of the 1-alkyl group diminishes the antiproliferative activity of (1*E*,4*E*)-1,5-bis(1-alkyl-1*H*-imidazol-2-yl)penta-1,4-diene-3-ones (**2**-**4**). This suggests that introduction of an appropriate metabolically stable group to *N*1 position of imidazole moiety is indispensable for both potency and bioavailability.

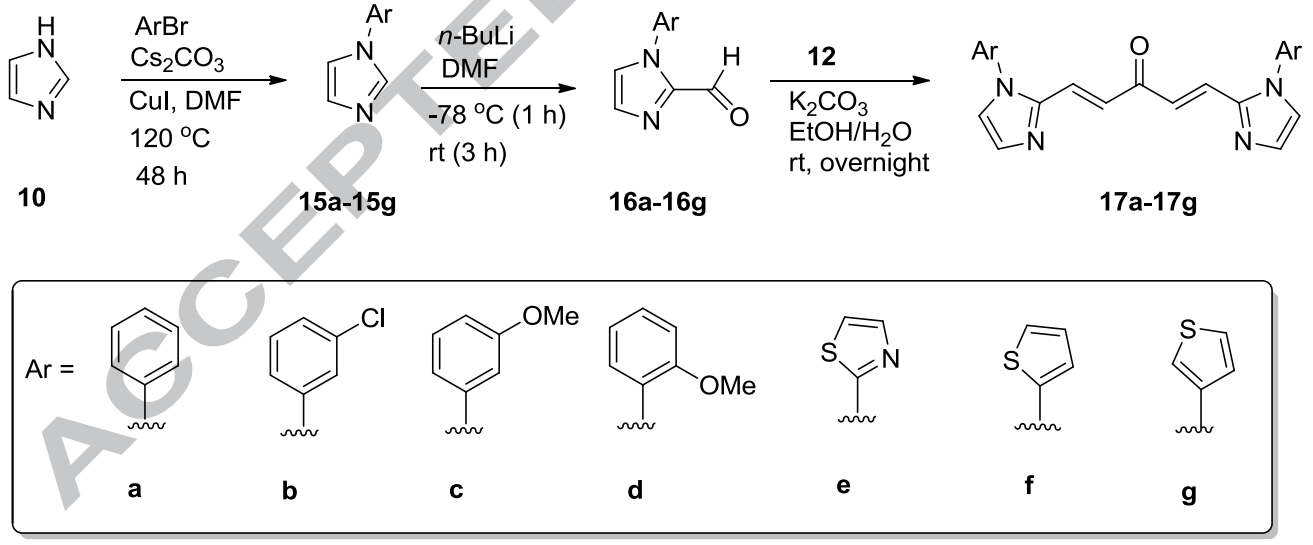
2.2 Design and Synthesis of (1*E*,4*E*)-1,5-bis(1-aryl-1*H*)-heteroaryl-2-yl)penta-1,4-diene-3-ones:

In order to further optimize (1*E*,4*E*)-1,5-bis(1-alkyl-1*H*)-imidzaole-2-yl)penta-1,4-diene-3-ones (**2**-**4**) and (1*E*,4*E*)-1,5-bis(1-alkyl-1*H*-benzo[*d*]imidazole-2-yl)penta-1,4-diene-3-ones (**5**-**6**), we envisioned that *N*-aryl substitution to exclude the C-H bond on the carbon adjacent to the *N*1 position (α-H) may

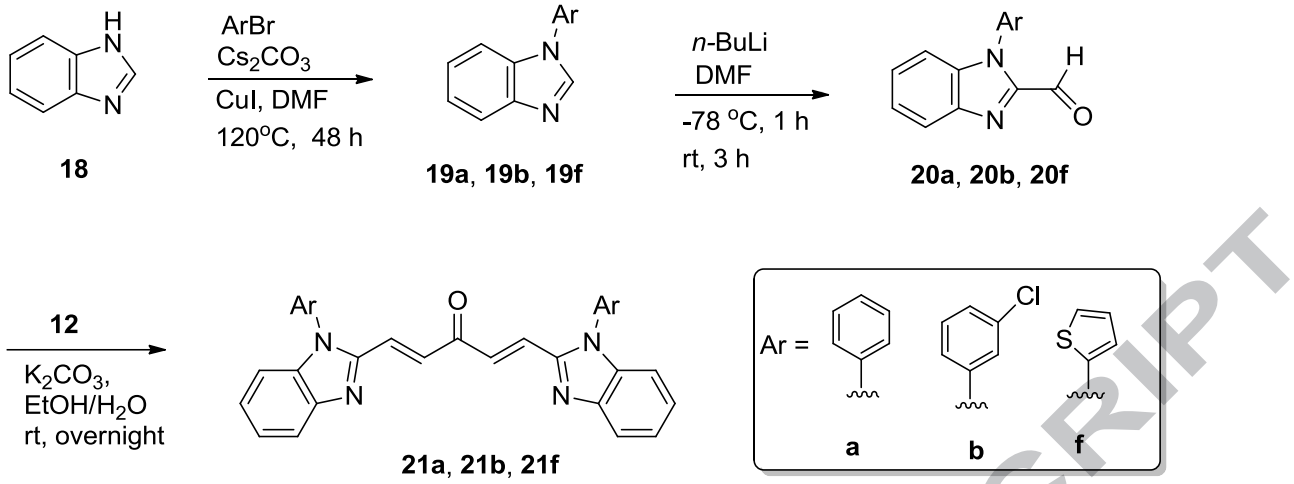
increase the metabolic stability. Seven 5- and 6-membered aryl rings (**a** – **g**, Scheme 2) were thus chosen to substitute the alkyl groups at the *N*1 position of the imidazole or benzo[d]imidazole moiety. Consequently, seven (1*E*,4*E*)-1,5-bis(1-aryl-1*H*-imidazol-2-yl)penta-1,4-dien-3-ones (**17a**-**17g**, Scheme 2) and three (1*E*,4*E*)-1,5-bis(1-aryl-1*H*-benzo[d]imidazol-2-yl)penta-1,4-dien-3-ones (**21a**, **21b**, and **21f**, Scheme 3), as well as three (1*E*,4*E*)-1,5-bis(1-aryl-1*H*-pyrrolo[3,2-*b*]pyridine-2-yl)penta-1,4-dien-3-ones (**25a**, **25c**, and **25f**, Scheme 4), were synthesized for the evaluation of their antiproliferative activity against three prostate cancer cell lines. Compounds **25a**, **25c**, and **25f** were also selected due to the similar shape and size between 4-azaindole and benzimidazole. Each of the thirteen pentadienones was synthesized through a three-step transformation as illustrated in Schemes 2-4. Specifically, the 1-aryl-heteroaromatics (**15a**-**15g**, **19a**, **19b**, **19f**, **23a**, **23c**, and **23f**) were prepared by arylation of imidazole (**10**), benzimidazole (**18**), and 4-azaindole (**22**), respectively, with an appropriate aryl bromide through Ullmann condensation catalyzed by copper iodide and cesium carbonate.[12] The aryl substituted heteroaromatics (**15a**-**15g**, **19a**, **19b**, **19f**, **23a**, **23c**, and **23f**) have their most acidic hydrogen at C-2, which can be deprotonated by *tert*-butyllithium under argon. The generated carbanions at C-2 are allowed to react with electrophile dimethylformamide (DMF)[13] to give 1-aryl-heteroaromatic carbaldehydes (**16a**-**16g**, **20a**, **20b**, **20f**, **24a**, **24c**, and **24f**), which were then subjected to the Horner-Wadsworth-Emmons (HWE) reaction with 1,3-bis(diethylphosphonato)acetone (**12**)[14] to give the desired 1,5-diaryl-1,4-pentadienones (**17a**-**17g**, **21a**, **21b**, **21f**, **25a**, **25c**, and **25f**) according to the reported procedure.[10]



