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# Triarylethylene-indolin-2,3-dione molecular conjugates: design, synthesis, docking studies and anti-proliferation evaluation†

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A series of 1*H*-1,2,3-triazole-linked ospemifene-isatin and *O*-methylated ospemifene-isatin conjugates were synthesized and assayed for their anti-proliferative activities against estrogen-responsive as well as estrogen-non-responsive cells. The non-cytotoxic conjugate **14e**, with an optimal combination of bromo substituents at the C-5/C-7 positions of isatin, proved to be a promising hit with an IC<sub>50</sub> value of 31.62 μM against MCF-7 and 19.23 μM against MDA-MB-231. The observed anti-proliferative activities of active conjugates were further corroborated *via* docking studies carried out on estrogen receptor subtypes α and β.

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## Introduction

Breast cancer (BC) is the second-leading cancer worldwide, and shows a high incidence of morbidity and mortality. The major risk factor for BC is being of the female sex since a high level of estrogen in females not only fuels the division of breast cells but also escalates the damage to DNA. BC is more prevalent in the age groups 14–30 (younger cells more prone to carcinogens) and above 40 (lifestyle and menopause).<sup>1,2</sup> The low rate of breast feeding in nations with high resources is also considered to be a contributing factor for the disease, rendering BC a classical cancer of these nations. The Global Cancer Observatory (GLOBOCAN) estimated that 2 088 849 new cases of BC with 626 679 deaths occurred worldwide in 2018, with India accounting for 17% of the world's population that suffer from this disease.<sup>3</sup>

Triarylethylenes constitute a well-known pharmacophore with non-steroidal and non-hormonal properties. The core is present in non-steroidal architecturally varied collections of compounds called selective estrogen receptor modulators (SERMs) that function by binding estrogen receptors. These compounds are different from pure anti-estrogens in their

action, as SERMs act variedly in different tissues, selectively inhibiting or stimulating estrogen-like actions.<sup>4,5</sup> Tamoxifene (TAM), toremifene (TMF) and clomifene are clinically approved SERMs for the treatment of BC and display estrogenic effects in bones and anti-estrogenic effects in breast and endometrium tissues. Further side effects related to TAM have been shown to include hot flashes, insomnia, depression and dizziness.<sup>6–8</sup> Ospemifene, a hydroxylated TAM metabolite Y, is involved in a metabolic pathway similar to that for TAM and is recommended as a first-line drug for moderate to severe dyspareunia associated with vulvar and vaginal atrophy (VVA).<sup>9,10</sup>

Use of isatin (1*H*-indole 2,3-dione) as a pharmacophore is of great interest and has been associated with a diverse range of biological activities such as anti-cancer, anti-depressant, anti-convulsant, anti-fungal, anti-HIV and anti-angiogenic activities.<sup>11–16</sup> Inhibitions of tyrosine kinase and cyclin-dependent kinases are some of the mechanistic pathways through which isatin exerts its anticancer potential. Bazedoxifene (BZA), an indole-based SERM, has been approved for the prevention and treatment of post-menopausal osteoporosis and displays slightly higher binding affinity to ER-α than to ER-β. Recent studies have shown that BZA, when given in combination with conjugated estrogens, relieves hot flashes and also improves vulvovaginal atrophy and its symptoms.<sup>17,18</sup> The structures of various United States Food and Drug Administration (US-FDA)-approved drugs displaying relatively substantial affinity for hormonal receptors are provided in Fig. 1.

Recent reports from our laboratory have disclosed the synthesis and anti-proliferative activities of ospemifene-isatin conjugates with promising results against MCF-7 cells, in contrast to the results against MDA-MB-231 cells, with the most active conjugate of the series exhibiting an IC<sub>50</sub> value of 1.56 μM.<sup>22</sup> The currently described work was a continuation and

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† Electronic supplementary information (ESI) available: <sup>1</sup>H and <sup>13</sup>C NMR data of all the synthesized conjugates along with scanned (<sup>1</sup>H, <sup>13</sup>C, DEPT, D<sub>2</sub>O) NMR spectra for representative compounds *viz.* **13a**, **13b**, **14a**, **14b**, **14c**, **14e**, **15c**, **15d**. See DOI: 10.1039/c9ra08776a



