

**The scope of the Heck reaction in the synthesis of of a new family of anthracene diacrylamide G-quadruplex ligands**

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## Graphical Abstract



**The scope of the Heck reaction in the synthesis of of a new family of anthracene diacrylamide G-quadruplex ligands**

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### Abstract

The use of the Heck reaction in the synthesis of anthracene-9-monoacrylamide and anthracene-9,10-bisacrylamides as potential G-quadruplex ligands and preliminary biological testing is reported.

### Keywords

Heck, anthracene, G-quadruplex, acrylamide

### Introduction

The G-quadruplex can be described as the macromolecular structure formed when a guanine rich oligonucleotide sequence forms several Hoogsteen bonded G-tetrads.<sup>[1]</sup> These guanine rich sequences at the end of chromosomes are termed telomeres and their depletion in normal healthy somatic cells has been linked to cellular senescence, whereas their regeneration, via the telomerase pathway, in 90% of tumour cells has been linked to cancer cell “immortality”.<sup>[2]</sup>

The last 10 years has seen interest in the exploitation of telomerase mediated tumour cell immortality grow exponentially, with approaches to inducing telomere mediated apoptosis including the development of oncolytic viruses, vaccines for hTR and stabilising of the G-quadruplex structure, which must be “unravelling” before telomeric elongation can occur.<sup>[3]</sup>

The importance of the G-quadruplex structure, which is formed from the guanine rich 3' overhang in chromosomes, as an attractive target for anticancer treatment, has been reported in a number of detailed reviews.<sup>[4]</sup> A number of classes of G-quadruplex ligands, ranging from acridones to porphyrins have been reported,<sup>[5],[6],[7],[9]</sup> however, no G-quadruplex ligands have yet come to market.<sup>[8]</sup> In terms of rationalisation of G-quadruplex binding, some structure-activity relationships have already been identified using assays, NMR, UV-vis and CD spectroscopy, include;<sup>[10]</sup>

1. An extended planar structure to aid intercalation of the ligand in the stacked Hoogsteen bonded G-tetrads.
2. The presence of cationic or hydrogen bonding groups to bind to the anionic phosphate backbone.

Furthermore, we believe that any new class of compound should be amenable to further reversible functionalisation to increase the number and diversity of possible ligands for screening as exploited by Balasubramanian (DCL).<sup>[10], [11], [12]</sup>

In light of the trend for planar, nitrogen rich species to have been shown to interact with quadruplex DNA, the anthracene diacrylamide core found in **10** not only possesses the correct geometry to sit between the G-tetrads, but also can undergo reversible conjugate addition with a range of nucleophiles.<sup>[13]</sup>

## Results and Discussion

### (FIGURE 1)

An anthracene unit possessing several hydrogen bond donors/acceptors was conceived as a potential G-quadruplex ligand and a series of anthracene diacrylamides possessing various functionalities was created in an effort to consider the scope of the Heck reaction in generating a suitable library and to understand the steric and intermolecular bonding that may affect the activity of this class of ligand and how it may interact both with duplex and quadruplex DNA motifs.

### Acrylamides

Acrylamides **4a-e**, **4f**, & **4k** were synthesised using the method summarised in the experimental section. Acrylamides **4g-j** were obtained from Sigma-Aldrich and used without further purification. These acrylamides were chosen to represent a broad range of polar/lipophilic binding motifs,

### Ligands

The Heck reaction was optimised in terms of ligand (PPh<sub>3</sub> or DiPhenylPhosphinoPropane -DPPP), acrylamide ratio and anthracene precursor as indicated in table I. Early attempts to

carry out the Heck coupling using the traditional PPh<sub>3</sub> Ligand were unsuccessful (see Table I) and only 9,10-dibromoanthracene showed any appreciable reaction within the timescales indicated in the presence of an excess of acrylamide and the bidentate ligand diphenylphosphinopropane (DPPP). Interestingly, attempts to couple acrylamide **4g** to the anthracene-9,10-ditriflate resulted in the formation of dibenzoquinone, which could be the result of hydrolysis of the triflate moiety followed by oxidation.