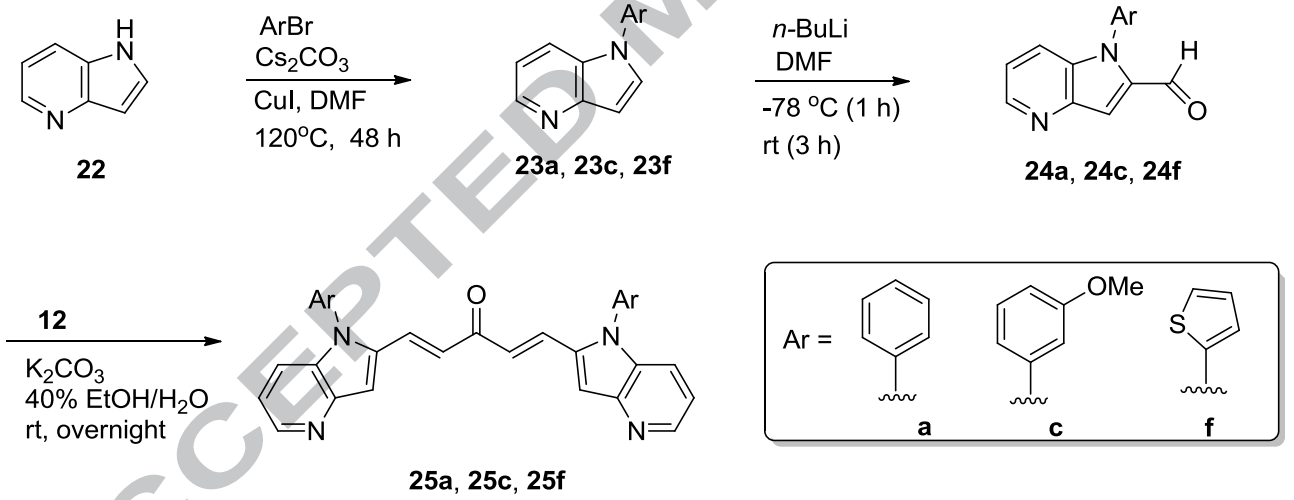
Scheme 1. Synthesis of (1*E*,4*E*)-1,5-bis(1*H*-imidazol-2-yl)penta-1,4-diene-3-one (**14**).



Scheme 2. Synthesis of (1*E*,4*E*)-1,5-bis(1-aryl-1*H*-imidazol-2-yl)penta-1,4-dien-3-ones (**17a-17g**).



Scheme 3. Synthesis of (1*E*,4*E*)-1,5-bis(1-aryl-1*H*-benzo[*d*]imidazole-2-yl)penta-1,4-dien-3-ones (**21a**, **21b**, & **21f**)



Scheme 4. Synthesis of (1*E*,4*E*)-1,5-bis(1-aryl-1*H*-pyrrolo[3,2-*b*]pyridine-2-yl)penta-1,4-dien-3-ones (**25a**, **25c**, **25f**).

2.3 Anti-proliferative activities of (1*E*,4*E*)-1,5-bis(1-aryl-1*H*)-heteroaryl-2-yl)penta-1,4-diene-3-ones (17a-17g, 21a, 21b, 21f, 25a, 25c, and 25f) towards prostate cancer cell lines.

The anti-proliferative activities of these 1,5-diaryl-1,4-dien-3-ones toward prostate cancer cells were evaluated. The WST-1 cell proliferation assay was used to assess the potency change resulting from replacing the 1-alkyl group in (1*E*,4*E*)-1,5-bis(1-alkyl-1*H*-imidazol-2-yl)penta-1,4-diene-3-ones (**2-4**) and (1*E*,4*E*)-1,5-bis(1-alkyl-1*H*-benzo[d]imidazole-2-yl)penta-1,4-diene-3-ones (**5-6**) with a 1-aryl moiety. The IC_{50} values for these newly made compounds are summarized in Table 1. (1*E*,4*E*)-1,5-Bis(1-aryl-1*H*-imidazol-2-yl)penta-1,4-dien-3-ones (**17a**-**17f**) are six optimal compounds, exhibiting 24- to 375-fold improved potency as compared with curcumin. These compounds (e.g. **17a** and **17d**) possess even greater potency than (1*E*,4*E*)-1,5-bis(1-alkyl-1*H*-imidazol-2-yl)penta-1,4-diene-3-ones (**2-4**). Replacement of the imidazole (**17a**, **17b**, **17c**, and **17f**) with a bulkier benzoimidazole (**21a, 21b,** and **21f**) and 4-azaindole (**25a**, **25c**, and **25f**) resulted in substantial decreases in the potency.

To further study the potency toward castration resistant prostate cancer models, compound **17a**, one of the optimal compounds, was evaluated towards enzalutamide-resistant LNCaP95, VCaP and 22Rv1 cell lines[15-16] by the trypan blue exclusion assay after 5 days exposure. Compound **17a** is also very promising in suppressing cell proliferation towards LNCaP95, VCaP and 22Rv1 cell lines, with IC_{50} values of 0.15 μM, 0.18 μM, and 0.30 μM, respectively.

Table 1. Anti-proliferative activity of 1,5-diheteroarylpenta-1,4-dien-3-ones

Compd	IC_{50} (μM)[a]			IC_{50} (curcumin)/IC_{50}(dienone)		
	PC-3[b]	DU145[c]	LNCaP[d]	PC-3[b]	DU145[c]	LNCaP[d]
curcumin	25.43 ± 2.15	26.23 ± 0.65	13.61 ± 2.69	_	_	_
14	304.89 ± 34.95	236.30 ± 19.33	72.82 ± 1.85	0.08	0.11	0.19
17a	0.12 ± 0.03	0.07 ± 0.02	0.22 ± 0.11	212	375	62
17b	0.23 ± 0.09	0.21 ± 0.04	0.58 ± 0.03	111	125	24
17c	0.22 ± 0.09	0.18 ± 0.06	0.23 ± 0.07	116	146	59

17d	0.11 ± 0.04	0.14 ± 0.01	0.29 ± 0.06	231	187	47
17e	0.26 ± 0.07	0.22 ± 0.09	0.32 ± 0.07	98	119	43
17f	0.26 ± 0.08	0.10 ± 0.02	0.32 ± 0.03	98	262	43
17g	7.76 ± 0.69	7.62 ± 0.49	6.61 ± 1.57	3.3	3.4	4.1
21a	2.73 ± 0.53	2.82 ± 0.82	5.36 ± 1.79	9	9	2.5
21b	23.14 ± 0.54	19.25 ± 6.74	30.47 ± 3.53	1.1	1.4	0.5
21f	1.14 ± 0.19	2.01 ± 0.75	7.50 ± 0.66	22	13	2
25a	1.02 ± 0.25	0.80 ± 0.11	1.71 ± 0.36	25	33	8
25c	> 50	47.28 ± 11.10	38.21 ± 1.35	< 0.5	0.6	0.4
25f	> 10	> 10	> 10	< 2.5	< 3	< 1.4

[a] IC_{50} is the compound concentration effective in inhibiting 50% of the cell viability measured by WST-1 cell proliferation assay after 3 days exposure. The data were presented as the mean ± standard deviation of the mean.

[b] Human androgen-insensitive prostate cancer cell line derived from bone metastasis of prostate tumor

[c] Human androgen-insensitive prostate cancer cell line derived from brain metastasis of prostate tumor

[d] Human androgen-sensitive prostate cancer cell line

2.4 Pharmacokinetic Studies: (1*E*,4*E*)-1,5-Bis(1-phenyl-1*H*-imidazol-2-yl)penta-1,4-dien-3-one (**17a**) was selected for pharmacokinetic studies in Sprague Dawley rats due to its promising *in vitro* anti-proliferative potency in three prostate cancer cell models. The blood samples of rats, administered with **17a** via oral gavage at a single dose of 10 mg/kg, were collected at 1, 3, 6, and 24 h after oral administration. Plasma was prepared from the blood samples and was analyzed by HPLC-MS/MS for determination of drug concentration as described in the Experimental Section. The PK parameters for **17a** could not be calculated because detectable plasma concentrations could barely be achieved at the 1h time point, suggesting the poor pharmacokinetic profile of **17a**. This may be due to its poor water solubility caused by its structural coplanarity. At this point, (1*E*,4*E*)-1,5-bis(1-(2-methoxyphenyl)-1*H*-imidazol-2-yl)penta-1,4-dien-3-one (**17d**) with similar *in vitro* antiproliferative potency was chosen for

further pharmacokinetic studies because the methoxyl group at the 2-position of the phenyl ring can break the coplanarity of the phenyl and the imidazole and lead to enhanced water solubility. The pharmacokinetic parameters for **17d**, as summarized in Table 2, imply that **17d** does afford greater bioavailability than **17a**. Its peak plasma concentration at 149.6 ng/mL (0.35 μM) exceeds its IC_{50} values of 0.11-0.29 μM in three human prostate cancer cell lines. Compound **17d** affords an AUC value of 1800.45 ng/mL*h versus 5.04 ng/mL*h for (1*E*,4*E*)-1,5-bis(1-isopentyl-1*H*-imidazol-2-yl)penta-1,4-dien-3-one (**3**)[10] and 2.43 ng/mL*h for curcumin[10], suggesting its appreciably improved therapeutic potential as compared with curcumin and parental compound **3**." The bioavailability of **17d**, as demonstrated by its peak plasma concentration and AUC value, is thus sufficient to provide the therapeutic efficacy necessary to suppress *in vivo* tumor growth at doses that are ≥ 10 mg/kg.

