Bioorganic & Medicinal Chemistry 21 (2013) 333–347

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Focused library development of 2-phenylacrylamides as broad spectrum cytotoxic agents

Mark Tarleton [a], Lauren Dyson [a], Jayne Gilbert [b], Jennette A. Sakoff [b], Adam McCluskey [a,*]

[a] Centre for Chemical Biology, Chemistry, The University of Newcastle, University Drive, Callaghan, NSW 2308, Australia
[b] Medical Oncology, Calvary Mater Newcastle, Edith Street, Waratah, NSW 2298, Australia

ARTICLE INFO

Article history:
Received 27 June 2012
Revised 19 September 2012
Accepted 3 October 2012
Available online 23 October 2012

Keywords:
Focused library
Acrylamides
Cytotoxicity
Synthesis

ABSTRACT

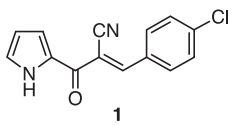
With our lead compound (*E*)-3-(4-chlorophenyl)-2-(1*H*-pyrrole-2-carbonyl)acrylonitrile (**1**) inducing 50% growth inhibition of 11 cancer cell lines at 27–61 μM, potency enhancements were rapidly established through the synthesis of a series of focused compound libraries. Six highly focused libraries (46 compounds in total) were synthesised. Each library allowed the identification of a new lead compound, viz *Library A* identified (*E*)-3-(pentafluorophenyl)-2-(1*H*-pyrrole-2-carbonyl)acrylonitrile (**11**) and (*E*)-3-(1*H*-indol-3-yl)-2-(1*H*-pyrrole-2-carbonyl)acrylonitrile (**13**) as inhibitors with improved cytotoxicity. Synthesis of discrete libraries of amidoacrylamide analogues (Ar–C═C(CN)–Ar✠Ar–C═C(CN)–C(═O)NH)–Ar) resulted in a series of analogues significantly more potent that the lead, **1**. Three furan three analogues: (*E*)-3-(5-chlorofuran-2-yl)-2-cyano-*N*-(4-methoxybenzyl)acrylamide (**33**), (*E*)-3-(5-bromofuran-2-yl)-2-cyano-*N*-(4-methoxybenzyl)acrylamide (**34**) and (*E*)-2-cyano-3-(furan-3-yl)-*N*-(4-methoxybenzyl)acrylamide (**37**) returned broad spectrum growth inhibition (GI_{50} values of 5–16 μM). Replacement of the furan moiety with simple aromatics gave an additional three analogues: (*E*)-2-cyano-*N*-(4-methoxybenzyl)-3-phenylacrylamide (**39**), (*E*)-3-(4-chlorophenyl)-2-cyano-*N*-(4-methoxybenzyl)acrylamide (**41**) and (*E*)-2-cyano-*N*-(4-methoxyphenyl)-3-(naphthalen-1-yl)acrylamide (**45**) with GI_{50} values of 7–24 μM. The final library retained the aromatic substituents but introduced a 3,4-dichlorbenzylamine moiety to afford the 1-naphthyl substituted **52**, which was the most potent broad spectrum cytotoxic analogue produced here in with an average GI_{50} = 8.6 μM. This represents a fivefold potency enhancement relative to **1** and a new cytotoxic scaffold suitable for further development.

1. Introduction

Cancer is a debilitating, life-threatening disease that will affect 1 in 3 people during the course of their lives.[1] Current treatment strategies for cancer have limited efficacy, especially in the common malignancies such as breast, colon and lung cancer. Since the 1960's cancer drug discovery development has provided about 100 approved products for the treatment of malignancy. While major advances have been made in the chemotherapeutic management of patients, one-half of all cancer patients either, do not respond to therapy or relapse following initial response, and ultimately die from their metastatic disease. Better targeted therapies are clearly needed in the fight against cancer.

We have multiple research programs targeting novel modes of action for anti-cancer drugs including protein phosphatase inhibitors that accelerate the cell cycle leading to cell death and dynamin inhibitors that affect cell cycle progression at the abscission stage.[2–12] Most recently our anti-cancer drug development program facilitated the development of a family of (*Z*)-2-phenylacrylonitriles. In this latter report we observed modest levels of cytotoxicity with the related (*E*)-2-(1*H*-pyrrole-2-carbonyl)-3-(aromatic) acrylonitriles such as **1** (Fig. 1).[13]

Over the past decade there has been an increasing prevalence in the number of biologically active compounds that contain an acrylonitrile moiety similar to those reported herein.[14–23] The acrylonitrile pharmacophore is active across multiple cellular pathways known to be involved in the production of cytotoxic effects in cell line models of cancer. These pathways include tubulin polymerisation inhibition,[14–16,18] cell death via apoptosis,[20–22] and



1

Figure 1. (*E*)-3-(4-Chlorophenyl)-2-(1*H*-pyrrole-2-carbonyl)acrylonitrile (**1**) inhibits the growth of eleven human cancer cell lines displaying a 31–84% growth inhibition at 100 μM drug concentration. See Table 1 for details of cell lines examined were.

* Corresponding author. Tel.: +61 249 216486; fax: +61 249 215472.
E-mail address: Adam.McCluskey@newcastle.edu.au (A. McCluskey).

0968-0896/$ - see front matter © 2012 Published by Elsevier Ltd.
http://dx.doi.org/10.1016/j.bmc.2012.10.003

tyrosine kinase inhibition.[17] Indeed it could be argued that our leads are structurally related to the monomeric tyrphostins, which are known kinase inhibitors. There are also reports of selectivity between cytotoxicity and antifungal activity.[19]

Building on our medicinal chemistry paradigm of iterative focused library synthesis, biological screening, re-design and library synthesis,[2–13] we have identified (*E*)-3-(4-chlorophenyl)-2-(1*H*-pyrrole-2-carbonyl)acrylonitrile (**1**) as a synthetically accessible anti-cancer lead compound. Our lead acrylonitrile (**1**) was accessed in two simple steps from pyrrole, cyanoacetic acid and *p*-chlorobenzaldehyde. The commercial availability of a wide range of aldehydes allowed for rapid exploration of structure activity relationships (SAR). Herein we report an exploration of the SAR associated with **1** via the synthesis and biological evaluation of a series of focused compound libraries.

2. Results and discussion

Our focused compound library development commenced with the synthesis of (*E*)-3-(4-chlorophenyl)-2-(1*H*-pyrrole-2-carbonyl)acrylonitrile (**1**). In a typical synthesis, cyanoacetic acid was mixed with acetic anhydride followed by the addition of pyrrole and the mixture heated at 75 °C for 35 min, extractive work up and silica gel chromatography afforded 3-oxo-3-(1*H*-pyrrol-2-yl)propanenitrile (**4**). Treatment of **4** in ethanol with *p*-chlorobenzaldehyde and a catalytic quantity of piperidine, after work up gave **1** in a 39% yield (two steps) (Scheme 1).[24]

In the development of our first focused library (*Library A*), **4** was treated with ten aldehydes (see Table 1 for details),[13,25–31] and the resultant compounds (**1**, **5**–**13**) were screened for growth inhibition against a panel of eleven cancer cell lines: HT29 and SW480 (colon carcinoma), MCF-7 (breast carcinoma), A2780 (ovarian carcinoma), H460 (lung carcinoma), A431 (skin carcinoma), DU145 (prostate carcinoma), BEC-2 (neuroblastoma), SJ-G2 (glioblastoma), MIA (pancreatic carcinoma) and SMA (spontaneous murine astrocytoma).[6] In vitro cytotoxicity assays have been used for decades as a tool to understand hypothesis driven questions regarding drug action. Our efforts in this area do not include the use of normal cell lines as a single in vitro screening assay as normal cell lines fail to provide a 'go/no-go' step in the drug development process. Indeed, when used in a prospective manner, they have not been highly predictive of in vivo toxicity.[32] A single in vitro screening platform is unlikely to provide the data required to evaluate risk and predict human toxicity. In this regard, it is widely accepted that additional models using a tiered toxicity screening approach are required in order to define and predict clinical toxicity. As part of our drug development strategy small molecules that satisfy specific drugability characteristics as well as cytotoxicity will undergo further biological evaluation in animal models.

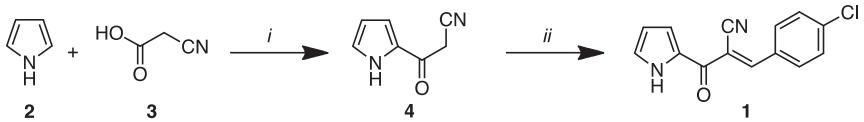
Initial cytotoxicity efficacy was determined at 25 μM drug concentration. Two of the ten *Library A* analogues were sufficiently active at (or near) our screening threshold (90% growth inhibition at 25 μM drug concentration, see also Supplementary data Tables S1–S6) to warrant the determination of GI_{50} values. These data are presented in Table 1. The lead 4-Cl (**1**) and pentafluorophenyl (**11**) returned average GI_{50} values of 40 and approximately 70 μM, respectively across the 11 cell lines examined. This suggested that the presence of an electron withdrawing group may be important and imparted favourable growth inhibition. Of the other *Library A* analogues only the indole substituted **13** showed even a moderate level of potency at the initial 25 μM concentration, and most notably a ~50% growth inhibition against the SW480, MCF-7 and BE2-C cell lines (Supplementary data, Table S1). This level of growth inhibition while low was deemed encouraging enough to continue our studies through the development of *Library B*.