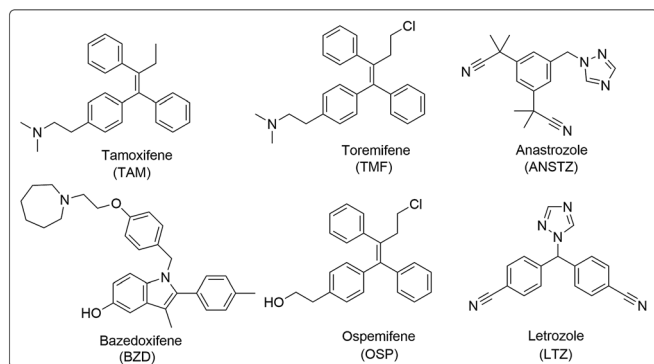


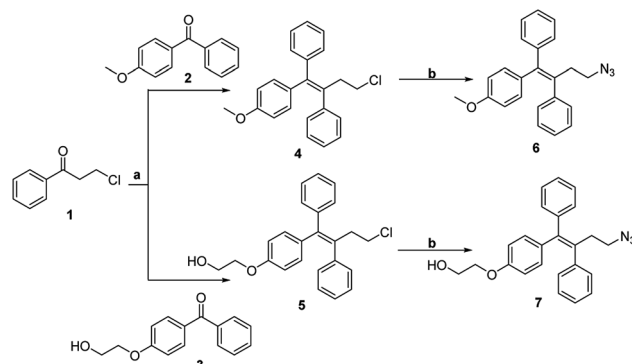
Fig. 1 US-FDA-approved active SERMs (TAM, TMF, BZD and OSP) and estrogen synthesis inhibitors (ANSTZ and LTZ).

logical extension of our interests<sup>19–21</sup> and involved the use of a 1*H*-1,2,3-triazole core to link C-5-functionalized isatin to the alkyl side chain of ospemifene and methylated ospemifene. The use of triazole as a linker was further supported by its presence in anastrozole, an aromatase inhibitor used in BC chemotherapy.<sup>23</sup> The present series of compounds was designed based on these literature rationales, and this design is depicted in Fig. 2.

## Results and discussion

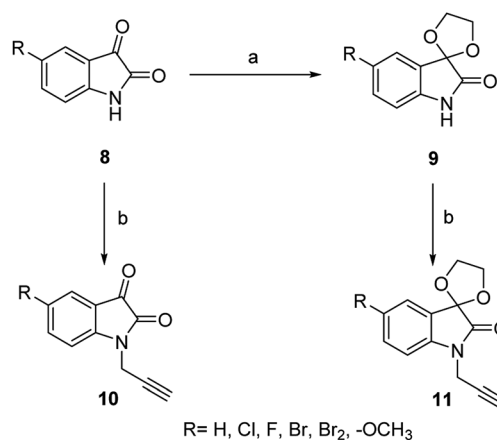
### Synthetic chemistry

The methodology for the synthesis of the click chemistry precursors (*Z*)-2-(4-(4-azido-1,2-diphenylbut-1-en-1-yl)phenoxy)ethan-1-ol **7** and its derivative (*Z*)-(4-azido-1-(4-methoxyphenyl)but-1-ene-1,2-diyl)dibenzene **6** involved an initial McMurry reaction between 3-chloro-1-phenylpropan-1-one **1** with (4-methoxyphenyl)(phenyl)methanone **2** or (4-(2-hydroxyethoxy)phenyl)(phenyl)methanone **3** under refluxing conditions in a nitrogen atmosphere using Zn/TiCl<sub>4</sub> in anhydrous tetrahydrofuran (THF) to afford **4** and **5**, in a *Z/E* ratio of >98%.<sup>24</sup> Sodium azide promoted nucleophilic substitution of **4** and **5** in anhydrous dimethylformamide (DMF) and gave the desired precursors **6** and **7**, respectively (Scheme 1).



Scheme 1 Synthesis of ospemifene and the *O*-methoxy derivative of ospemifene. Reagents and conditions: (a) Zn/TiCl<sub>4</sub>, anhydrous THF, rt to reflux, 6 h. (b) NaN<sub>3</sub>, DMF, 60 °C, 4 h.

The second precursors, *viz.* *N*-propargylated isatin **10** and *N*-propargylated isatin-spiroketal **11**, were obtained by deploying a previously reported methodology<sup>25,26</sup> as shown in Scheme 2.