Table 2. Pharmacokinetic parameters for **17d**

Parameter	**Unit**	**17d**
Lambda_z	1/h	0.14 ± 0.02
$t_{1/2}$	h	4.82 ± 0.06
T_{max}	h	2.67 ± 0.58
C_{max}	ng/ml	149.62 ± 5.70
Tlag	h	0
Clast_obs/Cmax		0.050 ± 0.006
AUC 0-t	ng/ml*h	1748.44 ± 164.51
AUC 0-inf_obs	ng/ml*h	1800.45 ± 170.09
AUC 0-t/0-inf_obs		0.97 ± 0.02
AUMC 0-inf_obs	ng/ml*h^2	11086.59 ± 1195.10
MRT 0-inf_obs	h	6.16 ± 0.14
Vz/F_obs	(mg/kg)/(ng/ml)	0.039 ± 0.003
Cl/F_obs	(mg/kg)/(ng/ml)/h	0.0056 ± 0.001

2.5 Metabolic stability studies

To compare the metabolic stability, under both phase I oxidation and phase II glucuronidation conditions, of our newly synthetic compounds (**17a** and **17d**) with that of curcumin and (1*E*,4*E*)-1,5-bis(1-isopentyl-1*H*-imidazol-2-yl)penta-1,4-dien-3-one (**3**), each of curcumin, **3**, **17a**, and **17d** were incubated with rat liver microsomes, NADPH, and UGT reaction mixtures. The incubation concentrations of each test compound in liver microsomes were measured by a UHPLC-TSQ mass spectrometer. The incubation concentrations of curcumin, **3**, **17a**, and **17d** in rat liver microsomes at different time points were listed in Table 3. We can conclude from these data that the intrinsic clearance is 161.2 mL/min/kg for curcumin, 39.2 mL/min/kg for **3**, 60.4 mL/min/kg for **17a**, 7.96 mL/min/kg for **17d**, indicating all these three curcumin analogues (**3**, **17a**, **17d**) have higher metabolic stability than curcumin. Among them, **17d** has highest metabolic stability.

Table 3. The incubation concentrations of curcumin, **3**, **17a**, and **17d** in rat liver microsomes

Time points (min)	Concentration of test compound (nM)			
	Curcumin	**3**	**17a**	**17d**
0	1135.2±20.0	1017.6±24.8	1039.7±6.9	1000.6±35.5
5	589.6±20.4	850.0±26.0	624.9±24.4	922.1±29.8
15	200.0±7.0	706.2±6.7	311.5±11.3	914.7±22.8
30	54.6±3.4	644.6±19.0	84.5±6.4	879.8±58.5
45	17.6±1.0	387.9±7.2	34.8±2.0	827.8±16.1
60	9.5±0.4	296.0±10.2	19.6±1.7	757.1±32.8

3 Conclusion

The poor antiproliferative potency of (1*E*,4*E*)-1,5-bis(1*H*-imidazol-2-yl)penta-1,4-diene-3-one (**14**) in three human prostate cancer cell lines suggests the critical role of an appropriate group on the *N*1 position for the potency of 1,5-bis(1-alkyl-1*H*-imidazol-2-yl)penta-1,4-diene-3-ones (**2-4**). Thirteen new diarylpentadienones (**17a-17g**, **21a**, **21b**, **21f**, **25a**, **25c**, and **25f**) were then designed and

synthesized through a three-step transformation. The six optimal (1*E*,4*E*)-1,5-bis(1-aryl-1*H*-imidazol-2-yl)penta-1,4-dien-3-ones (**17a**-**17f**) exhibit 24- to 375-fold improved potency in three prostate cancer cell models, as compared with curcumin. Replacement of the imidazole (**17a**, **17c**, and **17f**) with bulkier benzoimidazole (**21a, 21b,** and **21f**) and 4-azaindole (**25a**, **25c**, and **25f**) resulted in substantial decrease in the potency. (1*E*,4*E*)-1,5-Bis(1-phenyl-1*H*-imidazol-2-yl)penta-1,4-dien-3-one (**17a**) possesses a poor pharmacokinetic profile probably due to its poor water solubility caused by its structural coplanarity. Instead, (1*E*,4*E*)-1,5-bis(1-(2-methoxyphenyl)-1*H*-imidazol-2-yl)penta-1,4-dien-3-one (**17d**) was demonstrated to have both good potency and bioavailability sufficient to provide the therapeutic efficacy necessary to suppress *in vivo* tumor growth.

4 Experimental

4.1 General Procedures. HRMS were obtained on an Orbitrap mass spectrometer with electrospray ionization (ESI). NMR spectra were obtained on a Bruker Fourier 300 spectrometer in $CDCl_3$, CD_3OD, or DMSO-d_6. The chemical shifts are given in ppm referenced to the respective solvent peak, and coupling constants are reported in Hz. Anhydrous THF was purified by PureSolv MD 7 solvent purification system from Innovative Technologies (MB-SPS-800). All other reagents and solvents were purchased from commercial sources and were used without further purification. Silica gel column chromatography was performed using silica gel (32-63 μM). Preparative thin-layer chromatography (PTLC) separations were carried out on thin layer chromatography plates loaded with silica gel 60 GF254 (EMD Millipore Corporation, MA, USA). 1,3-Bis(diethylphosphonato)acetone was synthesized using the procedure illustrated in the literature.[14] The purities of compounds **14**, **17a**-**17g**, **21a**, **21b**, **21f**, and **25f** were determined by HPLC. The peaks were monitored by a diode array detector (ADA) at 325 ± 100 nm. The HPLC analyses were performed on an Agilent Hewlett-Packard 1100 series HPLC DAD system using a 5 μM C18 reversed phase column (4.6 mm × 250 mm) and a diode array detector.

4.2 Synthesis of 1-trityl-1*H*-imidazole-2-carbaldehyde (9): A solution of triphenylmethylchloride (640 mg, 2.3 mmol) in dichloromethane (1 mL) was added to a mixture of 2-imidazolecarboxadehyde (200 mg, 2.1 mmol) and potassium carbonate (1.44 g, 10.4 mmol) in dimethylformamide (1.5 mL). The mixture was stirred at 60 °C overnight and then cooled down to room temperature. The reaction mixture was extracted with ethyl acetate, the combined extracts were dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by preparative thin layer chromatography eluting with 40% ethyl acetate in hexane to provide **9** as a white to light-yellow solid in 32% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.23 (s, 1H), 7.38-7.29 (m, 10 H), 7.13-7.10 (m, 6 H), 7.02 (s, 1H). The ^{1}H NMR data are consistent with those reported in the literature.[17]

4.3 Synthesis of (1*E*,4*E*)-1,5-bis(1-trityl-1*H*-imidazol-2-yl)penta-1,4-dien-3-one (13): A solution of 1-trityl-1*H*-imidazole-2-carbaldehyde (**9**, 0.61 mmol) and 1,3-bis(diethylphophonato)acetone (**12**, 0.10 g, 0.29 mmol) in ethanol (1.2 mL) was added a solution of potassium carbonate (0.20 g, 1.4 mmol) in water (1.7 mL). The reaction was stirred at room temperature and monitored by TLC. When the reaction was complete, the reaction mixture was then extracted with ethyl acetate. The organic extracts were dried over anhydrous sodium sulfate and concentrated. The crude product was subjected to PTLC purification eluting with 5% methanol in DCM to generate the desired product in 51% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32-7.25 (m, 18H), 7.09-7.06 (m, 14H), 6.85 (d, J = 1.1 Hz, 2H), 6.72 (d, J = 15.2 Hz, 2H), 6.50 (d, J = 15.2 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.1, 145.5, 142.5, 130.6, 129.9, 128.32, 128.27, 128.1, 126.7, 124.7, 75.9. IR (film) ν_{max} 1650, 1615, 1596, 1492, 1444, 1403, 1336, 1262, 1220, 1168, 1121, 1097, 1032, 1001, 975, 744, 700, 675, 650, 616 cm^{-1}; HRMS (ESI): *m/z* calculated for $C_{49}H_{39}N_4O$ $[M+H]^+$: 699.3124. Found: 699.3107.