**10** was fully characterised using <sup>1</sup>H COSY NMR and HETCOR and the  $\gamma$ -trans coupling of the acrylamide (as evidenced by the trans olefin doublets J =15-16 Hz) is observed exclusively for all reactions.

### (TABLE I)

Efforts to synthesise the N,N-dimethyl acrylamide derivative yielded poor results with trace quantities of **5** evidenced by <sup>1</sup>H NMR. In the case of 9,10-dibromoanthracene a 2:1 ratio of acrylamide/dibromoanthracene was shown to favour the formation of the monocoupled product and it was necessary to use a significant excess (6:1) of acrylamide to achieve 80% di-coupled product.

The equivalent reaction to generate **13** demanded a significant excess of acryloyl morpholine (8:1), however the good yield of **7/12** obtained indicated the reaction is not restricted to primary acrylamides despite longer reaction times being required in the case of the tertiary acrylamide.

### (TABLE II)

Using the available acrylamides **4a-4k** and an optimised Heck reaction with 9,10-dibromoanthracene, a series of anthracene diacrylamides were synthesised. acrylamides **4b** & **4d-g** failed to undergo reaction within a reasonable timeframe, however **6, 7, 9, 10, 11, 12** & **13** were all obtained in good yield and with  $\gamma$ -trans coupling. It is thought that complexation of the Pd(OAc)<sub>2</sub> catalyst especially in the case of **4b, 4d, & 4f** could interfere with the reaction pathway. **8** was obtained as a mixture of mono and diacrylamide, which could not be separated.

### Biological activity

After characterisation of the anthracene diacrylamides compounds **10** and **12** were selected, based on preliminary molecular modelling data using Chem3D energy minimisation and their having a Log P value of around 5.

Evaluation of **10** for anti-cancer activity in MCF7 and Caco-2 cell culture using MTT Cell viability assay indicates no appreciable apoptosis after 48 hrs in the presence of **10**. A 10 – day evaluation of **10** shows an IC<sub>50</sub> value of 2.5 $\mu$ M and over 80% loss of viability over the 10 day period. Interestingly MTT viability assay of **12** in MCF7 culture shows a rapid loss of cell viability over only 24hrs, with a 50% loss at concentrations as low as 5 $\mu$ M. The variation in the loss of viable cells between the two compounds suggests a differing mode of action and this is being investigated further.

### (FIGURE 2)

The in vitro formation of a tetramolecular G–quadruplex using 7-mer strand TTGGGGT (Biomers, GmbH) has recently been reported and has been visualised using <sup>1</sup>H NMR, in the presence and absence of a putative ligand. A 1mM concentration of TTGGGGT oligonucleotide, was shown not to form a quadruplex in PBS D<sub>2</sub>O/d<sub>6</sub>-DMSO (9:1) over 48hrs, however as evidenced by <sup>1</sup>H NMR, a signal correlating to the tetramolecular quadruplex in the presence of

**10** was observed after only a few minutes, suggesting that **10** can induce and stabilise this tetramolecular quadruplex.<sup>[13], [14]</sup>

**(FIGURE 3)**

**(FIGURE 4)**

Clearly duplex/quadruplex specificity needs to be investigated further and this is being carried out using the recently reported fluorescence displacement assay and further confirmation of complexation with monomolecular G-quadruplex forming oligonucleotides is underway, however the preliminary data indicates G-quadruplex stabilisation as a possible mode of action for **10** and the negligible cytotoxic effects on endothelial cells when compared to the MCF-7 cell line and the lack of immediate toxicity (as evidence for Caco-2 cell lines) suggests this class of ligand is worthy of further investigation.<sup>[14]</sup>

## Conclusions

We have conducted preliminary optimisation of the conditions for these C-C coupling reactions and the restrictions imposed on the halide and acrylamide groups for such reactions and have fully characterised 7 previously unreported compounds, which have the potential not only to be potent G-quadruplex ligands but afford a route to a range of conjugate addition products for the development of a G-quadruplex-templated dynamic combinatorial library. [4], [11], [12], [16] The promotion of quadruplex DNA formation as observed in solution by NMR coupled with initial biological data, suggests **10** possesses an anticancer activity, which renders this family of compounds worthy of further investigation in terms of both duplex/quadruplex selectivity, bioavailability and expansion of the series to better understand any QSAR that may exist.