Given the modest level potency, but apparent cell line specificity, noted with (**13**) we chose to examine the effect of a simple pyrrole to indole replacement through application of the same chemistry (commencing with indole) and the same family of aldehydes as described in Scheme 1. This led to the synthesis of *Library B* comprising the indolylcarbonylacrylamide analogues **14**-**23**. The growth inhibiton screening data is presented in Table 2.

From *Library B*, three analogues, the 4-NO_2 (**18**), pentafluoro (**21**) and bis-indole (**23**) proceeded to GI_{50} determination. The introduction of the indole nucleus saw a significant reduction in cytotoxicity previously observed with the pyrroles (Table S2, Supplementary data), cf. indoles **15** and **14** compared with pyrroles **1** and **5.** As with the pyrrole analogue, the pentafluorophenyl substituted **21** was the most active in this library, and we note that the 4-NO_2 substituted **18** was also active. As with *Library A*, we note that electron withdrawing groups on the phenyl ring conferred higher levels of cell growth inhibition compared with the indolylacrylamide analogues of *Library B*.

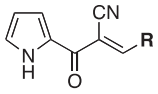
We next turned our attention to the possible effect of introducing additional functionality to the linker chain with the synthesis of *Library C* which introduced an amide moiety. In designing our next library we combined the most favourable properties of the pyrrole *Library A* with the 4-OCH_3 and 3,4-dicholoro phenyl substituents that afforded high levels of activity in our original phenylacrylonitrile compound series.[13] Accordingly we set about developing an expedient route to simple analogues that combined theses characteristics with the additional requirement of introducing an amide moiety. Treatment of 4-methoxybenzylamine and 3,4-dichlorobenzylamine with methyl cyanoacetate afforded the cyanoamides **25** and **26** in excellent yields. Subsequent treatment of **25** and **26** with 1*H*-pyrrole-2-carbaldehyde and furfural afforded *Library C* analogues **27**–**30** with the desired amide moiety installed.[25–31]

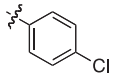
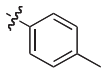
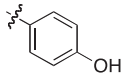
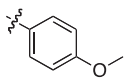
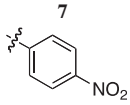
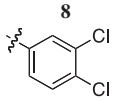
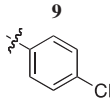
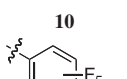
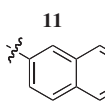
Cytotoxicity screening of **27**–**30** (*Library C*, Table 3) gave rise to a number of interesting outcomes. Firstly the 4-OCH_3 furan analogue **29** returned the highest level of activity noted thus far with GI_{50} values of 16–33 μM. Secondly, analogues **27**, **28** and **30** showed activity in specific cell lines rather than broad anti-cancer activity across all cell lines. Analogue **27** returned GI_{50} values of 36 and 47 μM for the MCF-7 and the BE2-C cell lines, respectively. Against all other cell lines **27** was inactive (GI_{50} >50 μM). Pyrrole **28** showed a similar cytotoxicity profile to **27**, however, this analogue displayed significant selectivity towards the MCF-7 breast cancer cell line; GI_{50} = 6 μM, six times more active than the 4-OCH_3 analogue, **27**. This was the most potent analogue thus far and represented a fivefold increase relative to the lead (**1**) and 15-fold MCF-7 selectivity. Of equal note was that the simple bioisosteric replacement of the pyrrole NH to the furan O atom gave two analogues with good activity against the cell lines examined. Furan **30** showed a similar selectivity profile to that observed with



Scheme 1. Reagents and conditions: (i) Ac_2O, 85 °C, 5 min; (ii) RCHO (see table for details), piperidine (cat), EtOH reflux 2 h.

Table 1
Evaluation of the cytotoxicity (GI_{50} (μM)) of *Library A* derivatives **1**, and **5**–**13** against a panel of eleven cancer cell lines



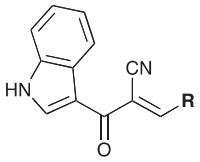
Compound	HT29[a]	SW480[a]	MCF-7[b]	A2780[c]	H460[d]	A431[e]	DU145[f]	BE2-C[g]	SJ-G2[h]	MIA[i]	SMA[j]
 **1**	36 ± 5	34 ± 3	27 ± 3	35 ± 4	43 ± 7	52 ± 11	61 ± 10	34 ± 3	37 ± 7	48 ± 17	38 ± 6
 **5**	–[k]	–	–	–	–	–	–	–	–	–	–
 **6**	–	–	–	–	––	–	–	–	–	–	–
 **7**	–	–	–	–	–	–	–	–	–	–	–
 **8**	–	–	–	–	–	–	–	–	–	–	–
 **9**	–	–	–	–	–	–	–	–	–	–	–
 **10**	224	>100	23 ± 14	64 ± 24	31 ± 10	64 ± 9	>100	14 ± 3	23 ± 13	25 ± 4	>100
 **11**	–	–	–	–	–	–	–	–	–	–	–
 **12**	–	43%[l]	56%[l]	–	–	–	–	49%[l]	–	–	–
13											

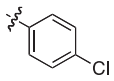
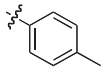
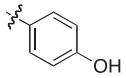
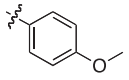
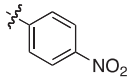
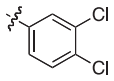
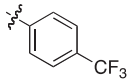
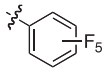
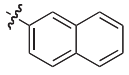
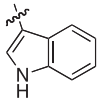
[a] HT29 and SW480 (colon carcinoma).
[b] MCF-7 (breast carcinoma).
[c] A2780 (ovarian carcinoma).
[d] H460 (lung carcinoma).
[e] A431 (skin carcinoma).
[f] DU145 (prostate carcinoma).
[g] BEC-2 (neuroblastoma).
[h] SJ-G2 (glioblastoma).
[i] MIA (pancreatic carcinoma).
[j] SMA (spontaneous murine astrocytoma).
[k] '—' = Insufficient growth inhibition at 25 μM drug concentrations to proceed to full dose response evaluation, percentage growth inhibition values are tabulated in Table S1 (Supplementary data).
[l] Percentage growth inhibition at 25 μM drug concentration.

28. It thus appeared that the 3,4-dicholorophenyl moiety played a role in imparting cancer cell line specificity. Overall the furans **29** and **30** are 2- to 3-fold more potent than **1**.

Given the potency we noted with the furans **29** and **30** we expanded the *Library C* to developed a new focused library, *Library D*, in which we retained the 4-OCH_3Ph moiety of **29** as it had given

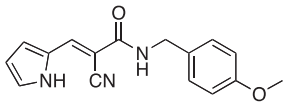
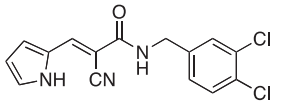
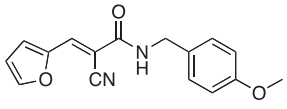
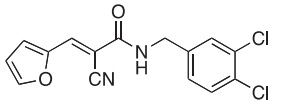
Table 2
Evaluation of the cytotoxicity (GI_{50} (μM)) of *Library B* analogues **14**–**23** against a panel of eleven cancer cell lines



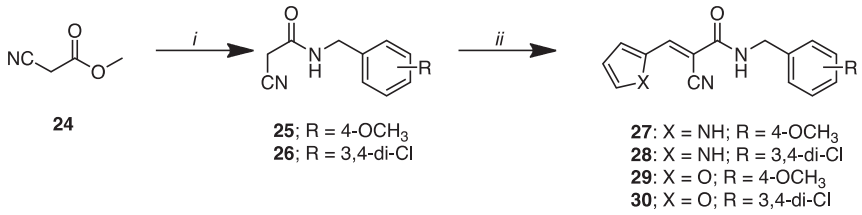
Compound	HT29[a]	SW480[a]	MCF-7[b]	A2780[c]	H460[d]	A431[e]	DU145[f]	BE2-C[g]	SJ-G2[h]	MIA[i]	SMA[j]
 **14**	–[k]	–	–	–	–	–	–	–	–	–	–
 **15**	–	–	–	–	–	–	–	–	–	–	–
 **16**	–	–	–	–	–	–	–	–	–	–	–
 **17**	–	–	–	–	–	–	–	–	–	–	–
 **18**	41 ± 1	42 ± 3	35 ± 3	48 ± 6	47 ± 4	46 ± 6	59 ± 0	40 ± 5	37 ± 4	46 ± 9	60 ± 6
 **19**	–	33%[l]	42%[l]	32%[l]	–	–	–	33%[l]	–	–	–
 **20**	–	–	–	–	–	–	–	–	–	–	–
 **21**	18 ± 3	18 ± 3	13 ± 4	11 ± 0	35 ± 7	19 ± 1	30 ± 1	10 ± 2	14 ± 1	21 ± 5	20 ± 1
 **22**	–	–	40%[l]	–	–	–	–	–	–	–	–
 **23**	6.0 ± 0.1	8.3 ± 0.4	11 ± 1	9.3 ± 0.2	7.6 ± 0.3	7.6 ± 0.1	17 ± 1	12 ± 0	13 ± 0	14 ± 0	15 ± 1

[a] HT29 and SW480 (colon carcinoma).
[b] MCF-7 (breast carcinoma).
[c] A2780 (ovarian carcinoma).
[d] H460 (lung carcinoma).
[e] A431 (skin carcinoma).
[f] DU145 (prostate carcinoma).
[g] BEC-2 (neuroblastoma).
[h] SJ-G2 (glioblastoma).
[i] MIA (pancreatic carcinoma).
[j] SMA (spontaneous murine astrocytoma).
[k] '—' = Insufficient growth inhibition at 25 μM drug concentrations to proceed to full dose response evaluation, percentage growth inhibition values are tabulated in Table S2 (Supplementary data).
[l] Percentage growth inhibition at 25 μM drug concentration.