4.4 Synthesis of (1*E*,4*E*)-1,5-di(1*H*-imidazol-2-yl)penta-1,4-dien-3-one (14): A solution of (1*E*,4*E*)-1,5-bis(1-trityl-1*H*-imidazol-2-yl)penta-1,4-dien-3-one (**13**, 1 mmol) in 1M hydrochloric acid (10 mmol) was refluxed for 2 hours. Then the reaction mixture was cooled down and extracted with ethyl acetate. The combined organic layer was washed with saturated potassium bicarbonate. Light yellow solid was obtained in 100% yield. M.p. 200 °C (decomposed). ^{1}H NMR (300 MHz, CD_3OD) δ 7.77 (s, 4H), 7.70 (s, 2H), 7.68 (s, 2H). ^{13}C NMR (75 MHz, CD_3OD) δ 187.1, 142.1, 133.6, 124.1, 123.0. IR (film) ν_{max} 1653, 1618, 1440, 1265, 1156, 1100, 976, 730, 699, 668, 644, 617 cm^{-1}. HRMS (ESI): *m/z* calculated for $C_{11}H_{11}N_4O$ $[M+H]^+$: 215.0933. Found: 215.0925. HPLC purity 97.6% (30 min run of 1-20% CH_3CN in H_2O with 30 min gradient, 1.0 mL/min).

4.5. General Procedure for *N*-Arylation: To a solution of heteroaromatic compound (8.0 mmol), copper iodide (20 mol%), and cesium carbonate (11 mmol) in DMF (11 mL) was added aryl bromide (5.7 mmol) under argon atmosphere, and the reaction mixture was stirred at room temperature for 30 min prior to being refluxed for 48 hours. The reaction mixture was cooled down to room temperature and diluted with ethyl acetate. The subsequent mixture was filtered through a pad of silica gel. The filtrate was concentrated to give a residue, which was subjected to preparative thin layer chromatography eluting with 50% ethyl acetate in hexane.

4.5.1 1-Pheny-1*H*-imidazole (15a): The residue was purified by column chromatography eluting with 5% methanol in dichloromethane[12] to provide the title compound as a clear oil in 40% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.52 – 7.45 (m, 2H), 7.42 – 7.34 (m, 3H), 7.29 (s, 1H), 7.22 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.4, 135.7, 130.4, 129.9, 127.6, 121.5, 118.3.

4.5.2 1-(3-Chlorophenyl)-1*H*-imidazole (15b): Yellow oil was obtained in 98% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.47 – 7.39 (m, 2H), 7.38 – 7.31 (m, 1H), 7.30 – 7.27 (m, 2H), 7.24 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.4, 135.8, 135.6, 131.2, 130.5, 127.9, 121.9, 119.7, 118.3.

4.5.3 1-(3-Methoxyphenyl)-1*H*-imidazole (15c): Yellow oil was obtained in 88% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.38 (t, J = 7.8 Hz, 1H), 7.28 (s, 1H), 7.21 (s, 1H), 6.98 (d, J = 7.8 Hz, 1H), 6.92 (s, 1H), 6.91 (d, J = 7.8 Hz, 1H), 3.86 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.9, 138.5, 135.7, 130.9, 130.2, 118.6, 113.9, 113.0, 108.0, 55.7.

4.5.4 1-(2-Methoxyphenyl)-1*H*-imidazole (15d): Yellow oil was obtained in 55% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.36 (ddd, J = 9.3, 7.5, 1.8 Hz, 1H), 7.28 (dd, J = 7.5, 1.5 Hz, 1H), 7.21 (t, J = 1.2 Hz, 1H), 7.18 (s, 1H), 7.05 (d, J = 8.7 Hz, 1H), 7.04 (dt, J = 7.2, 1.2 Hz, 1H), 3.85 (s, 3H).

4.5.5 1-(Thiazole-2-yl)-1*H*-imidazole (15e): Yellow solid was obtained in 85% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (s, 1H), 7.59 (d, J = 3.6 Hz, 1H), 7.52 (s, 1H), 7.20 (s, 1H), 7.17 (d, J = 3.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.7, 140.9, 135.7, 130.8, 118.0, 115.9.

4.5.6 1-(Thiophen-2-yl)-1*H*-imidazole (15f): Yellow oil was obtained in 66% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.21 (s, 1H), 7.19 (s, 1H), 7.16 (dd, J = 5.1, 1.5 Hz, 1H), 7.03– 6.97 (overlapped, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.9, 137.1, 129.8, 126.6, 122.2, 120.6, 119.5.

4.5.7 (1-(Thiophen-3-yl)-1*H*-benzo[*d*]imidazole (15g): Yellow solid was obtained in 35% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.46 (dd, J = 5.2, 3.2 Hz, 1H), 7.28-7.26 (overlapped, 1H), 7.27 (s, 1H), 7.21 (s, 1H), 7.21-7.19 (overlapped, 1H).

4.5.8 1-Phenyl-1*H*-benzo[*d*]imidazole (19a): Iodobenzene instead of bromobenzene was used in a same equivalent. The residue was purified by preparative thin layer chromatography eluting with 5% methanol in dichloromethane to provide the title compound as a yellow oil in 57.5% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.91 – 7.88 (m, 1H), 7.61 – 7.43 (m, 6H), 7.37 – 7.32 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.8, 142.3, 136.4, 133.8, 130.2, 128.3, 124.3, 123.9, 123.1, 120.6, 110.7.

4.5.9 1-(3-Chlorophenyl)-1*H*-benzo[*d*]imidazole (19b): Beige solid was obtained in 25% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37 (s, 1H), 7.94 (d, J = 5.2 Hz, 1H), 7.58 (t, J = 1.8 Hz, 1H), 7.54 (d, J = 7.5 Hz, 1H), 7.48 (dt, J = 6.3, 1.8 Hz, 2H), 7.43 – 7.39 (overlapped, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.7, 137.1, 136.1, 131.4, 128.9, 124.8, 124.5, 124.0, 122.4, 120.3, 110.8.

4.5.10 1-(Thiophen-2-yl)-1*H*-benzo[d]imidazole (19f): Yellow oil was obtained in 60% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.90-7.87 (m, 1H), 7.59-7.55 (m, 1H), 7.40-7.36 (m, 2H), 7.33 (d, J = 5.1 Hz, 1H), 7.19 (d, J = 2.2 Hz, 1H), 7.12 (dd, J = 5.3, 3.7 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.1, 142.9, 136.9, 134.7, 126.7, 124.6, 123.9, 123.7, 122.4, 120.5, 110.8.

4.5.11 1-Phenyl-1*H*-pyrrolo[3,2-*b*]pyridine (23a): Iodobenzene instead of bromobenzene was used in a same equivalent. Yellow oil was obtained in 62% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.54 (d, J = 4.6 Hz, 1H), 7.94 (d, J = 8.4 Hz, 1H), 7.67 (d, J = 3.4 Hz, 1H), 7.61-7.55 (m, 2H), 7.49-7.41 (m, 3H), 7.25 - 7.20 (m, 1H), 7.01 (d, J = 3.2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.1, 143.5, 139.0, 131.5, 130.2, 130.1, 127.3, 124.3, 118.5, 117.3, 104.4.

4.5.12 1-(3-Methoxyphenyl)-1*H*-pyrrolo[3,2-b]pyridine (23c): Yellow oil was obtained in 52% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.52 (d, J = 4.4 Hz, 1H), 7.92 (d, J = 8.3 Hz, 1H), 7.63 (d, J = 3.3 Hz,

1H), 7.45 (t, *J* = 8.1 Hz, 1H), 7.19 (dd, *J* = 8.3, 4.8 Hz, 1H), 7.06 (d, *J* = 8.0 Hz, 1H), 7.00 (s, 1H), 6.95 (d, *J* = 8.6 Hz, 1H), 6.94 (d, *J* = 2.4 Hz, 1H), 3.88 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.9, 146.7, 143.1, 140.0, 131.8, 130.9, 129.4, 118.9, 117.2, 116.4, 112.7, 110.4, 104.2, 55.7.

4.5.13 1-(Thiophen-2-yl)-1*H*-pyrrolo[3,2-*b*]pyridine (23f): Yellow oil was obtained in 70% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.53 (d, *J* = 4.4 Hz, 1H), 7.88 (d, *J* = 8.3 Hz, 1H), 7.55 (d, *J* = 3.3 Hz, 1H), 7.26 – 7.22 (m, 2H), 7.09 – 7.06 (overlapped, 2H), 6.90 (t, *J* = 3.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.2, 144.3, 141.6, 140.3, 132.5, 128.9, 124.2, 120.6, 118.3, 117.8, 105.2.