Scheme 2 Syntheses of *N*-propargylated C-5-substituted isatin **10** and spiroketal-*N*-propargylated C-5-substituted isatin **11**. Reagents and conditions: (a) 2-bromoethan-1-ol, NaH, DMF, 80 °C, 6 h. (b) Propargyl bromide, NaH, DMF, 80 °C, 6 h.

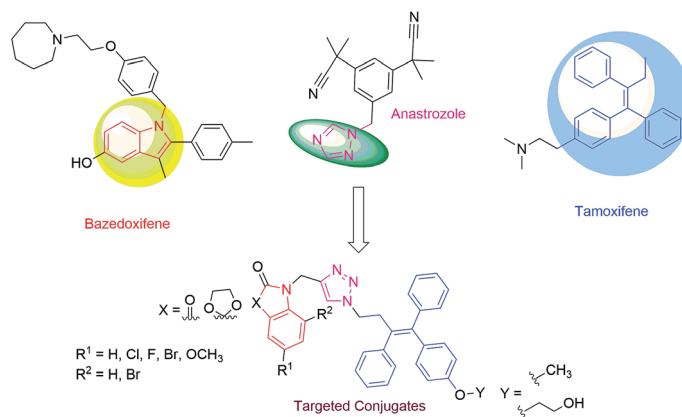


Fig. 2 Design of the targeted 1*H*-1,2,3-triazole-linked ospemifene–isatin and *O*-methylated ospemifene–isatin conjugates.



A Cu(I)-promoted azide-alkyne 1,3-dipolar cycloaddition reaction of appropriate precursors, namely **6** with **10** and **11**, afforded the targeted 1*H*-1,2,3-triazole-linked *O*-methylated ospemifene-isatin/spiroisatins **12** and **13**, while similar cycloaddition reactions of **7** with **10** and **11** gave ospemifene-isatin/spiroisatin conjugates **14** and **15** (Scheme 3).

The synthesized conjugates were purified *via* column chromatography using an ethylacetate : hexane (70 : 30) mixture as the eluent. The structure to the synthesized compounds was assigned on the basis of spectral data and analytical evidence. Compound **14b**, for example, exhibited a molecular ion peak at *m/z* 604.1881 ( $M^+$ ) in its high-resolution mass spectrum (HRMS). Its  $^1\text{H}$  NMR spectrum included the characteristic signals at  $\delta$  2.97 (t,  $J = 7.2$  Hz), 3.86 (t,  $J = 4.0$  Hz), 3.94 (t,  $J = 4.7$  Hz), 4.26 (t,  $J = 7.4$  Hz) and 4.94 (s), corresponding to its different methylenes. Characteristic absorptions at  $\delta$  157.3 and 182.4 in its  $^{13}\text{C}$  NMR spectrum, corresponding to isatin ring carbonyls, further corroborated the assigned structure.

### Anti-proliferative activities of synthesized conjugates against MCF-7 (ER+) and MDA-MB-231 (ER-) cells

The synthesized ospemifene and *O*-methylated ospemifene-isatin conjugates were evaluated for their anti-proliferative activities against estrogen-dependent ER(+) and non-estrogen-dependent ER(-) cells using the MTT assay with plumbagin as a positive control. Their percentage growth inhibitions for various concentrations *viz.* 1, 5, 10, 20, 40, 50 and 100  $\mu\text{M}$  were

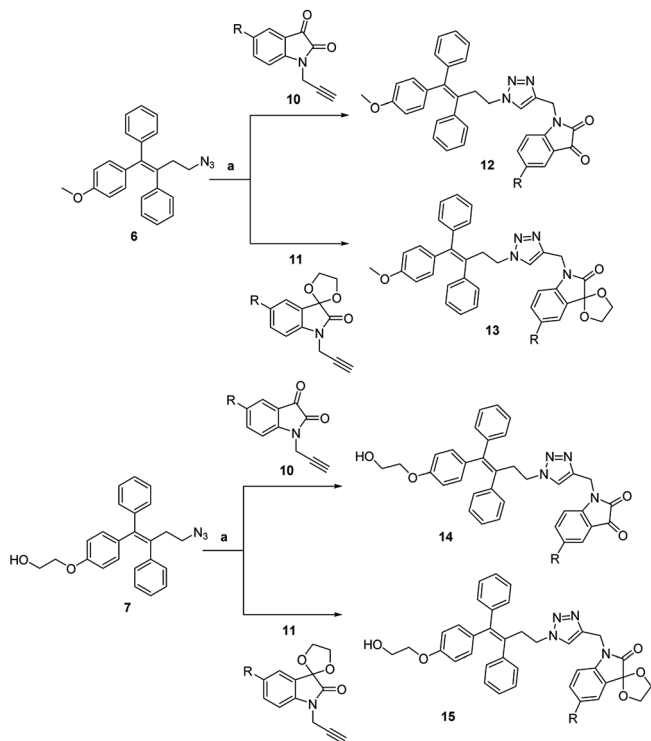
determined and the results are provided in Fig. S1–S4 (see ESI $^\dagger$ ), while the IC<sub>50</sub> data are listed in Table 1.