Table 3
Evaluation of the cytotoxicity (GI_{50} (μM)) of *Library C* analogues **27**–**30** against a panel of eleven cancer cell lines

Compound	HT29[a]	SW480[a]	MCF-7[b]	A2780[c]	H460[d]	A431[e]	DU145[f]	BE2-C[g]	SJ-G2[h]	MIA[i]	SMA[j]
 **27**	>50	>50	34 ± 6	>50	>50	>50	>50	47 ± 2	>50	>50	>50
 **28**	85 ± 12	>50	6 ± 1	>50	>50	>50	>50	43 ± 4	>50	>50	>50
 **29**	22 ± 5	31 ± 2	27 ± 6	24 ± 4	32 ± 1	16 ± 1	29 ± 1	24 ± 4	31 ± 1	34 ± 3	33 ± 2
 **30**	20 ± 6	>50	20 ± 5	>50	>50	>50	24 ± 7	>50	>50	>50	38 ± 7

[a] HT29 and SW480 (colon carcinoma).
[b] MCF-7 (breast carcinoma).
[c] A2780 (ovarian carcinoma).
[d] H460 (lung carcinoma).
[e] A431 (skin carcinoma).
[f] DU145 (prostate carcinoma).
[g] BEC-2 (neuroblastoma).
[h] SJ-G2 (glioblastoma).
[i] MIA (pancreatic carcinoma).
[j] SMA (spontaneous murine astrocytoma).



Scheme 2. Reagents and conditions: (i) MeOH, MW, 200 W, 120 °C, 15 min; (ii) 1*H*-pyrrole-2-carbaldehyde or furfural, piperidine (cat), EtOH, MW, 200 W, 120 °C, 15 min.

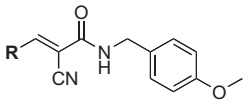
rise to the broad spectrum cytotoxicity and modified the furan nucleus. *Library D* was prepared as per Scheme 2, and screened for cytotoxicity as before and these data are presented in Table 4.

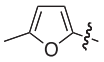
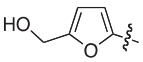
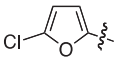
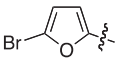
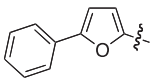
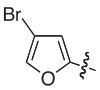
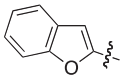
On examination of the data presented in Table 4 it was immediately apparent that bulky or electron donating 5-substituted-(furan-2yl)acrylamide derivatives (**31**, **32**, and **35**) lost the broad spectrum activity of the furan lead, **29**. Furan **31** was largely inactive, but did show a toxicity profile similar to indole **13**. Analogue **35** showed a 20-fold specificity towards the MCF-7 breast cancer cell line (GI_{50} = 3 ± 1 μM). Fusing the phenyl ring in the form of the benzofuran analogue **38** resulted in a loss of MCF-7 selectivity with **38** inactive across all cell lines examined. Electron withdrawing substituents were well tolerated with the 5-Cl (**33**) and 5-Br (**34**) highly cytotoxic with average GI_{50} values of 12 and 13 μM, respectively. Interestingly the 4-bromo (**36**) (cf. 5-bromo **34**) saw a marked reduction in potency from an average GI_{50} = 13 μM to ⩾53 μM, indicating a high level of substituent pattern dependence. This positional dependence was also apparent with the furan-3-ylacrylamide analogue (**37**) which was the most active analogue generated thus far with an average GI_{50} = 7 μM, four times more potent than the equivalent furan-2-ylacrylamide (**29**, Table 3).

Having established that multiple variations in the furan moiety were permitted we extended the scope of these studies and explored replacement of the furan ring with other simple aromatic systems while retaining the 4-OCH_3Ph moiety, using the same chemistry as in Scheme 2 to afford *Library E* analogues **39**-**45**, which were subsequently screened against our panel of eleven cancer cell lines. These data are presented in Table 5.

As can be seen from the data presented in Table 5, again the position and type of substituent on the newly introduced aromatic ring had a pronounced effect on the observed cytotoxicity. Those analogues containing a small electron withdrawing group or positioned the electron density at the C2′/C3′ region returned a significantly higher level of broad spectrum cytotoxicity than those lacking such a substituent. This is particularly evident on comparison of the C4′-Cl (**41**) with the C4′-OCH_3 (**43**) with the former returning an average GI_{50} value of 11 μM, while the latter was essentially inactive. Also of note again, was the positional dependence of a fused aromatic system such as the C1′- and C2′-naphthyl analogues **45** and **44** with average GI_{50} values of ⩾51 and 15 μM, respectively. The C1' analogue **45** is roughly threefold more potent than the corresponding C2′ **44**. These findings are in keeping with

Table 4
Evaluation of the cytotoxicity(GI_{50} (μM)) of *Library D* analogues **31**–**38** against a panel of eleven cancer cell lines



Compound	HT29[a]	SW480[a]	MCF-7[b]	A2780[c]	H460[d]	A431[e]	DU145[f]	BE2-C[g]	SJ-G2[h]	MIA[i]	SMA[j]
 **31**	92 ± 6	29 ± 2	21 ± 1	60 ± 11	>100	58 ± 11	39 ± 6	21 ± 4	75 ± 14	51 ± 4	69 ± 14
 **32**	—[k]	—	—	—	—	—	—	—	—	—	—
 **33**	9 ± 1	13 ± 0	9 ± 1	9 ± 1	15 ± 0	9 ± 1	12 ± 1	11 ± 0	13 ± 1	15 ± 0	14 ± 0
 **34**	10 ± 1	14 ± 1	11 ± 2	12 ± 0	16 ± 1	9 ± 1	12 ± 1	13 ± 1	13 ± 0	16 ± 0	14 ± 0
 **35**	56 ± 8	>100	3 ± 1	>100	>100	>100	>100	>100	>100	>100	>100
 **36**	36 ± 8	>100	20 ± 2	28 ± 6	>100	14 ± 4	61 ± 17	36 ± 11	23 ± 0.3	65 ± 3	>100
 **37**	6 ± 1	8 ± 0	7 ± 1	6 ± 0	8 ± 0	5 ± 0	7 ± 0	7 ± 0	8 ± 0	8 ± 0	7 ± 0
 **38**	—	—	40%	—	—	—	—	—	—	34%	—

[a] HT29 and SW480 (colon carcinoma).
[b] MCF-7 (breast carcinoma).
[c] A2780 (ovarian carcinoma).
[d] H460 (lung carcinoma).
[e] A431 (skin carcinoma).
[f] DU145 (prostate carcinoma).
[g] BEC-2 (neuroblastoma).
[h] SJ-G2 (glioblastoma).
[i] MIA (pancreatic carcinoma).
[j] SMA (spontaneous murine astrocytoma).
[k] '—' = insufficient growth inhibition at 25 μM drug concentrations to proceed to full dose response evaluation, percentage growth inhibition values are tabulated in Table S4 (Supplementary data).

the general trends observed with the substituted furan analogues shown in Table 5.

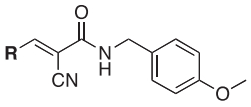
From the data obtained thus far a pharmacophore of broad spectrum cytotoxicity for these acrylamides has emerged that has identified the acrylamide moiety as essential, but permits the introduction of an amide spacer, considerably extending the scope for the development of these analogues. This pharmacophore was applied in the design and development of our final focused library, *Library F*, in which the 3,4-dichlorophenyl moiety was re-introduced. Note that with the parent pyrrole series this 3,4-dichlorophenyl moiety afforded high levels of MCF-7 specificity, but with this extended pharmacophore we anticipated more broad spectrum activity would be observed. As anticipated, the data in Table 6 shows four analogues (**46**, **48**, **51** and **52**) with average GI_{50} values ranging from ca. 10 to 70 μM. The trends in activity matched that predicted, viz the most active analogue was C1'-naphthyl (**52**), with an average GI_{50} value of 8.6 μM.

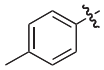
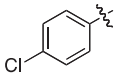
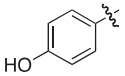
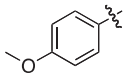
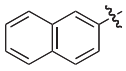
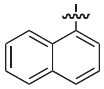
3. Conclusion

Replacement of the 4-ClPh moiety of the lead **1**, typically removed all vestiges of activity against the panel of eleven cell lines examined herein. Only the pentafluorophenyl substituted **11** saw a similarly modest level of potency, but not across all the cell lines examined. Pentafluoro **11** was inactive against the SW480, DU145 and the SMA cell lines. Indole **13** showed modest specificity towards the SW480, MCF-7 and BE2-C cell lines. Replacement of the pyrrole moiety with an indole gave three analogues; **18**, **21** and **23**; with average GI_{50} values of 46, 19 and 11 μM, respectively.