## Experimental

Electronic Supplementary Information (ESI) available: HETCOR, 2D COSY NMR for **10**, G-quadruplex formation <sup>1</sup>H NMR spectrum and general biological experimental.

<sup>1</sup>H, <sup>13</sup>C, COSY and HETCOR NMR spectra were recorded on a JEOL ECP 400MHz. Chemical shifts are reported as ( values in ppm relative to TMS (( 0.00). All coupling constants are quoted in Hz. Elemental analysis were made on a Leeman Labs CE440 Elemental Analyzer.

Infrared spectra were determined on a ThermoNicolet 380 FT-IR. The mass spectra (*m/z*) were recorded on a Varian CP-3800 Gas Chromatograph with Varian 1200L Quadrupole Mass Spectrometer. Anthracene-9,10-ditriflate was synthesised using standard procedure and all other chemicals were purchased from the Aldrich Chemical Company.

## General preparation of acrylamide precursor

### N-(quinolin-6-yl)acrylamide (**4c**)

Et<sub>3</sub>N (8.23 ml) and the amine (27 mmol) were stirred in DCM 75 ml for 10 min at rt. Acryloyl chloride (2.66 ml) was very slowly added with the temperature being maintained at room temperature. The reaction was monitored via TLC or NMR. Upon completion, the reaction was quenched with iced water (200 ml) and the organic component extracted with DCM (3 × 50 ml). The combined organic extracts were washed with HCl (3 × 40 ml, 3 M), water (2 × 50 ml) NaOH (3 × 30 ml, 2 M) and again with water (2 × 50 ml). The organic extract was dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and evaporated under a reduced pressure. Solid acrylamides could be recrystallised from hot methanol and all acrylamides were stored below 0 °C or used immediately. Yields 70% and

above – pure by tlc - characterisation data for **4c** ( $^1\text{H}$ (400 MHz;  $d_6$ -DMSO) 10.47 (1H, s (broad), NH), 8.79 (1H, dd,  $^3J_{\text{HH}} = 2.5$  Hz,  $^4J_{\text{HH}} = 1.0$ , Ar-H), 8.46 (1H, d,  $^3J_{\text{HH}} = 2.3$  Hz, Ar-H), 8.29 (1H, dd,  $^3J_{\text{HH}} = 7.8$  Hz,  $^4J_{\text{HH}} = 1.0$  Hz, Ar-H), 7.99 (1H, d,  $^3J_{\text{HH}} = 9.0$  Hz, Ar-H), 7.88 (1H, dd,  $^3J_{\text{HH}} = 9.0$  Hz,  $^4J_{\text{HH}} = 2.3$  Hz, Ar-H), 7.49 (1H, dd,  $^3J_{\text{HH}} = 7.8$  Hz,  $^4J_{\text{HH}} = 2.5$  Hz, Ar-H), 6.52 (1H, dd,  $^3J_{\text{HH}} = 17.0$  Hz,  $^4J_{\text{HH}} = 10.0$  Hz, COCH), 6.35 (1H, dd,  $^3J_{\text{HH}} = 17.0$  Hz,  $^4J_{\text{HH}} = 2.0$  Hz,  $\text{CH}_a\text{H}_b$ ), 5.81 (1H, dd,  $^3J_{\text{HH}} = 10.0$  Hz,  $^4J_{\text{HH}} = 2.0$  Hz,  $\text{CH}_a\text{H}_b$ ), ( $^13\text{C}$  ( $d_6$ -DMSO) 164.1, 149.7, 145.4, 137.5, 136.1, 132.3, 130.1, 128.9, 127.8, 124.0, 122.4, 115.9;  $m/z$  (EI) 198[M+].