Analysis of these data revealed an interesting structure activity relationship (SAR), one depending on the nature of the substituents at the C-5/C-7 positions as well as the nature of the functional group at the C-3 position of the isatin ring. Of the *O*-methylated ospemifene-isatin conjugates, **12a** and **12b** were selective against MDA-MB-231 cells while **12c**, having bromo substituents at the C-5 and C-7 positions of the isatin ring, displayed IC<sub>50</sub> values of 13.06 and 14.79  $\mu\text{M}$  against estrogen-responsive and estrogen-non-responsive cells, respectively. The replacement of the keto-carbonyl with a spiroketal at the C-3 position of the isatin core in conjugates **13a–c** proved to be detrimental, except in the case of **13a**, which exhibited IC<sub>50</sub> values of 21 and 20.39  $\mu\text{M}$  against MCF-7 and MDA-MB-231 cells, respectively. Among the ospemifene-isatin conjugates **14a–e**, the presence of a halogen substituent at the C-5 position of the isatin ring improved the anti-proliferative activities, with the order of preference being  $-\text{Cl} > -\text{Br} > -\text{F}$ . The replacement of keto-carbonyl with spiroketal at the C-3 position of the isatin ring again resulted in a deterioration of the anti-proliferative activities, as evident by compounds **15a–d**, which were inactive against cells from both cell lines. Of the most active conjugates, **14b** and **14e** were selective for the estrogen-independent MDA-MB-231 cells.

Based on the observed activity profiles, a generalized SAR for the series of synthesized ospemifene-isatin/isatin/spiroketal and *O*-methylated ospemifene-isatin/isatin/spiroketal compounds was derived, and this SAR is illustrated in Fig. 3. The results indicated that the inclusion of bromo substituents at C-5/C-7, a keto-carbonyl at the C-3 position of the isatin ring, and *O*-methylation at the C-4 position of ospemifene improved the anti-proliferative activity.

### Molecular docking studies

Molecular docking was performed on a set of test compounds *viz.* **12c**, **13a**, **14b** and **14e** against the two estrogen receptor subtypes  $\alpha$  and  $\beta$  in order to identify the critical ligand-protein interactions. Compound **12c** was the most potent inhibitor of the cells from both cell lines. In the docking, the binding of **12c** to the  $\beta$ -subtype was supported by two hydrophobic interactions from residue Glu108 and the ligand at bond distances of 3.64 and 3.78 Å. These interactions were accompanied by three hydrogen bonds involving residues Glu28 and Gly109 as H-bond donors and residue Cys106 and the oxygen moiety of the ligand as H-bond acceptors (with bond distances of 2.33, 2.57 and 1.59 Å, respectively, and bond angles of 115.58°, 127.29° and 175.71°, respectively). According to the dockings, compound **13a** shared a similar binding profile with **12c** and also showed two hydrophobic interactions with residue Glu108, here with bonding distances of 3.68 and 3.82 Å, and a single hydrogen bond with donor residue Gly109, with a bond distance of 3.11 Å and bond angle of 133.67°. Compound **14b** displayed two hydrophobic interactions with Gly108 and the ligand (with bond distances of 3.57 and 3.92 Å). These interactions were accompanied by three hydrogen bonds between donor residues Glu28, Gly109 and



Scheme 3 Syntheses of 1*H*-1,2,3-triazole-linked ospemifene-isatin/spiroisatin and *O*-methylated ospemifene-isatin/spiroisatin conjugates. Reagent and conditions: (a)  $\text{CuSO}_4$ , sodium ascorbate, ethanol :  $\text{H}_2\text{O}$  (9 : 1), rt, 6–8 h.