4.6 General Procedure for formylation. *t*-BuLi (1.9 M, 0.87 mmol) was added to a solution of arylatedheteroaromatic (0.78 mmol) in tetrahydrofuran (7.6 mL) dropwise under argon atmosphere at -78 °C, and the reaction mixture was stirred for 1 hour at the same temperature before adding DMF (0.98 mmol). The reaction mixture was then warmed up to room temperature and the completion of reaction was monitored by TLC. The reaction was quenched with saturated ammonium chloride solution and diluted with brine, and the subsequent mixture was extracted by dichloromethane. The organic layer was dried with sodium sulfate followed by evaporation of the solvent. The residue was purified by preparative thin layer chromatography eluting with 50% ethyl acetate in hexane.

4.6.1 1-Phenyl-1*H*-imidazole-2-carbaldehyde (16a): *n*-BuLi (2.5 M) and diethyl ether were used instead of *t*-BuLi (1.9 M) and tetrahydrofuran in the same equivalent. White solid was obtained in 66% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.78 (s, 1H), 7.47 – 7.41 (m, 3H), 7.37 (s, 1H), 7.33 – 7.28 (m, 2H), 7.25 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.2, 143.3, 136.7, 131.9, 129.20, 129.18, 127.2, 125.7.

4.6.2 1-(3-Chlorophenyl)-1*H*-imidazole-2-carbaldehyde (16b): Diethyl ether was used instead of tetrahydrofuran. Light yellow solid was obtained in 18% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.85 (s, 1H), 7.49 (t, J = 8.1, 1.5 Hz, 1H), 7.45 (d, J = 7.8 Hz, 1H), 7.42 (d, J = 7.8 Hz, 1H), 7.36 (t, J = 1.8 Hz, 1H), 7.27 – 7.23 (overlapped, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.4, 143.2, 137.8, 135.0, 131.9, 130.4, 129.7, 127.1, 126.3, 124.4.

4.6.3 1-(3-Methoxyphenyl)-1*H*-imidazole-2-carbaldehyde (16c): Yellow oil was obtained in 62% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.84 (s, 1H), 7.42 (s, 1H), 7.37 (d, J = 8.1 Hz, 1H), 7.28 (s, 1H), 7.02 (dd, J = 7.8, 1.8 Hz, 1H), 6.92 (d, J = 7.8 Hz, 1H), 6.87 (t, J = 2.1 Hz, 1H), 3.84 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.3, 160.2, 143.5, 137.8, 131.9, 130.1, 127.2, 118.1, 115.0, 112.0, 55.7.

4.6.4 1-(2-Methoxyphenyl)-1*H*-imidazole-2-carbaldehyde (16d): Yellow oil was obtained in 54% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.81 (s, 1H), 7.45 (d, J = 8.4 Hz, 1H), 7.43 (s, 1H), 7.25 (d, J = 8.4 Hz, 1H), 7.19 (s, 1H), 7.07 (t, J = 7.8 Hz, 2H), 3.76 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.2, 154.1, 144.0, 131.3, 130.8, 127.3, 127.1, 126.1, 120.8, 112.1, 55.9.

4.6.5 1-(Thiazol-2-yl)-1*H*-imidazole-2-carbaldehyde (16e): Yellow solid was obtained in 26% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.67 (s, 1H), 7.78 (s, 1H), 7.71 (d, J = 3.0 Hz, 1H), 7.43 (s, 1H), 7.41 (d, J = 3.3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.7, 156.1, 143.4, 140.4, 132.1, 126.2, 120.4.

4.6.6 1-(Thiophen-2-yl)-1*H*-imidazole-2-carbaldehyde (16f): Brown oil was obtained in 39% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.84 (s, 1H), 7.40 (s, 1H), 7.32 (dd, J = 5.7, 1.5 Hz, 1H), 7.30 (s, 1H), 7.12 (dd, J = 3.6, 1.2 Hz, 1H), 7.03 (dd, J = 5.7, 3.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.1, 144.2, 136.9, 131.9, 128.4, 126.0, 125.03, 125.01.

4.6.7 1-(Thiophen-3-yl)-1*H*-imidazole-2-carbaldehyde (16g): Brown oil was obtained in 12% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.88 (s, 1H), 7.94 (s, 1H), 7.85 (d, J = 5.1 Hz, 1H), 7.30 (s, 2H), 7.22 (d, J = 5.2 Hz, 1H).

4.6.8 1-Phenyl-1*H*-benzo[d]imidazole-2-carbaldehyde (20a): *n*-BuLi (2.5 M) and diethyl ether were used instead of *t*-BuLi (1.9 M) and tetrahydrofuran in the same equivalent. Yellow solid was obtained in 44% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.10 (s, 1H), 8.02 – 7.96 (m, 1H), 7.60-7.57 (m, 3H), 7.46 – 7.42 (m, 2H), 7.40 – 7.37 (m, 2H), 7.29 – 7.25 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 182.9, 145.9, 142.6, 137.5, 135.2, 130.1, 129.6, 127.4, 127.1, 124.6, 122.3, 111.7.

4**.6.9 1-(3-Chlorophenyl)-1*H*-benzo[d]imidazole-2-carbaldehyde (20b)**: Beige solid was obtained in 53% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.09 (s, 1H), 7.99 (t, J = 6.0 Hz, 1H), 7.57-7.52 (m, 2H), 7.49 – 7.44 (m, 2H), 7.40 (s, 1H), 7.31 – 7.24 (overlapped, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.0, 147.6, 145.9, 142.7, 136.5, 135.3, 130.7, 129.8, 127.8, 127.53, 125.6, 125.0, 122.5, 111.6.

4.6.10 1-(Thiophen-2-yl)-1*H*-benzo[d]imidazole-2-carbaldehyde (20f): Yellow oil was obtained in 45% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.03 (s, 1H), 7.91 (d, J = 7.5 Hz, 1H), 7.43-7.37 (overlapped, 3H), 7.30-7.27 (m, 1H), 7.08-7.05 (overlapped, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 182.5, 146.7, 142.4, 138.5, 135.2, 127.9, 126.3, 126.0, 125.0, 122.4, 111.9.

4.6.11 1-Phenyl-1*H*-pyrrolo[3,2-*b*]pyridine-2-carbaldehyde (24a): Diethyl ether was used instead of tetrahydrofuran. Yellow solid was obtained in 57% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.55 (s, 1H), 8.73 (dd, J = 4.5, 0.9 Hz, 1H), 8.26 (s, 1H), 7.92 (d, J = 8.1 Hz, 1H), 7.3 (t, J = 6.9 Hz, 2H), 7.56 – 7.48 (m, 3H), 7.34 (dd, J = 8.4, 4.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.0, 145.6, 137.5, 136.7, 130.6, 130.5, 129.0, 127.7, 124.7, 120.0, 119.0, 118.2.

4.6.12 1-(3-Methoxyphenyl)-1*H*-pyrrolo[3,2-*b*]pyridine-2-carbaldehyde (24c): Beige solid was obtained in 12% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.46 (s, 1H), 8.71 (d, J = 4.6 Hz, 1H), 8.22 (s, 1H), 7.88 (d, J = 8.4 Hz, 1H), 7.50 (t, J = 8.0 Hz, 1H), 7.29 (overlapped, 1H), 7.09 (d, J = 8.4 Hz, 1H), 7.04 (d, J = 8.7 Hz, 1H), 7.03 (s, 1H), 3.89 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.1, 161.1, 146.4, 144.7, 138.7, 136.3, 131.2, 130.3, 119.4, 119.0, 118.5, 116.6, 114.2, 110.6, 55.8.

4.6.13 1-(Thiophen-2-yl)-1*H*-pyrrolo[3,2-b]pyridine-2-carbaldehyde (24f): Yellow solid was obtained in 57% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.90 (s, 1H), 8.59 (d, J = 4.2 Hz, 1H), 8.12 (d, J = 8.4 Hz, 1H), 7.78 (d, J = 4.1 Hz, 1H), 7.66 (d, J = 3.5 Hz, 1H), 7.31 (dd, J = 8.4, 4.8 Hz, 1H), 7.19 (d, J = 4.1 Hz, 1H), 7.02 (dd, J = 3.5, 0.7 Hz, 1H).

4.7. General Procedure for the Synthesis of (1*E*,4*E*)-1,5-bis(1-aryl-1*H*-heteroaromatic-2-yl)penta-1,4-dien-3-ones: A solution of appropriate aldehyde (0.61 mmol) and 1,3-bis(diethylphophonato)acetone (0.10 g, 0.29 mmol) in ethanol (1.2 mL) was added a solution of potassium carbonate (0.20 g, 1.4 mmol) in water (1.7 mL). The reaction was stirred at room temperature and monitored by TLC until the completion. The reaction mixture was then extracted with ethyl acetate, the combined extracts were dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was subjected to PTLC purification eluting with 7% methanol in dichloromethane.