The introduction of an amide moiety was explored with the synthesis of *Library C*, and this produced an immediate increase in potency with the furan analogue **29** displaying good broad spectrum activity with an average GI_{50} value of 27 μM. Within *Library C* the pyrrole analogues displayed preferential activity towards the

Table 5
Evaluation of the cytotoxicity (GI_{50} (μM)) of *Library E* analogues **39**–**45**, against a panel of eleven cancer cell lines



Compound	HT29[a]	SW480[a]	MCF-7[b]	A2780[c]	H460[d]	A431[e]	DU145[f]	BE2-C[g]	SJ-G2[h]	MIA[i]	SMA[j]
 **39**	9 ± 1	14 ± 0	18 ± 2	9 ± 1	18 ± 1	9 ± 1	13 ± 2	15 ± 0	17 ± 1	24 ± 3	16 ± 1
 **40**	36 ± 3	34 ± 3	36 ± 2	33 ± 2	41 ± 4	26 ± 5	34 ± 3	35 ± 3	39 ± 6	38 ± 6	42 ± 5
 **41**	7 ± 0	10 ± 0	11 ± 1	7 ± 0	14 ± 1	6 ± 0	7 ± 1	12 ± 0	11 ± 0	16 ± 1	17 ± 0
 **42**	–[k]	–	–	–	–	–	–	–	–	–	–
 **43**	–	–	–	–	–	–	–	–	–	–	–
 **44**	54 ± 9	41 ± 1	33 ± 3	40 ± 2	>100	37 ± 3	80 ± 16	42 ± 2	40 ± 4	49 ± 8	43 ± 4
 **45**	13 ± 1	14 ± 1	16 ± 0	16 ± 0	15 ± 0	15 ± 1	16 ± 0	14 ± 2	15 ± 1	15 ± 1	15 ± 0

[a] HT29 and SW480 (colon carcinoma).
[b] MCF-7 (breast carcinoma).
[c] A2780 (ovarian carcinoma).
[d] H460 (lung carcinoma).
[e] A431 (skin carcinoma).
[f] DU145 (prostate carcinoma).
[g] BEC-2 (neuroblastoma).
[h] SJ-G2 (glioblastoma).
[i] MIA (pancreatic carcinoma).
[j] SMA (spontaneous murine astrocytoma).
[k] '—' = insufficient growth inhibition at 25 μM drug concentrations to proceed to full dose response evaluation, percentage growth inhibition values are tabulated in Table S5 (Supplementary data).

MCF-7 cell line with pyrrole **27** a 34 μM and **28** a 6 μM potent inhibitor of cell growth.

Exploration of the furan moiety with *Library D* afforded three highly potent analogues. Furans **33**, **34** and **37** were 12, 13 and 7 μM potent across the cell lines examined. The 3-furanyl **37**, was the most active furan analogue in this series. The phenyl substituted was MCF-7 specific returning the best activity yet noted with $GI_{50MCF\text{-}7}$ = 3 μM. Replacement of the furan moiety with *Library E* gave five analogues that proceeded to GI_{50} determination. The most noteworthy analogues in this library were the phenyl **39**, 4-chlorphenyl **41** and 1-naphthyl **45** with average GI_{50} values of 15, 11 and 15 μM, respectively. In the final library introduction of the 3,4-dichlorobenzyl moiety produced a further increase in potency for the 1-naphthyl substituted **52** to 8.6 μM.

Herein from six focused libraries comprising a total of 46 analogues we have identified eleven analogues with GI_{50} <15 μM; an average of threefold more active than the lead. The most potent analogue were **28** (6 μM), **37** (7 μM) and **52** (8.6 μM). Of the remaining analogues, the furan **35** displayed the highest level of specificity towards the MCF-7 cell line (3 μM). The development of the analogues herein clearly demonstrated that the cytotoxicity of these acrylamide analogues was not derived solely from the electron withdrawing effect, with other characteristics such as orientation of electron density and lone electron pairs having a pronounced effect.

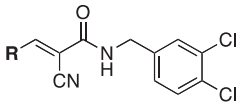
While some of our molecules show potent in vitro cytotoxicity in a range of cancer cell lines additional biological models will need to be utilised in order to define the in vivo efficacy and toxicity of these small molecules. These findings will be reported in due course.

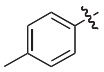
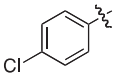
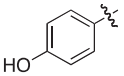
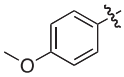
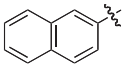
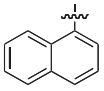
4. Experimental section

4.1. Materials

All starting materials were purchased from Aldrich Chemical Co. and Lancaster Synthesis. Solvents were bulk, and distilled from glass prior to use. Reaction progress was monitored by TLC, on alu-

Table 6
Evaluation of the cytotoxicity (GI_{50} (μM)) of *Library F* analogues **46–52** against a panel of eleven cancer cell lines



Compound	HT29[a]	SW480[a]	MCF-7[b]	A2780[c]	H460[d]	A431[e]	DU145[f]	BE2-C[g]	SJ-G2[h]	MIA[i]	SMA[j]
 **46**	70 ± 15	49 ± 7	29 ± 5	49 ± 6	61 ± 6	43 ± 6	71 ± 15	32 ± 1	43 ± 2	47 ± 2	43 ± 8
 **47**	–[k]	–	–	–	–	–	–	–	–	–	–
 **48**	33 ± 1	30 ± 0	21 ± 1	32 ± 1	33 ± 0	30 ± 0	30 ± 1	31 ± 0	30 ± 0	31 ± 1	33 ± 2
 **49**	–	–	–	–	–	–	–	–	–	–	–
 **50**	>100	95 ± 0	45 ± 7	86 ± 11	>100	90 ± 8	70 ± 6	93 ± 2	>100	79 ± 11	>100
 **51**	44 ± 2	50 ± 4	29 ± 1	44 ± 4	>100	50 ± 6	77 ± 7	40 ± 0	49 ± 8	44 ± 1	64 ± 20
 **52**	7 ± 0	11 ± 0	8 ± 1	7 ± 0	7 ± 0	8 ± 0	12 ± 1	7 ± 0	13 ± 1	8 ± 0	7 ± 0

[a] HT29 and SW480 (colon carcinoma).
[b] MCF-7 (breast carcinoma).
[c] A2780 (ovarian carcinoma).
[d] H460 (lung carcinoma).
[e] A431 (skin carcinoma).
[f] DU145 (prostate carcinoma).
[g] BEC-2 (neuroblastoma).
[h] SJ-G2 (glioblastoma).
[i] MIA (pancreatic carcinoma).
[j] SMA (spontaneous murine astrocytoma).
[k] '—' = insufficient growth inhibition at 25 μM drug concentrations to proceed to full dose response evaluation, percentage growth inhibition values are tabulated in Table S2 (Supplementary data).

minium plates coated with silica gel with fluorescent indicator (Merck 60 F254) and flash chromatography was conducted utilizing SNAP Biotage KP-SIL columns. ^1H and ^{13}C spectra were recorded on a Bruker Advance AMX 300 MHz spectrometer at 300.13 and 75.48 MHz, respectively. Chemical shifts are relative to TMS as internal standard. All compounds returned satisfactory mass spectra were obtained using a micromass liquid chromatography Z-path (LCZ) platform spectrometer. Mass to charge ratios (m/z) are stated with their peak intensity as a percentage in parentheses. All mass spectra were obtained via the ES method thus fragmentation patterns were not observed. The University of Wollongong, Australia, Biomolecular Mass Spectrometry Laboratory, analyzed samples for HRMS. The spectra were run on a micromass QTof2 spectrometer using polyethylene glycol or polypropylene glycol as the internal standard. Compound purity was confirmed by a combination of LC–MS (HPLC), micro and/or high resolution mass spectrometry and NMR analysis. All analogues are ⩾95% purity.

4.1.1. Cell culture and stock solutions[22,23]

Stock solutions were prepared as follows and stored at −20 °C: drugs were prepared as 40 mM solutions in DMSO. All cell lines were cultured at 37 °C, under 5% CO_2 in air and were maintained in Dulbecco's modified Eagle's medium (Trace Biosciences, Australia) supplemented with 10% foetal bovine serum, 10 mM sodium bicarbonate penicillin (100 μg mL^{-1}), streptomycin (100 μg mL^{-1}), and glutamine (4 mM).

4.1.2. In vitro growth inhibition assays

Cells in logarithmic growth were transferred to 96-well plates. Cytotoxicity was determined by plating cells in duplicate in medium (100 μL) at a density of 2500–4000 cells/well. On day 0 (24 h after plating), when the cells were in logarithmic growth, medium (100 μL) with or without the test agent was added to each well. After 72 h of drug exposure, growth inhibitory effects were evaluated using the MTT (3-[4,5-dimethyltiazol-2-yl]-2,5-diphenyltetrazolium bromide) assay and their absorbance was read at

540 nm. Percentage growth inhibition was determined at a fixed drug concentration of 25 μM. A value of 100% is indicative of total cell growth inhibition. Those analogues showing appreciable percentage growth inhibition underwent further dose response analysis to allow the calculation of GI_{50} values. The GI_{50} value is defined as the drug concentration at which cell growth is 50 % inhibited based on the difference between the optical density values on day 0 and those at the end of drug exposure.[33]

4.2. Chemistry

4.2.1. General methods

THF was freshly distilled from sodium–benzophenone. Flash chromatography was carried out using silica gel 200–400 mesh (60 Å). ^{1}H and ^{13}CNMR were recorded at 300 and 75 MHz, respectively using a Bruker Avance 300 MHz spectrometer in $CDCl_3$, acetone-d_6 and DMSO-d_6. GCMS was performed using a Shimadzu GCMS-QP2100. The instrument uses a quadrupole mass spectrometer and detects samples via electron impact ionization (EI). The Children's Medical Research Institute, Cell Signalling Unit Mass Spectrometry Laboratory analyzed samples for HRMS. The spectra were run on the VG Autospec-oa-tof tandem high resolution mass spectrometer using CI (chemical ionization), with methane as the carrier gas and PFK (perfluorokerosene) as the reference. All samples returned satisfactory analyses.