### Example preparation of acrylamide

#### 3-[10-(2-Carbamoyl-vinyl)-anthracen-9-yl]-acrylamide (10)

Triethylamine (6.6 ml, 4.81 g, 47.6 mmol) and acrylamide (3.38 g, 47.6 mmol) were added to a stirred solution of 9,10-dibromo anthracene (2.00 g, 5.9 mmol) in dimethylformamide (50 ml) accompanied by vigorous stirring at room temperature followed by addition of palladium acetate (0.27 g, 1.2 mmol) and 1,3-bis(diphenylphosphino)propane (0.49 g, 1.2 mmol). The mixture was heated to 90°C for 48hrs under an atmosphere of nitrogen. The reaction was allowed to cool and dilute HCl (15 ml, 2M) was added. The resulting precipitate was filtered and washed with water (3 x 20 ml) and diethyl ether (3 x 15 ml) and dried under vacuum before being recrystallised from ethanol to afford the diacrylamide **10** (1.49 g, 80 %) as a yellow powder; mp- 338.2 °C; ( $^13\text{C}$  ( $d_6$ -DMSO) 166.0, 158.2, 149.4, 143.2, 142.2, 126.6, 125.8, 125.5, 123.4, 121.8, 121.4, 116.1, 72.4, 32.3, 31.4, 31.0, 19.3, 14.1;  $m/z$  (EI) 316[M+]. Found C, 75.49; H, 5.51%; N, 8.91.  $\text{C}_{20}\text{H}_{16}\text{N}_2\text{O}_2$  requires C, 75.93; H, 5.10%; N, 8.85%.

### Characterisation

#### 3-[10-Bromo-anthracen-9-yl]-acrylamide (6)

mp- 258.0 °C; ( $^13\text{C}$  ( $d_6$ -DMSO) 166.0, 141.5, 134.9, 129.5, 129.4, 129.3, 128.3, 128.6, 127.3, 126.3; ( $^1\text{H}$ (400 MHz;  $d_6$ -DMSO) 8.50 (2H, d,  $^3J_{\text{HH}} = 8.8$  Hz, Ar-H), 8.26 (1H, d,  $^3J_{\text{HH}} = 16.1$  Hz), 8.24 (2H, d,  $^3J_{\text{HH}} = 8.8$  Hz, Ar-H), 7.76 (4H, ddd,  $^3J_{\text{HH}} = 8.9$  Hz,  $^3J_{\text{HH}} = 6.4$  Hz,  $^4J_{\text{HH}} = 0.9$  Hz, Ar-H), 7.66 (4H, ddd,  $^3J_{\text{HH}} = 8.9$  Hz,  $^3J_{\text{HH}} = 6.4$  Hz,  $^4J_{\text{HH}} = 0.9$  Hz, Ar-H), 7.41 (2H, s (broad),  $\text{NH}_2$ ), 6.46 (1H, d,  $^3J_{\text{HH}} = 16.1$  Hz, =CHCO), ( $^13\text{C}$  ( $d_6$ -DMSO) 166.0, 141.5, 134.9, 129.5, 129.4, 129.3, 128.3, 128.6, 127.3, 126.3;  $m/z$  (EI) 326 [M+]. Found C, 61.89; H, 3.72%; N, 4.18%.  $\text{C}_{17}\text{H}_{12}\text{BrNO}$  requires C, 62.60%; H, 3.71%; N, 4.29%.