4.7.1 (1*E*,4*E*)-1,5-Bis(1-phenyl-1*H*-imidazol-2-yl)penta-1,4-dien-3-one (17a): The yellow solid was obtained in 26% yield. M.p. 200 – 204 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55-7.48 (m, 6H), 7.40 (d, J = 15.3 Hz, 2H), 7.34 (d, J = 15.3 Hz, 2H), 7.31-7.28 (m, 6H), 7.22 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.0, 143.6, 136.7, 131.0, 130.0, 129.4, 128.3, 128.0, 126.2, 124.2. IR (film) ν_{max} 1651, 1618, 1596, 1498, 1450, 1418, 1344, 1311, 1247, 1175, 1094, 978, 765, 732, 696, 646 cm^{-1}; HRMS

(ESI): *m/z* calculated for $C_{23}H_{19}N_4O$ $[M+H]^+$: 367.1559. Found: 367.1558. HPLC purity 93.7% (30 min run of 10-85% CH_3CN in H_2O with 30 min gradient, 1.0 mL/min).

4.7.2 (1*E*,4*E*)-1,5-Bis(1-(3-chlorophenyl)-1*H*-imidazol-2-yl)penta-1,4-dien-3-one (17b): Yellow solid was obtained in 62% yield. M.p. 214 °C (decomposed). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51–7.47 (m, 4H), 7.41 (d, J = 15.3 Hz, 2H), 7.34 (s, 2H), 7.34-7.31 (overlapped, 2H), 7.32 (d, J = 15.3 Hz, 2H), 7.23-7.20 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.6, 143.5, 137.6, 135.6, 131.3, 130.9, 129.6, 128.4, 127.5, 126.4, 124.5, 123.9. IR (film) ν_{max} 1625, 1592, 1480, 1388, 1338, 1097, 765, 744, 693, 669 cm^{-1}. HRMS (ESI): *m/z* calculated for $C_{23}H_{17}Cl_2N_4O$ $[M+H]^+$: 435.0779; 437.0750; 439.0720. Found: 435.0777; 437.0745; 439.0716. HPLC purity 95.1% (30 min run of 10-85% CH_3CN in H_2O with 30 min gradient, 1.0 mL/min).

4.7.3 (1*E*,4*E*)-1,5-Bis(1-(3-methoxyphenyl)-1*H*-imidazol-2-yl)penta-1,4-dien-3-one (17c): Yellow solid was obtained in 30% yield. M.p. 134-135 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (t, J = 7.8 Hz, 2H), 7.33 – 7.19 (overlapped, 6H), 7.19 (s, 2H), 7.12 (s, 2H), 7.06 (d, J = 7.3 Hz, 4H), 3.77 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.4, 154.4, 144.4, 131.1, 130.6, 128.5, 128.4, 127.6, 125.3, 124.7, 121.2, 112.6, 56.0. IR (film) ν_{max} 1651, 1621, 1596, 1507, 1466, 1448, 1420, 1346, 1313, 1283, 1247, 1180, 1134, 1093, 1047, 1022, 1001, 977, 755, 734, 669, 644 cm^{-1}. HRMS (ESI): *m/z* calculated for $C_{25}H_{23}N_4O_3$ $[M+H]^+$: 427.1770. Found: 427.1771. HPLC purity 98.4% (30 min run of 30-85% CH_3CN in H_2O with 30 min gradient, 1.0 mL/min).

4.7.4 (1*E*,4*E*)-1,5-Bis(1-(2-methoxyphenyl)-1*H*-imidazol-2-yl)penta-1,4-dien-3-one (17d): Yellow solid was obtained in 30% yield. M.p. 98-99 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (t, J = 8.1 Hz, 2H), 7.39 (d, J = 15.3 Hz, 2H), 7.38 (s, 2H), 7.25 (d, J = 1.2 Hz, 2H), 7.09 – 6.97 (m, 4H), 6.92 (d, J = 7.8 Hz, 2H), 6.83 (t, J = 2.1 Hz, 2H), 3.86 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.9, 160.8, 143.4, 137.4,

130.9, 129.2, 127.7, 127.1, 124.1, 118.5, 115.2, 112.2, 55.8. IR (film) ν_{max} 1649, 1619, 1605, 1590, 1492, 1469, 1446, 1418, 1344.2, 1289, 1236, 1223, 1174, 1126, 1097, 1045, 1015, 978, 866, 817, 781, 732, 695, 681, 650 cm^{-1}. HRMS (ESI): *m/z* calculated for $C_{25}H_{23}N_4O_3$ $[M+H]^+$: 427.1770. Found: 427.1768. HPLC purity 96.9% (30 min run of 15-70% CH_3CN in H_2O with 30 min gradient, 1.0 mL/min).

4.7.5 (1*E*,4*E*)-1,5-Bis(1-(thiazol-2-yl)-1*H*-imidazol-2-yl)penta-1,4-dien-3-one (17e): Yellow solid was obtained in 95% yield. M.p. 135-137 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 8.09 (d, J = 15.6 Hz, 2H), 7.79 (d, J = 3.3 Hz, 2H), 7.72 (d, J = 15.9 Hz, 2H), 7.47 (s, 2H), 7.39 (d, J = 3.3 Hz, 2H), 7.35 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.2, 156.9, 144.1, 141.6, 131.6, 129.9, 128.7, 122.8, 118.9. IR (film) ν_{max} 1649, 1618, 1591, 1525, 1509, 1462, 1400, 1328, 1290, 1254, 1178, 1154, 1095, 973, 754, 725 cm^{-1}; HRMS (ESI): *m/z* calculated for $C_{17}H_{13}N_6OS_2$ $[M+H]^+$: 381.0592. Found: 381.0587. HPLC purity 95.0% (30 min run of 15-85% CH_3CN in aqueous solution of ammonium formate (1.26 g ammonium formate in 1000 mL water), with 30 min gradient, 1.0 mL/min).

4.7.6 (1*E*,4*E*)-1,5-Bis(1-(thiophen-2-yl)-1*H*-imidazol-2-yl)penta-1,4-dien-3-one (17f): Yellow solid was obtained in 59% yield. M.p. 190 °C (decomposed). ^1H NMR (300 MHz, $CDCl_3$) δ 7.59 (d, J = 13.8 Hz, 2H), 7.46 (d, J = 15.6 Hz, 2H), 7.37 (d, J = 4.8 Hz, 2H), 7.34 (s, 2H), 7.28-7.21 (overlapped, 2H), 7.11-7.08 (overlapped, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.0, 145.0, 136.9, 131.2, 128.7, 127.5, 126.6, 125.5, 125.4, 125.2. IR (film) ν_{max} 1651, 1621, 1590, 1550, 1456, 1439, 1409, 1335, 1291, 1256, 1220, 1173, 1122, 1094, 975, 874, 729, 702, 669, 639 cm^{-1}. HRMS (ESI): *m/z* calculated for $C_{19}H_{15}N_4OS_2$ $[M+H]^+$: 379.0687. Found: 379.0682. HPLC purity 92.4% (30 min run of 10-85% CH_3CN in H_2O with 30 min gradient, 1.0 mL/min).

4.7.7 (1*E*,4*E*)-1,5-Bis(1-(thiophen-3-yl)-1*H*-imidazol-2-yl)penta-1,4-dien-3-one (17g): Orange solid was obtained in 10% yield. M.p. 200.0 °C (decomposed). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.00 (s, 2H), 7.93 (dd, J = 5.4, 0.6 Hz, 2H), 7.54 (s, 2H), 7.48 (dd, J = 15.6, 0.6 Hz, 2H), 7.34 (d, J = 5.4 Hz, 2H), 7.18 (s, 2H), 7.07 (d, J = 15.6 Hz, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 186.3, 138.0, 137.7, 131.0, 130.1, 129.8, 129.4, 126.6, 126.2, 121.2. IR (film) ν_{max} 1600, 1541, 1487, 1315, 1246, 1101, 1069, 1022, 734, 658 cm^{-1} HRMS (ESI): *m/z* calculated for $C_{19}H_{15}N_4OS_2$ $[M+H]^+$: 379.0687. Found: 379.0676. HPLC purity 95.2% (30 min run of 10-85% CH_3CN in H_2O with 30 min gradient, 1.0 mL/min).