4.2.2. (*E*)-3-(4-Chlorophenyl)-2-(1*H*-pyrrole-2-carbonyl)acrylonitrile (1)

Cyanoacetic acid (1.360 g, 16 mmol) was added to Ac_2O (8 mL) and the resultant suspension was stirred and heated to 50 °C upon which the solid material dissolved. Pyrrole (1.073 g, 16 mmol) was then added and the solution was heated at 75 °C for 35 min. The solution was then diluted with EtOAc (20 mL) and washed with 0.1 M NaOH (3 × 10 mL). The organic layer was then collected and dried using $MgSO_4$. The solvent was then removed under vacuum and the residue purified by flash silica chromatography (1:10 EtOAc/Hexanes to 1:1 EtOAc/Hexanes) to afford 3-oxo-3-(1*H*-pyrrol-2-yl)propanenitrile, 70%. Next, to an ethanolic solution (10 mL) of 4-methylbenzaldehyde (1.57 mmol) was added an ethanolic solution (10 mL) of 3-oxo-3-(1*H*-pyrrol-2-yl)propanenitrile (1.49 mmol). This mixture was heated to 70 °C at which time, piperidine (2 drops) was added, and the solution was then heated under reflux for an additional 2 h. After this time, the solution was cooled and the solvent removed in vacuo to afford a brown oil which was purified by flash chromatography (1:10 EtOAc/Hexanes) to afford (**1**), as a yellow solid; 39%; 192–194 °C.

^{1}H NMR (Acetone-d_6) (300 MHz): δ 11.30 (br, NH), 8.28 (s, 1H, CH═C), 8.13–8.11 (m, 2H, Ar H2 + Ar H6), 7.66–7.63 (m, 2H, Ar H3 + Ar H5), 7.45–7.44 (m, 1H, Pyr H5), 7.35–7.34 (m, 1H, Pyr H3), 6.38–6.36 (m, 1H, Pyr H4);

^{13}C NMR (Acetone-d_6) (75 MHz): δ 173.6, 151.1, 137.4, 131.7 (2 × Ar), 130.8, 128.8 (2 × Ar), 126.9, 119.7, 118.7, 116.6, 110.4, 109.5;

IR (KBr) cm^{-1}: 3284 (NH), 2211 (CN), 1627 (C═O);

LRMS: (APCI M+1) 257. HRMS: Calcd for $C_{14}H_9ClN_2O$: 256.0403, found (ACPI M+1) 257.0478.

4.2.3. (*E*)-2-(1*H*-Pyrrole-2-carbonyl)-3-*p*-tolylacrylonitrile (5)

Synthesized using the general procedure as for (**1**), from 3-oxo-3-(1*H*-pyrrol-2-yl)propanenitrile and 4-chlorobenzaldehyde to afford (**5**) as a yellow solid; 81%; 242–244 °C.

^{1}H NMR (DMSO-d_6) (300 MHz): δ 12.22 (br, NH), 8.24 (s, 1H, CH═C), 7.95 (d, J = 8.0 Hz, 2H, Ar H2 + Ar H6), 7.37 (d, J = 8.0 Hz, 2H, Ar H3 + Ar H5), 7.29–7.26 (m, 2H, Pyr H3 + Pyr H5), 6.33–6.30 (m, 1H, Pyr H4), 2.37 (s, 3H, CH_3);

^{13}C NMR (DMSO-d_6) (75 MHz): δ 174.8, 153.2, 143.5, 130.6 (2 × Ar), 129.7 (2 × Ar), 129.3, 129.0, 127.9, 119.3, 117.7, 110.8, 107.8, 21.2;

IR (KBr) cm^{-1}: 3291 (NH), 2210 (CN), 1622 (C═O);

LRMS: (APCI M+1) 237. HRMS: Calcd for $C_{15}H_{12}N_2O$; Exact mass: 236.0950, found (ACPI M+1) 237.1028.

4.2.4. (*E*)-3-(4-Hydroxyphenyl)-2-(1*H*-pyrrole-2-carbonyl)acrylonitrile (6)

Synthesized using the general procedure as for (**1**), from 3-oxo-3-(1*H*-pyrrol-2-yl)propanenitrile and 4-hydroxybenzaldehyde to afford (**6**) as an orange solid; 43%; 240–243 °C.

^{1}H NMR (DMSO-d_6) (300 MHz): δ = 12.07 (br, NH), 8.68 (br, OH), 8.18 (s, 1H, CH═C), 7.99 (d, J = 8.7 Hz, 2H, Ar H2 + Ar H6), 7.28–7.23 (m, 2H, Pyr H5 + Pyr H3), 6.94 (d, J = 8.7 Hz, 2H, Ar H3 + Ar H5), 6.30–6.27 (m, 1H, Pyr H4);

^{13}C NMR (DMSO-d_6) (75 MHz): δ 175.0, 162.3, 153.3, 133.6 (2 × Ar), 129.2, 127.3, 123.1, 118.6, 118.4, 116.2 (2 × Ar), 110.5, 104.1;

IR (KBr) cm^{-1}: 3419 (OH), 3290 (NH), 2218 (CN), 1617 (C═O), 1603 (Ar);

LRMS: (APCI M+1) 239. HRMS: Calcd for $C_{14}H_{10}N_2O_2$; Exact mass: 239.0829; found (ACPI M+1) 239.0829.

4.2.5. (*E*)-3-(4-Methoxyphenyl)-2-(1*H*-pyrrole-2-carbonyl)acrylonitrile (7)

Synthesized using the general procedure as for (**1**), from 3-oxo-3-(1*H*-pyrrol-2-yl)propanenitrile and 4-methoxybenzaldehyde to afford (**7**) as a yellow solid; 83%; 166–168 °C.

^{1}H NMR (DMSO-d_6) (300 MHz): δ 12.14 (br, NH), 8.24 (s, 1H, CH═C), 8.08 (d, J = 8.9 Hz, 2H, Ar H2 + Ar H6), 7.28–7.25 (m, 2H, Pyr H5 + Pyr H3), 7.13 (d, J = 8.9 Hz, 2H, Ar H3 + Ar H5), 6.31 (s, 1H, Pyr H4), 3.85 (s, 3H, OCH_3);

^{13}C NMR (DMSO-d_6) (75 MHz): δ 174.9, 163.0, 153.0, 133.1 (2 × Ar), 129.1, 127.5, 124.6, 118.9, 118.2, 114.8 (2 × Ar), 110.6, 105.5, 55.6;

IR (KBr) cm^{-1}: 3306 (NH), 2209 (CN), 1617 (C═O), 1507 (Ar);

LRMS: (APCI M+1) 253. HRMS: Calcd for $C_{15}H_{12}N_2O_2$; Exact mass: 252.0899, found (ACPI M+1) 253.0979.

4.2.6. (*E*)-3-(4-Nitrophenyl)-2-(1*H*-pyrrole-2-carbonyl)acrylonitrile (8)

Synthesized using the general procedure as for (**1**), from 3-oxo-3-(1*H*-pyrrol-2-yl)propanenitrile and 4-nitrobenzaldehyde to afford (**8**) as a purple solid; 37%; 199–200 °C.

^{1}H NMR (DMSO-d_6) (300 MHz): δ 12.32 (br, NH), 8.40–8.38 (m, 3H, Ar H3 + Ar H5 + Pyr H5), 8.24–8.21 (m, 2H, Ar H2 + Ar H6), 7.24 (m, 2H, Pyr H5 + Pyr H3), 6.34 (s, 1H, Pyr H4);

^{13}C NMR (DMSO-d_6) (75 MHz): δ 174.2, 150.6, 148.8, 138.2, 131.3 (2 × Ar), 130.6, 128.7, 124.0 (2 × Ar), 120.3, 116.6, 113.1, 111.1;

IR (KBr) cm^{-1}: 3308 (NH), 2228 (CN), 1633 (C═O), 1517 (NO) 1343 (NO);

LRMS: (APCI M+1) 268. HRMS: Calcd for $C_{14}H_9N_3O_3$; Exact mass: 267.0644, found (ACPI M+1) 268.0717.

4.2.7. (*E*)-3-(3,4-Dichlorophenyl)-2-(1*H*-pyrrole-2-carbonyl)acrylonitrile (9)

Synthesized using the general procedure as for (**1**), from 3-oxo-3-(1*H*-pyrrol-2-yl)propanenitrile and 3,4-dichlorobenzaldehyde to afford (**9**) as a yellow solid; 66%; 178–181 °C.

^{1}H NMR (Acetone-d_6) (300 MHz): δ 11.31 (br, NH), 8.29–8.27 (m, 2H, Ar H5 + CH═C), 8.11–8.08 (m, 1H, Ar H6), 7.84–7.81 (m, 1H, Ar H2), 7.45–7.36 (m, 2H, Pyr H5 + Pyr H3), 6.39–6.37 (m, 1H, Pyr H4);

^{13}C NMR (Acetone-d_6) (75 MHz): δ 173.4, 149.6, 135.0, 132.4, 132.1, 131.7, 130.8, 129.3, 127.2, 127.0, 119.0, 116.3, 111.0, 110.5;

IR (KBr) cm^{-1}: 3310 (NH), 2222 (CN), 1632 (C=O);

LRMS: (APCI M+1) 290. HRMS: Calcd for $C_{14}H_8Cl_2N_2O$; Exact mass: 290.0014, found (ACPI M+1) 291.0079.

4.2.8. (*E*)-2-(1*H*-Pyrrole-2-carbonyl)-3-(4-(trifluoromethyl) phenyl)acrylonitrile (10)

Synthesized using the general procedure as for (**1**), from 3-oxo-3-(1*H*-pyrrol-2-yl)propanenitrile and 4-trifluoromethylbenzaldehyde to afford (**10**) as a yellow solid; 41%; 160–162 °C.