Table 1 IC<sub>50</sub> values of the test compounds in MCF-7 and MDA-MB-231 cells

Code	Structure	MCF-7 (μM)	MDA-MB-231 (μM)	Code	Structure	MCF-7 (μM)	MDA-MB-231 (μM)
12a		>100	52.26	14c		70.71	70.71
12b		>100	75.92	14d		>100	>100
12c		13.06	14.79	14e		31.62	19.23
13a		21	20.39	15a		>100	>100
13b		>100	>100	15b		>100	>100
13c		>100	>100	15c		>100	>100
14a		>100	>100	15d		>100	>100
14b		33.13	18.11	OSP		55	>100
				TAM		50	75
				Plumbagin		3.5	4.4

Glu112 and the oxygen of the ligand (with bond distances of 2.95, 2.96 and 2.91 Å and bond angles of 146.92°, 148.12° and 160.53°, respectively). Compound 14e displayed, according to the dockings, a more extensive binding interaction network: including two hydrophobic interactions with residue Glu108 at bonding distances of 3.47 and 3.94 Å; five hydrogen bonds observed between residues Glu28, Ala29, Gly109 and Glu112 and the oxygen groups of the ligand (bond distances of 3.04, 3.96, 2.87/2.99 and 2.94 Å, and bond angles of 136.45°, 155.75°, 129.58°/154.86° and 165.31°, respectively); and a single electrostatic interaction between the bromine of the ligand and Lys214 (bond distance of 3.43 Å and bond angle of 151.48°) (Fig. S5, see ESI†).

The volume of the ligand-binding domain of ER-α has been found to be much greater than that of ER-β, and this greater

volume allowed for an improved interaction with the ligand in our dockings. Here, the interaction profile of compound 12c comprised three distinct sets of features: six hydrophobic interactions, five hydrogen bonds and a π-stacking. The hydrophobic interactions were observed between residues Leu49, Trp78, Lys224, Val228, Pro230 and Leu234 and the hydrophobic pharmacophores of the ligand (bond distances of 3.90, 3.92, 3.73, 3.34, 3.92 and 3.72 Å, respectively). The five hydrogen bonds involved residues Gly75, Lys224 and Tyr232 as donors and residue Glu75 as the acceptor (bond distances of 2.44, 3.77, 3.18 and 2.44/2.50 Å, and bond angles of 102.63°, 119.34°, 158.60° and 171.15°/161.49°, respectively). A P-type π-stacking was established between residue Trp78 and the ligand at a distance of 4.05 Å and angle of 24.79°. Compound 14e displayed a similar binding landscape with extensive



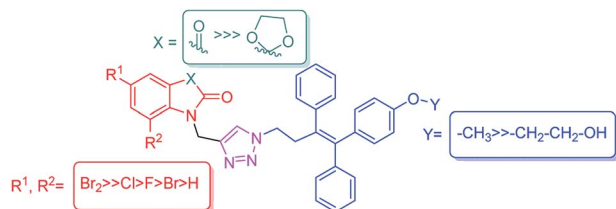


Fig. 3 Generalized structure activity relationship of the synthesized conjugates.

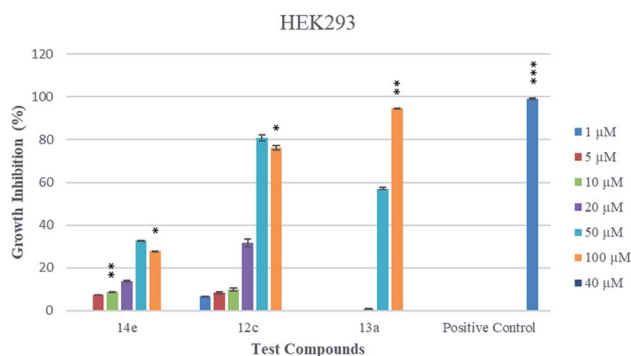


Fig. 4 Representative graph of the cell death percentages of HEK293 cells at selected concentrations of test compounds **14e**, **12c** and **13a**. Plumbagin at a concentration of 40  $\mu\text{M}$  was used as a positive control. Data are shown as mean  $\pm$  standard deviation S.D. ( $n = 3$ ), where \* $p \leq 0.05$ , \*\* $p \leq 0.01$  and \*\*\* $p \leq 0.001$  each indicate the significance of the difference with the untreated control.