#### 3-[10-Bromo-anthracen-9-yl]-acryloylmorpholine (7)

mp- 278.2 °C; ( $^13\text{C}$  ( $d_6$ -DMSO) 166.3, 145.4, 139.3, 138.2, 131.8, 127.7, 127.6, 126.7, 126.5, 121.8, 121.4, 126.3, 125.9, 43.0, 30.5; ( $^1\text{H}$ (400 MHz;  $d_6$ -DMSO) 8.48 (2H, d,  $^3J_{\text{HH}} = 8.6$  Hz, Ar-H), 8.31 (2H, d,  $^3J_{\text{HH}} = 15.7$  Hz, Ar-CH=), 8.20 (2H, d,  $^3J_{\text{HH}} = 8.6$  Hz, Ar-H), 7.64 (2H, ddd,  $^3J_{\text{HH}} = 10.0$  Hz,  $^3J_{\text{HH}} = 5.2$  Hz,  $^4J_{\text{HH}} = 1.1$  Hz, Ar-H), 7.54 (2H, ddd,  $^3J_{\text{HH}} = 10.0$  Hz,  $^3J_{\text{HH}} = 5.2$  Hz,  $^4J_{\text{HH}} = 1.1$  Hz, Ar-H), 6.93(2H, d,  $^3J_{\text{HH}} = 15.7$  Hz, =CHCO), 3.54-3.60 (16H, m,  $\text{OCH}_2\text{CH}_2\text{N}$ ). ( $^13\text{C}$  ( $d_6$ -DMSO) 166.3, 145.4, 139.3, 138.2, 131.8, 127.7, 127.6, 126.7, 126.5, 121.8, 121.4, 126.3, 125.9, 43.0, 30.5;  $m/z$  (EI) 393[M+]. Found C, 63.89%; H, 4.07%; N, 3.72%.  $\text{C}_{21}\text{H}_{16}\text{NO}_2\text{Br}$  requires C, 64.12%; H, 4.07%; N, 3.56%.

#### (2E,2'E)-3,3'-(anthracene-9,10-diyl)bis(1-(piperidin-1-yl)prop-2-en-1-one) (8)

mp- 294.4 °C; ( $^13\text{C}$  ( $d_6$ -DMSO) 166.0 (C=O), 1600 (C=C); ( $^1\text{H}$ (400 MHz;  $\text{CDCl}_3$ ) 8.53 (2H, d,  $^3J_{\text{HH}} = 15.6$  Hz, Ar-CH=), 8.28 (4H, dd,  $^3J_{\text{HH}} = 6.8$  Hz,  $^4J_{\text{HH}} = 3.3$  Hz, Ar-H), 7.50 (4H, dd,  $^3J_{\text{HH}} = 6.8$  Hz,  $^4J_{\text{HH}} = 3.3$  Hz, Ar-H), 6.84 (2H, d,  $^3J_{\text{HH}} = 15.6$  Hz, =CHCO), 3.77 (4H, m,  $\text{NCH}_a\text{H}_b$ ), 3.55

(4H, m, NCH<sub>a</sub>H<sub>b</sub>), 1.70 (8H, m, NCH<sub>a</sub>H<sub>b</sub>CH<sub>2</sub>), 1.61 (4H, m, NCH<sub>a</sub>H<sub>b</sub>CH<sub>2</sub>CH<sub>2</sub>); (c (CDCl<sub>3</sub>) 164.1, 138.2, 132.0, 129.0, 128.7, 126.5, 126.2, 46.9, 43.2, 24.7; *m/z* (EI) 452[M+]. Found C, 80.09%; H, 6.92%; N, 5.70%. C<sub>30</sub>H<sub>32</sub>N<sub>2</sub>O<sub>2</sub> requires C, 79.64%; H, 7.08%; N, 6.19%.