^{1}H NMR (DMSO-d_6) (300 MHz): δ 12.30 (br, 1H), 8.37 (s, 1H, CH=C), 8.19 (d, J = 8.1 Hz, 2H, Ar H2 + Ar H6), 7.94 (d, J = 8.1 Hz, 2H, Ar H3 + Ar H6), 7.32 (s, 2H, Pyr H5 + Pyr H3), 6.34 (s, 1H, Pyr H4);

^{13}C NMR (DMSO-d_6) (75 MHz): δ 174.4, 151.4, 136.0, 131.2, 130.8 (2 × Ar), 128.8, 128.5 (2 × Ar), 125.9, 125.8, 120.1, 116.8, 112.1, 111.0;

IR (KBr) cm^{-1}: 3295 (NH), 2228 (CN), 1637 (C=O), 1561 (Ar), 1325 (C–F);

LRMS: (ESI M−1) 289. HRMS: Calcd for $C_{15}H_9F_3N_2O$; Exact mass: 290.0667, found (ESI M−H) 289.0673.

4.2.9. (*E*)-3-(Pentafluorophenyl)-2-(1*H*-pyrrole-2-carbonyl)acrylonitrile (11)

Synthesized using the general procedure as for (**1**), from 3-oxo-3-(1*H*-pyrrol-2-yl)propanenitrile and 2,3,4,5-pentafluorobenzaldehyde to afford (**11**) as a white solid; 22%; 178–180 °C.

^{1}H NMR (Acetone-d_6) (300 MHz): δ 11.01 (br, NH), 7.35–7.32 (m, 1H, Pyr H5), 7.22–7.19 (m, 1H, Pyr H3), 6.41–6.38 (m, 1H, Pyr H4), 5.67 (s, 1H, CH=C);

^{13}C NMR (Acetone-d$_6$) (75 MHz): δ 174.3, 154.3, 142.5, 135.0, 134.7, 124.6 (2 × Ar), 120.2, 118.4, 114.7 (2 × Ar), 110.5, 106.3, 106.1;

IR (KBr) cm^{-1}: 3367 (NH), 2209 (CN), 1656 (C=C), 1608 (C=O);

LRMS: ESI (M−1) 311. HRMS: Calcd for $C_{14}H_5F_5N_2O$; Exact mass: 312.0322, found (ESI M−H) 311.1706.

4.2.10. (*E*)-3-(Naphthalen-2-yl)-2-(1*H*-pyrrole-2-carbonyl)acrylonitrile (12)

Synthesized using the general procedure as for (**1**), from 3-oxo-3-(1*H*-pyrrol-2-yl)propanenitrile and 2-naphthaldehyde to afford (**12**) as a brown solid; 35%; 140–142 °C.

^{1}H NMR (DMSO-d_6) (300 MHz): δ 12.27 (br, NH), 8.57 (s, 1H, Ar H1), 8.44 (s, 1H, CH=C), 8.23–8.21 (m, 1H, Ar H5), 8.11–7.99 (m, 3H, Ar H3 + Ar H4 + Ar H8), 7.70–7.60 (m, 2H, Ar H7 + Pyr H5), 7.35–7.31 (m, 2H, Ar H6 + Pyr H3), 6.35–6.34 (m, 1H, Pyr H4);

^{13}C NMR (DMSO-d_6) (75 MHz): δ 174.8, 153.2, 134.4, 133.4, 132.4, 129.7, 129.0, 128.9, 128.8, 128.7, 128.0, 127.7, 127.2, 124.7, 119.5, 119.2, 110.8, 109.1;

IR (KBr) cm^{-1}: 3291 (NH), 2215 (CN), 1617 (C=O);

LRMS: (ACPI M+1) 273. HRMS: Calcd for $C_{18}H_{12}N_2O$; Exact mass: 272.0950, found (ACPI M+1) 273.1028.

4.2.11. (*E*)-3-(1*H*-Indol-3-yl)-2-(1*H*-pyrrole-2-carbonyl)acrylonitrile (13)

Synthesized using the general procedure as for (**1**), from 3-oxo-3-(1*H*-pyrrol-2-yl)propanenitrile and 1*H*-indole-3-carbaldehyde to afford (**13**) as an orange solid; 95%; 300–302 °C.

^{1}H NMR (DMSO-d_6) (300 MHz): δ 12.49 (br, NH), 12.00 (br, NH), 8.67 (s, 1H, CH=C), 8.63 (s, 1H, Ind H2), 7.92–7.89 (m, 1H, Ind H7), 7.59–7.56 (m, 1H, Ind H4), 7.36–7.20 (m, 4H, Ind H5 + Ind H6 + Pyr H3 + Pyr H5), 6.31–6.29 (m, 1H, Pyr H4);

^{13}C NMR (DMSO-d_6) (75 MHz): δ 174.4, 145.7, 136.2, 131.9, 129.7, 127.2, 126.4, 123.5, 121.9, 120.3, 118.4, 117.5, 112.8, 110.4, 110.3, 99.4;

IR (KBr) cm^{-1}: 3260 (NH), 2212 (CN), 1611 (C=O);

LRMS: (ESI M−1) 260. HRMS: Calcd for $C_{16}H_{11}N_3O$; Exact mass: 261.0902, found (ESI M−H) 260.0807.

4.2.12. (*E*)-3-(4-Chlorophenyl)-2-(1*H*-indole-3-carbonyl)acrylonitrile (14)

Cyanoacetic acid (0.363, 4.26 mmol) was added to Ac_2O (8 mL) and the resultant solution was stirred and heated to 50 °C upon which the solid material dissolved. Indole (0.5 g, 4.26 mmol) was then added and the solution was heated at 85 °C for 5 min. The solution was cooled to 0 °C and the solid was collected under suction and washed with ice cold MeOH (2 × 5 mL) to afford 3-(1*H*-indol-3-yl)-3-oxopropanenitrile in a 76% yield. Next, to an ethanolic solution (10 mL) of 4-chlorobenzaldehyde (1.14 mmol) was added an ethanolic solution (10 mL) of 3-oxo-3-(1*H*-indol-3-yl)-3-oxopropanenitrile (1.08 mmol). This mixture was heated to 70 °C at which time, piperidine (2 drops) was added, and the solution was then heated under reflux for an additional 2 h. After this time, the solution was cooled and the solvent removed in vacuo to yield a yellow solid. The crude solid was then recrystallised from EtOH to afford (**14**) as a yellow solid; 80%; 230–232 °C.

^{1}H NMR (Acetone-d_6) (300 MHz): δ 11.31 (br, NH), 8.54 (s, 1H, Ind H2), 8.34–8.30 (m, 1H, Ind H4), 8.22 (s, 1H, CH=C), 8.11 (d, J = 8.7 Hz, 2H, Ar H2 + Ar H6), 7.66–7.57 (m, 3H, Ar H3 + Ar H5 + Ind H7), 7.32–7.27 (m, 2H, Ind H5 + Ind H6);

^{13}C NMR (Acetone-d_6) (75 MHz): δ 180.0, 149.8, 137.0, 136.3, 134.3, 131.4 (2 × Ar), 131.0, 128.7 (2 × Ar), 126.1, 123.2, 122.0, 121.4, 116.9, 113.9, 111.9, 111.6;

IR (KBr) cm^{-1}: 3175 (NH), 2211 (CN), 1636 (C=C), 1600 (C=O), 822 (Ar–Cl);

LRMS: (ESI M−1) 305. HRMS: Calcd for $C_{18}H_{11}ClN_2O$; Exact mass: 306.0560, found (ESI M−H) 305.0533.

4.2.13. (*E*)-2-(1*H*-Indole-3-carbonyl)-3-*p*-tolylacrylonitrile (15)

Synthesized using the general procedure as for (**14**), from 3-oxo-3-(1*H*-indol-3-yl)-3-oxopropanenitrile and 4-chlorobenzaldehyde to afford (**15**) as a yellow solid; 88% 216–219 °C.

^{1}H NMR (DMSO-d_6) (300 MHz): δ 12.26 (br, NH), 8.43 (s, 1H, Ind H2), 8.18–8.16 (m, 2H, Ind H4 + CH=C), 7.94 (d, J = 8.1 Hz, 2H, Ar H2 + Ar H6), 7.55–7.52 (m, 1H, Ind H7), 7.38 (d, J = 8.1 Hz, 2H, Ar H3 + Ar H5), 7.30–7.21 (m, 2H, Ind H5 + Ind H6), 2.37 (s, 3H, OCH_3);

^{13}C NMR (DMSO-d_6) (75 MHz): δ 181.3, 152.1, 142.9, 136.6, 135.7, 130.3 (2 × Ar), 129.7 (2 × Ar), 126.0, 123.4, 122.4, 122.3, 121.3, 117.8, 113.5, 112.4, 110.1, 21.2;

IR (KBr) cm^{-1}: 3262 (NH), 2216 (CN), 1636 (C=C), 1623 (C=O);

LRMS: (ESI M+1) 287. HRMS: Calcd $C_{19}H_{14}N_2O$; Exact mass: 286.1106, found (ESI M+H) 287.1210.

4.2.14. (*E*)-3-(4-Hydroxyphenyl)-2-(1*H*-indole-3-carbonyl)acrylonitrile (16)

Synthesized using the general procedure as for (**14**), from 3-(1*H*-indol-3-yl)-3-oxopropanenitrile and 4-hydroxybenzaldehyde to afford (**16**) as a yellow solid; 90%; 252–253 °C.