hydrophobic interactions between residues Trp78, Leu220, Tyr221 and Lys224 at bond distances of 3.56, 3.96/3.85, 3.76 and 3.99/3.51 Å. Hydrogen bond interactions were identified between donor residue Leu231 and acceptor residue Glu218 (bond distances of 4.02 and 3.00 Å, and bond angles of 155.26° and 158.19°, respectively) (Fig. S6, see ESI†). A T and P-type  $\pi$ -stacking was measured between Tyr221 and the ligand (distances of 5.24 and 4.17 Å, and angles of 89.17° and 24.76°, respectively). Compounds **13a** and **14b** shared similar binding profiles, differing only in the presence of a hydrogen bond network in compound **13a** between residues Ala45 and Leu231 (bond distances of 3.23 and 3.11 Å, and bond angles of 111.57° and 164.55°, respectively) and an electrostatic interaction in compound **14b** incorporating the chloride group and Arg89 (distance of 3.81 Å, angle of 142.51°). The complexes of **12c**, **13a**, **14b** and **14e** showed high binding affinities during the dockings in the active sites of estrogen receptors (PDB ID: 3OLS/PDB ID:

3ERT) and these results are shown in Table S1 (see ESI†). Three of the most active conjugates, namely **12c**, **13a** and **14e**, were selected for determining their cytotoxicity levels against the non-tumorigenic HEK-293 cells. The percentage growth inhibitions of these compounds are presented in Fig. 4 while their  $\text{IC}_{50}$  values are listed in Table 2. Conjugate **14e** proved to be non-cytotoxic against the HEK-293 cells while the conjugates **12c** and **13a** were moderately cytotoxic.

## Conclusion

In conclusion, a series of osemipifene–isatin and *O*-methylated osemipifene–isatin conjugates were synthesized using the McMurray reaction as the key synthetic step. The synthesized conjugates were assayed for their anti-proliferative activities against ER+ (MCF-7) and ER– (MDA-MB-231) cells. The replacement of the carbonyl core with a spiroketal at the C-3 position of the isatin ring resulted in the loss of anti-proliferative activity, except in the case of **13a**, which exhibited  $\text{IC}_{50}$  values of 21 and 20.39  $\mu\text{M}$  against MCF-7 and MDA-MB-231 cells. The most potent compound of the series, **12c**, with an optimum combination of bromo substituents at C-5/C-7 and a keto-carbonyl at C-3 of the isatin ring linked to *O*-methylated osemipifene, displayed  $\text{IC}_{50}$  values of 13.06 and 14.79  $\mu\text{M}$  against MCF-7 and MDA-MB-231 cells, respectively. However **12c** was moderately cytotoxic to HEK 293 cells. On the other hand, the non-cytotoxic conjugate **14e**, with similar structural characteristics of an isatin ring linked to osemipifene, was more selective towards the ER-cells, with which it displayed an  $\text{IC}_{50}$  of 19.23  $\mu\text{M}$ , and can hence be regarded as a promising hit.

## Abbreviations

BC	Breast cancer
ER	Estrogen receptor
GLOBOCAN	Global cancer observatory
SERMs	Selective estrogen receptor modulators
TAM	Tamoxifene
TMF	Toremifene
VVA	Vulvar and vaginal atrophy
BZA	Bazedoxifene
THF	Tetrahydrofuran
DMF	Dimethylformamide
SAR	Structure activity relationship
DMEM	Dulbecco's modified Eagle's medium

## Conflicts of interest

The authors declare no conflict of interest.

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Table 2 The  $\text{IC}_{50}$  values of selected test compounds in HEK293 cells

Compound	$\text{IC}_{50}$ value
<b>12c</b>	21.61
<b>13a</b>	43.87
<b>14e</b>	>100