4.7.8 (1*E*,4*E*)-1,5-Bis(1-phenyl-1*H*-benzo[*d*]imidazol-2-yl)penta-1,4-dien-3-one (21a): The yellow solid was obtained in 27% yield. M.p. 184-191 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, J = 7.8 Hz, 2H), 7.78 (d, J = 16.2 Hz, 2H), 7.61 (t, J = 7.5 Hz, 6H), 7.49 (d, J = 15.6 Hz, 2H), 7.42-7.30 (overlapped, 8H), 7.23 (d, J = 7.8 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.4, 148.1, 137.0, 134.8, 130.5, 130.4, 129.8, 127.6, 125.1, 124.5, 123.8, 120.9, 120.3, 111.1. IR (film) ν_{max} 1683, 1614, 1596, 1529, 1498, 1454, 1414, 1396, 1340, 1267, 1230, 1017, 760, 744, 696 cm^{-1}. HRMS (ESI): *m/z* calculated for $C_{31}H_{23}N_4O$ $[M+H]^+$: 467.1872. Found: 467.1869. HPLC purity 94.8% (30 min run of 30-85% CH_3CN in H_2O with 30 min gradient, 1.0 mL/min).

4.7.9 (1*E*,4*E*)-1,5-Bis(1-(3-chlorophenyl)-1*H*-benzo[*d*]imidazole-2-yl)penta-1,4-dien-3-one (21b): Yellow solid was obtained in 20% yield. M.p. 201-203 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (dd, J = 6.9, 0.6 Hz, 2H), 7.81 (d, J = 15.6 Hz, 2H), 7.59-7.57 (overlapped, 4H), 7.45 (d, J = 15.3 Hz, 2H), 7.45-7.42 (overlapped, 2H), 7.39 (dt, J = 7.2, 1.2 Hz, 2H), 7.36-7.29 (overlapped, 4H), 7.22 (dd, J = 7.5, 1.5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.2, 147.9, 142.5, 136.7, 136.1, 135.9, 132.4, 131.5, 130.2, 128.1, 127.8, 126.0, 125.4, 124.7, 120.4, 110.8. IR (film) ν_{max} 1654, 1591, 1389, 1338, 1268. HRMS (ESI): *m/z* calculated for $C_{31}H_{21}Cl_2N_4O$ $[M+H]^+$: 535.1092; 537.1063; 539.1033. Found:

535.1090; 537.1055; 539.1028. HPLC purity 98.3% (30 min run of 15-85% CH_3CN in aqueous solution of ammonium formate (1.26 g ammonium formate in 1000 mL water), with 30 min gradient, 1.0 mL/min).

4.7.10 (1*E*,4*E*)-1,5-Bis(1-(thiophen-2-yl)-1*H*-benzo[*d*]imidazol-2-yl)penta-1,4-dien-3-one (21f): Yellow solid was obtained in 55% yield. M.p. 175 °C (decomposed). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (dd, J = 6.3, 1.2 Hz, 2H), 7.69 (d, J = 15.6 Hz, 2H), 7.58 (d, J = 15.6 Hz, 2H), 7.47 (dd, J = 5.1, 1.8 Hz, 2H), 7.38 – 7.30 (overlapped, 6H), 7.19 – 7.15 (overlapped, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.4, 149.4, 143.1, 138.1, 135.0, 131.9, 128.4, 126.9, 126.8, 126.7, 125.4, 124.5, 120.6, 111.1. IR (film) ν_{max} 1616, 1548, 1453, 1386, 1356, 1324, 1228, 1176, 764, 746, 700, 669 cm^{-1}; HRMS (ESI): *m/z* calculated for $C_{27}H_{19}N_4OS_2$ $[M+H]^+$: 479.1000. Found: 479.0996. HPLC purity 93.6% (30 min run of 10-85% CH_3CN in H_2O with 30 min gradient, 1.0 mL/min).

4.7.11 (1*E*,4*E*)-1,5-Bis(1-phenyl-1*H*-pyrrolo[3,2-*b*]pyridin-2-yl)penta-1,4-dien-3-one (25a): The yellow solid was obtained in 23% yield. M.p. 195-197 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.52 (dd, J = 4.6, 1.1 Hz, 2H), 7.86 (d, J = 8.4 Hz, 2H), 7.61 (d, J = 3.3 Hz, 2H), 7.55 (t, J = 7.8 Hz, 6H), 7.49 – 7.45 (m, 4H), 7.40 (dt, J = 7.2, 1.2 Hz, 2H), 7.16 (dd, J = 8.4, 4.5 Hz, 2H), 6.92 (d, J = 3.3 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.8, 144.0, 135.6, 134.0, 131.2, 130.4, 129.5, 128.5, 128.2, 128.1, 127.4, 119.6, 118.8, 104.6. IR (film) ν_{max} 1654, 1617, 1595, 1507, 1489, 1456, 1412, 1332, 1297.1, 1240.6, 1187.0, 1147.0, 1101.0, 1057.1, 1033.1, 980.8, 950.7, 772.5, 728.1, 700.9, 668.7, 579.2, 564.3 cm^{-1}. HRMS (ESI): *m/z* calculated for $C_{31}H_{23}N_4O$ $[M+H]^+$: 467.1872. Found: 467.1867.

4.7.12. (1*E*,4*E*)-1,5-Bis(1-(3-methoxyphenyl)-pyrrolo[3,2-b]pyridine-2-yl)penta-1,4-dien-3-one (25c): Orange solid was obtained in 53% yield. M.p.109 – 112 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.53

(d, *J* = 3.9 Hz, 2H), 7.53 (d, *J* = 15.9 Hz, 2H), 7.45 (t, *J* = 8.4 Hz, 4H), 7.32 (s, 2H), 7.11 (dd, *J* = 8.4, 4.5 Hz, 2H), 7.06 (ddd, *J* = 8.4, 2.4, 0.6 Hz, 2H), 6.95 (d, *J* = 15.9 Hz, 2H), 6.94 – 6.90 (overlapped, 2H), 6.86 (t, *J* = 2.1 Hz, 2H), 3.84 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.1, 160.9, 145.6, 145.5, 138.6, 137.0, 133.5, 131.5, 130.8, 127.7, 120.4, 118.9, 118.4, 114.7, 114.1, 105.3, 55.8. IR (film) ν_{max} 1669, 1589, 1559, 1527, 1492, 1457, 1427, 1404, 1368, 1310, 1283, 1260, 1196, 1175, 1127, 1085, 1037, 996, 850, 773, 732, 715, 689, 629, 562, 535 cm^{-1}. HRMS (ESI): *m/z* calculated for $C_{33}H_{27}N_4O_3$ $[M+H]^+$: 527.2083. Found: 527.2081.

4.7.13 (1*E*,4*E*)-1,5-Bis(1-(thiophen-2-yl)-1*H*-pyrrolo[3,2-b]pyridin-2-yl)penta-1,4-dien-3-one (25f): Orange solid was obtained in 52% yield. M.p. 156 °C (decomposed). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.52 (s, 2H), 7.97 (d, *J* = 8.1 Hz, 2H), 7.79 (d, *J* = 15.3 Hz, 2H), 7.56 (d, *J* = 2.7 Hz, 2H), 7.29 (d, *J* = 3.6 Hz, 2H), 7.20 (dd, *J* = 8.1, 4.5 Hz, 2H), 7.03 (d, *J* = 3.6 Hz, 2H), 6.89 (s, 2H), 6.75 (d, *J* = 15.3 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.0, 147.7, 144.8, 143.3, 135.7, 135.5, 131.8, 131.6, 124.1, 119.9, 118.3, 118.0, 116.5, 106.4. IR (film) ν_{max} 1661, 1599, 1559, 1541, 1514, 1187, 1028, 777, 668 cm^{-1}. HRMS (ESI): *m/z* calculated for $C_{27}H_{19}N_4OS_2$ $[M+H]^+$: 479.1000. Found: 479.0998. HPLC purity 98.1% (30 min run of 10-85% CH_3CN in H_2O with 30 min gradient, 1.0 mL/min).

4.8 Cell culture.

All cell lines were initially purchased from American Type Culture Collection (ATCC). The PC-3 and LNCaP prostate cancer cell lines were routinely cultured in RPMI-1640 medium supplemented with 10% FBS and 1% penicillin/streptomycin. Cultures were maintained in a high humidity environment supplemented with 5% carbon dioxide at a temperature of 37ºC. The DU-145 prostate cancer cells were routinely cultured in Eagle's Minimum Essential Medium (EMEM) supplemented with 10% FBS and 1% penicillin/ streptomycin.