^{1}H NMR (DMSO-d_6) (300 MHz): δ 12.17 (br, NH), 8.40 (s, 1H, Ind H2), 8.17–8.13 (m, 2H, Ind H4 + CH=C), 7.98 (d, J = 8.8 Hz, 2H, Ar H2 + Ar H6), 7.53–7.51 (m, 1H, Ind H7), 7.27–7.23 (m, 2H, Ind H5 + Ind H6), 6.94 (d, J = 8.8 Hz, 2H, Ar H3 + Ar H5);

^{13}C NMR (DMSO-d_6) (75 MHz): δ 181.5, 162.0, 152.3, 136.5, 135.0, 133.2 (2 × Ar), 126.1, 123.3, 122.1, 121.7, 121.3, 118.6, 116.1 (2 × Ar), 113.7, 112.3, 106.4;

IR (KBr) cm^{-1}: 3351 (OH), 3232 (NH), 1606 (C=O);

LRMS: (ESI M+1) 289. HRMS: Calcd for $C_{18}H_{12}N_2O_2$; Exact mass: 288.0899, found (ESI M+H) 289.0929

4.2.15. (*E*)-2-(1*H*-Indole-3-carbonyl)-3-(4-methoxyphenyl)acrylonitrile (17)

Synthesized using the general procedure as for (**14**), from 3-(1*H*-indol-3-yl)-3-oxopropanenitrile and 4-methoxybenzaldehyde to afford (**17**) as a yellow solid; 92%; 256–258 °C.

^{1}H NMR (DMSO-d_6) (300 MHz): δ 12.21 (br, NH), 8.42 (s, 1H, Ind H2), 8.18–8.16 (m, 2H, Ind H4 + CH=C), 8.07 (d, J = 8.9 Hz, 2H, Ar H2 + Ar H6), 7.54–7.52 (m, 1H, Ind H7), 7.26–7.24 (m, 2H, Ind H5 + Ind H6), 7.14 (d, J = 8.9 Hz, 2H, Ar H3 + Ar H6), 3.86 (s, 3H, OCH_3);

^{13}C NMR (DMSO-d_6) (75 MHz): δ 181.4, 162.6, 151.9, 136.5, 135.3, 132.7 (2 × Ar), 126.2, 124.8, 123.4, 122.2, 121.3, 118.3, 114.7 (2 × Ar), 113.6, 112.3, 107.9, 55.6;

IR (KBr) cm^{-1}: 3220 (NH), 2221 (CN), 1591 (C=O), 1176 (C–O);

LRMS: (ESI M−1) 301. HRMS: Calcd for $C_{19}H_{14}N_2O_2$; Exact mass: 302.1055, found (ESI M−H) 301.1074.

4.2.16. (*E*)-2-(1*H*-Indole-3-carbonyl)-3-(4-nitrophenyl)acrylonitrile (18)

Synthesized using the general procedure as for (**14**), from 3-(1*H*-indol-3-yl)-3-oxopropanenitrile and 4-nitrobenzaldehyde to afford (**18**) as a red solid; 75%; 286–288 °C.

^{1}H NMR (DMSO-d_6) (300 MHz): δ 12.37 (br, NH), 8.50 (s, 1H, Ind H2), 8.40 (d, J = 8.8 Hz, 2H, Ar H3 + Ar H5), 8.34 (s, 1H, CH=C), 8.23–8.16 (m, 3H, Ar H2 + Ar H6 + Ind H4), 7.56–7.53 (m, 1H, Ind H7), 7.30–7.27 (m, 2H, Ind H5 + Ind H6);

^{13}C NMR (DMSO-d_6) (75 MHz): δ 180.7, 149.3, 148.6, 138.6, 136.8, 136.7, 131.0 (2 × Ar), 125.9, 123.9 (2 × Ar), 123.7, 122.5, 121.2, 116.7, 115.0, 113.3, 112.5;

IR (KBr) cm^{-1}: 3331 (NH), 2219 (CN), 1625 (C=C), 1599 (Ar), 1344 (N–O);

LRMS: (ESI M−1) 316. HRMS: Calcd for $C_{18}H_{11}N_3O_3$; Exact mass: 317.0800, found (ESI M−H) 316.0791.

4.2.17. (*E*)-2-(1*H*-Indole-3-carbonyl)-3-(3,4-dichlorophenyl) acrylonitrile (19)

Synthesized using the general procedure as for (**14**), from 3-(1*H*-indol-3-yl)-3-oxopropanenitrile and 3,4-dichlorobenzaldehyde to afford (**19**) as a yellow solid; 88%; 288–290 °C.

^{1}H NMR (DMSO-d_6) (300 MHz): δ 12.34 (br, NH), 8.46 (s 1H, Ar1 H2), 8.24–8.20 (m, 3H, Ar1 H4 + Ar1 H7 + CH=C), 8.05–8.01 (m, 1H, Ar2 H5), 7.89–8.86 (m, 1H, Ar2 H2), 7.54–7.52 (m, 1H, Ar2 H6), 7.34–7.25 (m, 2H, Ar1 H5 + Ar1 H6);

^{13}C NMR (DMSO-d_6) (75 MHz): δ 180.8, 149.0, 136.7, 136.6, 134.3, 133.0, 132.0, 131.7, 131.2, 129.4, 125.9, 123.6, 122.5, 121.2, 116.9, 116.8, 113.3, 112.4;

IR (KBr) cm^{-1}: 3230 (NH), 2223 (CN), 1635 (C=C), 1594 (C=O), 755 (Ar–Cl);

LRMS: (ESI M−1) 339. HRMS: Calcd for $C_{18}H_{10}Cl_2N_2O$; Exact mass: 340.0170, found (ESI M−H) 339.0198.

4.2.18. (*E*)-2-(1*H*-Indole-3-carbonyl)-3-(4-(trifluoromethyl) phenyl)acrylonitrile (20)

Synthesized using the general procedure as for (**14**), from 3-(1*H*-indol-3-yl)-3-oxopropanenitrile and 4-(trifluoromethyl)benzaldehyde to afford (**20**) as a yellow solid; 73%; 242–243 °C.

^{1}H NMR (DMSO-d_6) (300 MHz): δ 12.30 (br, NH), 8.48 (s, 1H, Ind H2), 8.31 (s, 1H, CH=C), 8.20–8.18 (m, 3H, Ar H2 + Ar H6 + Ind H4), 7.95 (d, J = 7.8 Hz, 2H, Ar H3 + Ar H5), 7.57–7.53 (m, 1H, Ind H7), 7.31–7.26 (m, 2H, Ind H5 + Ind H6);

^{13}C NMR (DMSO-d_6) (75 MHz): δ 180.8, 150.0, 136.7, 136.5, 136.4, 130.6 (2 × Ar), 125.9 (2 × Ar), 125.8, 125.7, 125.6, 123.6, 122.5, 121.2, 116.9, 114.2, 113.4, 112.6;

IR (KBr) cm^{-1}: 3211 (NH), 2223 (CN), 1596 (C=O), 1336 (C–F);

LRMS: (ESI M−1) 339. HRMS: Calcd for $C_{19}H_{11}F_3N_2O$; Exact mass: 340.0823, found ESI (M−H) 339.0829.

4.2.19. (*E*)-2-(1*H*-Indole-3-carbonyl)-3-(perfluorophenyl)acrylonitrile (21)

Synthesized using the general procedure as for (**14**), from 3-(1*H*-indol-3-yl)-3-oxopropanenitrile and 2,3,4,5,6-pentafluorobenzaldehyde to afford (**21**) as a yellow solid; 71%; 240–242 °C.

^{1}H NMR (DMSO-d_6) (300 MHz): δ 12.18 (br, NH), 8.39-8.38 (m, 1H, Ind H2), 7.97–7.94 (m, 1H, Ind H4), 7.56–7.52 (m, 1H, Ind H7), 7.31–7.17 (m, 3H, Ind H5 + Ind H6 + CH=C);

^{13}C NMR (DMSO-d_6) (75 MHz): δ 159.9, 138.2, 136.8, 136.0, 134.9, 130.4, 124.5, 123.9, 122.9, 122.7 (2 × Ar), 121.5 (2 × Ar), 121.2, 120.6, 119.2, 112.6, 105.1;

IR (KBr) cm^{-1}: 3283 (NH), 2212 (CN), 1655 (C=C), 1596 (C=O), 1207 (C–F);

LRMS: (ESI M−1) 361. HRMS: Calcd for $C_{18}H_7F_5N2O$; Exact mass: 362.0479, found (ESI M−H) 316.0465.

4.2.20. (*E*)-2-(1*H*-Indole-3-carbonyl)-3-(naphthalen-2-yl)acrylonitrile (22)

Synthesized using the general procedure as for (**14**), from 3-(1*H*-indol-3-yl)-3-oxopropanenitrile and 2-naphthaldehyde to afford (**22**) as a yellow solid; 72%; 302–304 °C.

^{1}H NMR (DMSO-d_6) (300 MHz): δ 12.29 (br, NH), 8.54–8.50 (m, 2H, Ind H2 + Ind H4), 8.38 (s, 1H, CH=C), 8.24–8.20 (m, 2H, Ar H5 + Ar H8), 8.11–7.99 (m, 3H, Ind H7 + Ar H1 + Ar H4), 7.70–7.54 (m, 3H, Ar H3 + Ar H6 + Ar H7), 7.32–7.24 (m, 2H, Ind H5 + Ind H6);

^{13}C NMR (DMSO-d_6) (75 MHz): δ 181.3, 152.0, 136.6, 135.9, 134.3, 132.8, 132.4, 130.0, 128.9, 128.6, 128.5, 127.7, 127.2, 126.1, 124.8, 123.5, 122.4, 121.3, 117.8, 112.5, 112.4, 111.4;

IR (KBr) cm^{-1}: 3174 (NH), 2214 (CN), 1597 (C=O), 1516 (Ar);

LRMS: (ESI M−1) 321. HRMS: Calcd for $C_{22}H_{14}N_2O$; Exact mass: 322.1106, found (ESI M−H) 321.1104.