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## Notes and references

- 1 B. Su, S. Landini, D. D. Davis and W. R. Brueggemeier, *J. Med. Chem.*, 2017, **50**, 1635.
- 2 American Cancer Society, *Cancer facts and figures 2017*, <https://www.cancer.org/research/cancer-facts-statistics/allcancer-facts-figures/cancer-factsfigures-2017.html>.
- 3 F. Bray, J. Ferlay, I. Soerjomataram, R. L. Siegel, L. A. Torre and A. Jemal, *Ca-Cancer J. Clin.*, 2018, **68**, 394.
- 4 G. Kaur, M. P. Mahajan, M. K. Pandey, P. Singh, S. R. Ramiseti and A. K. Sharma, *Eur. J. Med. Chem.*, 2014, **86**, 211.
- 5 G. Kaur, M. P. Mahajan, M. K. Pandey, P. Singh, S. R. Ramiseti and A. K. Sharma, *Bioorg. Med. Chem. Lett.*, 2016, **26**, 1963.
- 6 J. Ellmen, P. Hakulinen, A. Partanen and D. F. Hayes, *Breast Cancer Res. Treat.*, 2003, **82**, 103.
- 7 T. L. Taras, G. T. Wurz and M. W. DeGregorio, *J. Steroid Biochem. Mol. Biol.*, 2001, **77**, 271–279.
- 8 A. DeMichele, A. Bn. Troxel, J. A. Berlin, A. L. Weber, G. R. Bunin, E. Turzo, R. Schinnar, D. Burgh, M. Berlin, S. C. Rubin, T. R. Rebbeck and B. L. Strom, *J. Clin. Oncol.*, 2008, **26**, 4151–4159.
- 9 C. Descoteaux, V. Leblanc, G. Belanger, S. Parent, E. Asselin and G. Berube, *Steroids*, 2008, **73**, 1077.
- 10 S. Adsule, S. Banerjee, F. Ahmed, S. Padhye and F. H. Sarkar, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 1247.
- 11 H. S. Ibrahim, S. M. Abou-Seri, M. Tanc, M. M. Elaasser, H. A. Abdel-Aziz and C. T. Supuran, *Eur. J. Med. Chem.*, 2015, **103**, 583.
- 12 R. Rohini, P. M. Reddy, K. Shanker, K. Kanthaiah, V. Ravinder and A. Hu, *Arch. Pharmacol. Res.*, 2011, **34**, 1077.
- 13 M. Verma, S. N. Pandeya, K. N. Singh and J. P. Stables, *Acta Pharm.*, 2004, **54**, 49.
- 14 S. N. Pandeya, P. Yogeeshwari, D. Sriram and G. Nath, *Indian J. Pharm. Sci.*, 2002, **64**, 209.
- 15 P. Selvam, N. Muruges, M. Chandramohan, Z. Debyser and M. Witvrouw, *Indian J. Pharm. Sci.*, 2008, **70**, 779.
- 16 S. K. Sridhar and A. Ramesh, *Biol. Pharm. Bull.*, 2001, **24**, 1149.
- 17 D. M. Biskobing, *Clin. Interventions Aging*, 2007, **2**, 299.
- 18 R. Kagan, R. S. Williams, K. Pan, S. Mirkin and J. H. Pickar, *Menopause*, 2010, **2**, 281.
- 19 S. Kumar, L. Gu, G. Palma, M. Kaur, A. S. Pillay, P. Singh and V. Kumar, *New J. Chem.*, 2018, **42**, 3703.
- 20 A. Singh, S. T. Saha, S. Perumal, M. Kaur and V. Kumar, *ACS Omega*, 2018, **3**, 1263.
- 21 B. Sharma, A. Singh, L. Gu, S. T. Saha, A. S. Pillay, N. Cele, P. Singh, M. Kaur and V. Kumar, *RSC Adv.*, 2019, **9**, 9809.
- 22 S. Kumar, S. T. Saha, L. Gu, G. Palma, S. Perumal, A. S. Pillay, P. Singh, A. Anand, M. Kaur and V. Kumar, *ACS Omega*, 2018, **3**, 12106.
- 23 A. Mojaddami, A. Sakhteman, M. Fereidoonzhad, Z. Faghieh, A. Najdian, S. Khahnadideh, H. Sadeghpour and Z. Rezaei, *Res. Pharma. Sci.*, 2017, **12**, 21.
- 24 L. Eklund and J. Nilsson, *New Processes for Producing Benzophenone Derivatives*, PCT WO 2011/089385 A1, 2011.
- 25 K. Kumar, S. C. Kremer, L. Kremer, Y. Guérardel, C. Biot and V. Kumar, *Organometallics*, 2013, **32**, 5713.
- 26 K. Kumar, C. Biot, S. C. Kremer, L. Kremer, Y. Guérardel, P. Roussel and V. Kumar, *Organometallics*, 2013, **32**, 7386.