**(2E,2'E)-3,3'-(anthracene-9,10-diyl)bis(N-(1,3-dihydroxy-2-(hydroxymethyl)propan-2-yl)acrylamide) (11)**

mp- 250.2 °C; (max (Nujol)/cm<sup>-1</sup> 3400 (OH), 3250 (N-H), 1660 (C=O), 1600 (C=C); (H(400 MHz; d<sub>6</sub>-DMSO) 9.04 (2H, s (broad), NH), 8.25 (2H, d, <sup>3</sup>J<sub>HH</sub> = 16.0 Hz, Ar-CH=), 8.23 (4H, dd, <sup>3</sup>J<sub>HH</sub> = 6.5 Hz, <sup>4</sup>J<sub>HH</sub> = 3.3 Hz, Ar-H), 7.59 (4H, dd, <sup>3</sup>J<sub>HH</sub> = 6.5 Hz, <sup>4</sup>J<sub>HH</sub> = 3.3 Hz, Ar-H), 6.68 (2H, d, <sup>3</sup>J<sub>HH</sub> = 16.0 Hz, =CHCO), 4.84 (6H, t, <sup>3</sup>J<sub>HH</sub> = 5.8 Hz, OH), 3.68 (12H, d, <sup>3</sup>J<sub>HH</sub> = 5.8 Hz, CH<sub>2</sub>), (c (d<sub>6</sub>-DMSO) 165.7, 135.6, 132.6, 131.7, 129.0, 126.8, 126.4, 63.5, 61.0; *m/z* (EI) 524[M+]. Found C, 63.89; H, 5.92%; N, 5.69. C<sub>28</sub>H<sub>32</sub>N<sub>2</sub>O<sub>8</sub> requires C, 64.12; H, 6.11%; N, 5.34%.

**(2E,2'E)-3,3'-(anthracene-9,10-diyl)bis(1-morpholinoprop-2-en-1-one) (12)**

mp- 255 °C; (max (Nujol)/cm<sup>-1</sup> 1660 (C=O), 1600 (C=C); (H(400 MHz; CDCl<sub>3</sub>) 8.63 (2H, d, <sup>3</sup>J<sub>HH</sub> = 15.6 Hz, Ar-CH=), 8.26 (4H, dd, <sup>3</sup>J<sub>HH</sub> = 7.0 Hz, <sup>4</sup>J<sub>HH</sub> = 3.1 Hz, Ar-H), 7.52 (4H, dd, <sup>3</sup>J<sub>HH</sub> = 7.0 Hz, <sup>4</sup>J<sub>HH</sub> = 3.1 Hz, Ar-H), 6.79 (2H, d, <sup>3</sup>J<sub>HH</sub> = 15.6 Hz, =CHCO), 3.80 (16H, m (broad), NCH<sub>2</sub>CH<sub>2</sub>O), (c (d<sub>6</sub>-DMSO) 164.9, 140.8, 132.0, 128.9, 126.0, 66.8, 46.2, 42.6; *m/z* (EI) 479[M+Na]. Found C, 74.06; H, 5.92%; N, 5.92. C<sub>28</sub>H<sub>28</sub>N<sub>2</sub>O<sub>4</sub> requires C, 73.68%; H, 6.14%; N, 6.14%.

**(2E,2'E)-3,3'-(anthracene-9,10-diyl)bis(N-phenylacrylamide) (13)**

mp- 368.5 °C; (max (Nujol)/cm<sup>-1</sup> 3300 (N-H), 1663 (C=O), 1600 (C=C); (H(400 MHz; d<sub>6</sub>-DMSO) 10.40(2H, s (broad), NH), 8.50 (2H, d, <sup>3</sup>J<sub>HH</sub> = 15.9 Hz, Ar-CH=), 8.23 (4H, dd, <sup>3</sup>J<sub>HH</sub> = 6.8 Hz, <sup>4</sup>J<sub>HH</sub> = 3.3 Hz, Ar-H), 7.79 (4H, d, <sup>3</sup>J<sub>HH</sub> = 7.6 Hz, Ar-H (Aniline)), 7.66 (4H, dd, <sup>3</sup>J<sub>HH</sub> = 6.8 Hz, <sup>4</sup>J<sub>HH</sub> = 3.3 Hz, Ar-H), 7.39 (4H, t, <sup>3</sup>J<sub>HH</sub> = 7.6 Hz, Ar-H (Aniline)), 7.13 (4H, t, <sup>3</sup>J<sub>HH</sub> = 7.6 Hz, Ar-H (Aniline)), 6.75(2H, d, <sup>3</sup>J<sub>HH</sub> = 15.9 Hz, =CHCO), (c (d<sub>6</sub>-DMSO) 164.1, 155.9, 149.4, 134.0, 132.5, 132.1, 129.7, 128.9, 127.1, 125.4 121.8, 121.4; *m/z* (EI) 468[M+]. Found C, 81.87%; H, 5.51%; N, 5.69%. C<sub>32</sub>H<sub>24</sub>N<sub>2</sub>O<sub>2</sub> requires C, 82.05%; H, 5.13%; N, 5.98%.