4.9 WST-1 cell proliferation assay.

PC-3, DU-145, or LNCaP cells were plated in 96-well plates at a density of 3,200 each well in 200 µL of culture medium. The cells were then treated with curcumin, or synthesized analogs separately at different doses for 3 days, while equal treatment volumes of DMSO were used as vehicle control. The cells were cultured in a CO_2 incubator at 37 ^oC for three days. 10 µL of the premixed WST-1 cell proliferation reagent (Clontech) was added to each well. After mixing gently for one minute on an orbital shaker, the cells were incubated for additional 3 hours at 37 ^oC. To ensure homogeneous distribution of color, it is important to mix gently on an orbital shaker for one minute. The absorbance of each well was measured using a microplate-reader (Synergy HT, BioTek) at a wavelength of 430 nm. The IC_{50} value is the concentration of each compound that inhibits cell proliferation by 50% under the experimental conditions and is the average from triplicate determinations that were reproducible and statistically significant. For calculating the IC_{50} values, a linear proliferative inhibition was made based on at least five dosages for each compound.

4.10. Pharmacokinetic study (sampling and analysis).[18]

Male Sprague-Dawley rats, weighing between 250 and 300 g (Charles River Laboratories, Portage, MI) were used for the pharmacokinetic studies of **17a** and **17d**. Rats (n = 4) were given oral gavage containing 5% dimethyl sulfoxide (DMSO), 40% polyethylene glycol 400, 55% saline-dissolved compound at a single dose of 10 mg/kg. After oral administration, blood samples were collected from the lateral tail vein of the rats at 1, 3, 6, and 24 h. Rat blood was collected with a capillary into 1.5 mL microcentrifuge tubes containing 0.01 mL of 10% EDTA anticoagulant. Plasma was then separated from red cells by centrigugation in a refrigerated centrifuge at 4 ^oC and transferred to a separate tube. The plasma samples were frozen at -80 ^oC until analysis. All procedures involving these animals were conducted in compliance with state and federal laws, standards of the U.S. Department of Health and

Human Services, and guidelines established by Xavier University are accredited by the Association for the Assessment and Accreditation of Laboratory Animal Care.

4.11. High performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) for drug analysis in plasma Samples.

Plasma samples were extracted with chloroform/methanol (2:1) using traditional Folch method for lipid extraction. Methanol (1 mL) and chloroform (2 mL) were added to each plasma sample followed by addition of 5 ng of trans-tamoxifen-$^{13}C2$, ^{15}N to each sample as the internal standard. The mixtures were stored at -20 ^{o}C overnight. Next the samples were sonicated for 5 min and centrifuged with a Thermo Scientific Heraeus Megafuge 16 centriguge. The top layer was transferred to another test tube. The bottom layer was washed with 1 mL of chloroform/methanol (2:1), centrifuged, and the top layer was transferred and combined with the previous top layer. Eight-tenth of a milliliter of HPLC grade water was added to the extracts. After vortexing, the mixture was centrifuged. The bottom layer was dried out with nitrogen and re-suspended in 100 µL of HPLC grade acetonitrile. An aliquot of 10 µL of sample was injected onto a Hypersil Gold column (50 mm × 2.1 mm; particle size 1.9 µM, Thermo Scientific) on a Dionex Ultimate 3000 UPLC system equipped with a TSQ Vantage triple quadrupole mass spectrometer for analysis. A binary mobile phase (A, water with 0.05% formic acid; B, acetonitrile with 0.05% formic acid) was used to achieve the gradient of initial 30% B for 1 min and then to 80% B at 8 min. The settings of HESI source were as follows: spray voltage (3200 V); vaporizer temperature (365 ^{o}C); sheath gas pressure (45 psi); auxiliary gas pressure (10 psi); capillary temperature (330 ^{o}C). Nitrogen was used as the sheath gas and auxiliary gas. Argon was used as the collision gas.

4.12. Incubation of test compounds with liver microsomes (Total volume 500 µL).

Each test compound (curcumin, **3**, **17a**, and **17b**) was incubated with rat liver microsomes, NADPH, and UGT reaction mixtures to evaluate their metabolic stability under both phase I oxidation and phase II glucuronidation conditions. The incubation solution was prepared by adding 50 µL of potassium phosphate buffer (pH 7.4; 10×), 25 µL of NADPH solution A, 5 µL of NADPH solution B, 25 µL of pooled rat liver microsomes (Female; 20 mg/mL), 250 µL water, 100 µL of UGT Reaction Mix solution B, and 40 µL of UGT Reaction Mix solution A. The mixture was incubated at 37 ^{o}C for 5 min in incubator. Then, 5 µL of a 0.1 mM test compound dissolved in ethanol was added to the above mixture and incubated at 37 ^{o}C for 60 min in a temperature-controlled incubator. At the following time points an aliquot of 50 µL incubation mixture was sampled: 0, 5, 15, 30, 45, 60 mins. To the aliquot of incubation mixture was added 150 µL of MeOH to terminate the reaction and 5 ng of E-tamoxifen-2C13, N15 as internal standard for quantitative analysis. The MeOH-incubation mixture was then centrifuged at 10,000 × g for 4 min at 4 ^{o}C. The clear top layer supernatant was injected on a UHPLC-TSQ mass spectrometer to measure the concentration of the test compounds present in the incubation solution at different time points.

4.13. Statistical analysis

All data are represented as the mean ± standard deviation (S.D.) for the number of experiments indicated. Other differences between treated and control groups were analyzed using the Student's t-test. A p-value < 0.05 was considered statistically significant.

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Appendix A. Supplementary data.

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org//.

REFERENCES

1. Gupta SC, Prasad S, Kin JH, Patchva S, Webb LJ, Priyadarsini IK, Aggarwal BB. *Nat Prod Rep*. 2011;28:1937-1955.
2. Chen Q-H. *Anti-Cancer Agents Med Chem*. 2015;15:138-156.
3. Dorai T, Gehani N, Katz A. 2000;3:84-93.
4. Teiten M-H, Gaascht F, Eifes S, Dicato M, Diederich M. *Genes Nutr*. 2010;5:61-74.
5. Toennesen HH, Karlsen J, Mostad A. *Acta Chem Scand, Ser. B.* 1982;B36:475-479.
6. Anand P, Kunnumakkara AB, Newman RA, Aggarwal BB. *Mol Pharm*. 2007;4:807-818.
7. Garcea G, Jones DJ, Singh R, Dennison AR, Farmer PB, Sharma RA, Steward WP, Gescher AJ, Berry DP. *Br J Cancer*. 2004;90:1011-1015.
8. Shetty D, Kim YJ, Shim H, Snyder JP. *Molecules*. 2015;20:249-292.
9. Samaan N, Zhong Q, Fernandez J, Chen G, Hussain AM, Zheng S, Wang G, Chen Q-H. *Eur J Med Chem* 2014;75:123-131.
10. Wang R, Chen C, Zhang X, Zhang C, Zhong Q, Chen G, Zhang Q, Zheng S, Wang G, Chen Q-H, *J Med Chem*. 2015;58:4713-4726.
11. Meunier B, de Visser SP, Shaik S. *Chem Rev*. 2004;104:3947-3980.
12. Zhu L, Guo P, Li G, Lan J, Xie R, You J. *J Org Chem*. 2007;72:8535-8538.

13. Kenneth LK. *J Org Chem* 1978;43:4381-4383.

14. Corbel B, Medinger L, Haelters JP, Sturtz G, *Synthesis*. 1985:1048–1051.

15. Cao B, Qi Y, Zhang G, Xu D, Zhan Y, Alvarez X, Guo Z, Fu X, Plymate SR, Sartor O, Zhang H, Dong Y. *Oncotarget*. 2014;30:1646-1656.

16. Liu LL, Xie N, Sun S, Plymate S, Mostaghel E, Dong X. *Oncogene*. 2014;12:3140-3150.

17. Hack S, Wörlein B, Höfner G. Pabel J, Wanner KT. *Eur J Med Chem.* 2011;46:1483-1498.

18. Lee Y-Z, Yang C-W, Hsu H-Y, Qiu Y-Q, Yeh T-K, Chang H-Y, Chao Y-S, Lee S-J. *J Med Chem*. 2012;55:10363-10377.

Highlights

- In vitro potency of 1,5-bis(1*H*-imidazol-2-yl)penta-1,4-diene-3-one was evaluated
- Thirteen 1-aryl derivatives were synthesized through a three-step transformation
- Six bis(1-arylimidazol-2-yl)pentadienones exhibit superior potency than curcumin
- Bis(1-(2-methoxyphenyl)-1*H*-imidazol-2-yl)pentadienone has good bioavailability