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**Figure. 1** Reaction scheme for acylamide and anthracene diacrylamide synthesis (**4g, 4h, 4i & 4j** were obtained from Sigma-Aldrich)

SM(c)	Ligand	Ratio(d)	Acrylamide	Duration (Hrs)	Product (ratio)	Yield (%)
1	PPh3	2:1	g	130	-	0
1	DPPP	2:1	g	130	-	0
1	DPPP	2:1	h	125	5	5
2	PPh3	2:1	h	120	5	10
2	DPPP	2:1	g	150	4	5
2	DPPP	2:1	h	64	5	75
3	PPh3	2:1	h	120	-(a)	-
3	DPPP	2:1	h	120	-(a)	-

2	DPPP	4:1	h	72	5 & 9 (1:2.3)	30(b)
2	DPPP	6:1	h	72	5 & 9 (1:4)	70(b)
2	DPPP	8:1	h	48	9	80
2	DPPP	4:1	j	86	6	71
2	DPPP	8:1	j	96	6 & 11 (3:1)	73(b)

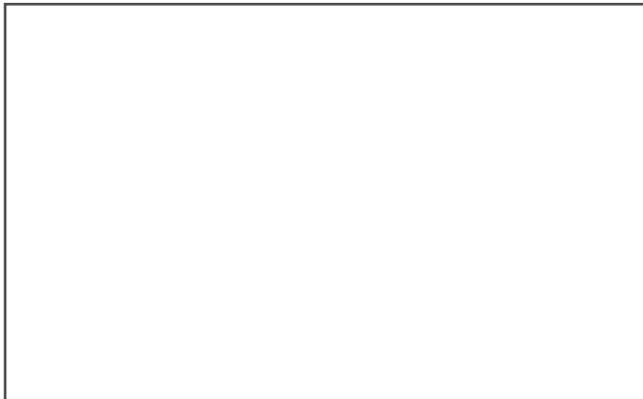
**Table I.** Optimisation of Heck reaction. <sup>(a)</sup>Dibenzoquinone was isolated as the sole product. <sup>(b)</sup>the yield is given as the combined yield of products. <sup>(c)</sup>SM: starting anthracene. <sup>(d)</sup>Ratio of Acrylamide:SM

Acrylamide	Duration (Hrs)	Product (ratio)	Yield (%)
4a	72	7	58
4b	150	-	-
4c	150	8	Mixture - mono/di
4d	150	-	-
4e	150	-	-
4f	150	-	-
4i	124	10	74
4j	110	11	81
4k	118	12	69

**Table 2.** Reaction data for acrylamides (8:1 ratio) **4a-f**, **4i** & **4j** with **2**.

**Figure 2.** Dose response curves for MCF7 cell line at 24hrs, 5 days and 10 days for **10** in (PBS/0.1% v/v DMSO)

**Figure 3.** Showing cell viability after 48hrs for Caco-2 cell line for range of concentrations of **10** (PBS / 0.1% v/v DMSO)



**Figure 4.** Showing cell viability after 24hrs for MCF-7 cell line for range of concentrations of **12** (PBS / 0.1% v/v DMSO)