4.2.21. (*E*)-3-(1*H*-Indol-3-yl)-2-(1*H*-indole-3-carbonyl)acrylonitrile (23)

Synthesized using the general procedure as for (**14**), from 3-(1*H*-indol-3-yl)-3-oxopropanenitrile 1*H*-indole-3-carbaldehyde to afford (**23**) as a yellow solid; 79%; 292–294 °C.

^{1}H NMR (DMSO-d_6) (300 MHz): δ 12.14 (br, 2H), 8.63 (s, 1H, Ind H2), 8.60 (s, 1H, CH=C), 8.47 (s, 1H, Ind2 H2), 8.24–8.22 (m, 1H, Ind H4), 7.94–7.91 (m, 1H, Ind2 H4), 7.59–7.53 (m, 2H, Ind H7 + Ind2 H7), 7.31–7.21 (m, 4H, Ind H5 + Ind H6 + Ind2 H5 + Ind2 H6);

^{13}C NMR (DMSO-d$_6$) (75 MHz): δ 180.7, 145.0, 136.3, 136.1, 133.7, 131.2, 127.2, 126.4, 123.3, 123.1, 121.9, 121.7, 121.5, 120.5, 118.5, 114.3, 112.7, 112.2, 110.3, 101.9;

IR (KBr) cm^{-1}: 3262 (NH), 2200 (CN), 1612 (C=O);

LRMS: (ESI M−1) 310. HRMS: Calcd for $C_{20}H_{13}N_3O$; Exact mass: 311.1059, found (ESI M−H) 310.0987.

4.2.22. (*E*)-2-Cyano-*N*-(4-methoxybenzyl)-3-(1*H*-pyrrol-2-yl) acrylamide (27)

Methyl 2-cyanoacetate (**24**) (0.72, 7.28 mmol) was added to a solution of (4-methoxybenzylamine (1.0 g, 7.28 mmol) in MeOH (4 mL). The resultant solution was heated under microwave radiation for 15 min at 200 W and 120 °C. After this period, the reaction was cooled in the freezer for 30 min upon which a crystalline solid was formed. The solid was collected by filtration, washed with ice cold MeOH (2 × 5 mL) and dried under vacuum to afford *N*-(4-methoxybenzyl)propionamide (25); 65%. Next, *N*-(4-methoxybenzyl)propionamide (3.77 mmol) was added to an ethanolic solution (4 mL) of 1*H*-pyrrole-2-carbaldehyde (4.15 mmol) and piperidine (2 drops). This mixture was heated under microwave radiation for 15 min at 200 W and 120 °C. After this period, the solution was cooled and the solvent removed in vacuo to yield a brown crude solid, which was purified by flash chromatography (2:8

EtOAc/Hexanes) to afford (**27**) as a brown solid; 81%; mp 203–204 °C.

^{1}H NMR (Acetone-d_6) (300 MHz): δ 10.94 (br, NH), 8.18 (s, 1H, CH═C), 7.65 (br, NH), 7.33–7.28 (m, 4H, Ar H2 + Ar H6 + Pyr H3 + Pyr H5), 6.87 (d, J = 8.7 Hz, 2H, Ar H3 + Ar H5), 6.43 (m, 1H, Pyr H4), 4.49 (d, J = 6.0 Hz, 2H, CH_2NH), 3.77 (s, 3H, OCH_3);

^{13}C NMR (Acetone-d_6) (75 MHz): δ 160.7, 158.4, 139.6, 131.3, 130.7, 128.4 (2 × Ar), 125.7, 117.1, 116.5, 113.1 (2 × Ar), 111.6, 94.8, 54.0, 42.4;

IR (KBr) cm^{-1}: 3360 (NH), 3234 (NH), 2202 (CN), 1650 (C═O);

LRMS: (ESI M+1) 282. HRMS: Calcd for $C_{16}H_{15}N_3O_2$; Exact mass: 281.1164, found (ESI M+H) 282.1208.

4.2.23. (*E*)-2-Cyano-*N*-(3,4-dichlorobenzyl)-3-(1*H*-pyrrol-2-yl) acrylamide (28)

Synthesized using the general procedure as for (**27**), from *N*-(3,4-dichlorobenzyl)propioamide and 1*H*-pyrrole-2-carbaldehyde to afford (**28**) as a yellow solid; 80%; 234–235 °C.

^{1}H NMR (DMSO-d_6) (300 MHz): δ 11.88 (br, NH), 8.67 (t, J = 5.9 Hz, NH), 8.05 (s, 1H, CH═C), 7.58–7.53 (m, 2H, Ar H5 + Ar H2), 7.30–7.26 (m, 3H, Ar H6 + Pyr H5 + Pyr H3), 6.42–6.40 (m, 1H, Pyr H4), 4.36 (d, J = 5.9 Hz, 2H, CH_2NH);

^{13}C NMR (DMSO-d_6) (75 MHz): δ 161.8, 141.1, 140.5, 140.3, 130.7, 130.4, 129.3, 127.7, 126.5, 126.3, 117.7, 115.5, 112.5, 94.3, 42.0;

IR (KBr) cm^{-1}: 3342 (NH), 3232 (NH), 2209 (CN), 1643 (C═O), 749 (Ar–Cl);

LRMS: (ESI M−1) 318. HRMS: Calcd for $C_{15}H_{11}Cl_2N_3O$; Exact mass: 319.0279, found (ESI M−H) 318.0198.

4.2.24. (*E*)-2-Cyano-3-(furan-2-yl)-*N*-(4-methoxybenzyl)acryl amide (29)

Synthesized using the general procedure as for (**27**), from *N*-(4-methoxybenzyl)propioamide and furan-2-carbaldehyde to afford (**29**) as a orange solid; 67%; 119–120 °C.

^{1}H NMR (Acetone-d$_6$) (300 MHz): δ 8.03 (s, 1H, CH═C), 7.94 (d, J = 1.6 Hz, 1H, Fur H5), 7.86 (br, NH), 7.36 (d, J = 3.6 Hz, 1H, Fur H3), 7.30 (d, J = 8.6 Hz, 2H, Ar H2 + Ar H6), 6.88 (d, J = 8.6 Hz, 2H, Ar H3 + Ar H5), 6.77 (dd, J = 1.6 Hz, 3.6 Hz, 1H, Fur H4), 4.50 (d, J = 5.9 Hz, 2H, CH_2NH), 3.77 (s, 3H, OCH_3);

^{13}C NMR (Acetone-d_6) (75 MHz): δ 159.7, 158.5, 148.6, 147.4, 135.7, 130.4, 128.5 (2 × Ar), 120.1, 115.3, 113.2 (2 × Ar), 113.0, 100.6, 54.1, 42.4;

IR (KBr) cm^{-1}: 3325 (NH), 2225 (CN), 1659 (C═O);

LRMS: (ESI M+1) 283. HRMS: Calcd for $C_{16}H_{14}N_2O_3$; Exact mass 282.1004, found (ESI M+H) 283.0989.

4.2.25. (*E*)-2-Cyano-*N*-(3,4-dichlorobenzyl)-3-(furan-2-yl)acryl amide (30)

Synthesized using the general procedure as for (**27**), from *N*-(3,4-dichlorobenzyl)propioamide and furan-2-carbaldehyde to afford (**30**) as a light yellow solid; 76%; 198–199 °C.

^{1}H NMR (DMSO-d_6) (300 MHz): δ 8.92 (t, J = 5.9 Hz, NH), 8.12 (d, J = 1.6 Hz, 1H, Fur H5), 7.99 (s, 1H, CH═C), 7.58 (d, J = 8.3 Hz, 1H, Ar H5), 7.55 (d, J = 2.0 Hz, 1H, Ar H1), 7.37 (d, J = 3.6 Hz, 1H, Fur H3), 7.29 (dd, J = 2.0, 8.3 Hz, 1H, Ar H6), 6.81 (dd, J = 1.6, 3.6 Hz, 1H, Fur H4), 4.37 (d, J = 5.9 Hz, 2H, CH_2NH);

^{13}C NMR (DMSO-d_6) (75 MHz): δ 161.0, 148.7, 148.3, 140.1, 136.1, 130.7, 130.4, 129.4, 127.7, 121.8, 116.0, 113.8, 103.4, 100.3, 42.1;

IR (KBr) cm^{-1}: 3358 (NH), 2216 (CN), 1671 (C═O), 757 (Ar–Cl);

LRMS: (ESI M−1) 319. HRMS: Calcd for $C_{15}H_{10}Cl_2N_2O_2$; Exact mass: 320.0119, found (ESI M−H) 319.0039.

4.2.26. (*E*)-2-Cyano-*N*-(4-methoxybenzyl)-3-(5-methylfuran-2-yl)acrylamide (31)

Synthesized using the general procedure as for (**27**), from *N*-(4-methoxybenzyl)propioamide and 5-methylfuran-2-carbaldehyde to afford (**31**) as a white solid; 92%; 146–147 °C.

^{1}H NMR ($CDCl_3$) (300 MHz): δ 7.94 (s, 1H, CH═O), 7.83 (br, NH), 7.32–7.26 (m, 3H, Ar H2 + Ar H6 + Fur H3), 6.88 (d, J = 8.7 Hz, 2H, Ar H3 + Ar H5), 6.43–6.42 (m, 1H), Fur H4), 4.49 (d, J = 5.9 Hz, 2H, CH_2NH), 3.77 (s, 3H, OCH_3), 2.42 (s, 3H, CH_3);

^{13}C NMR ($CDCl_3$) (75 MHz): δ 160.0, 158.4, 147.3, 135.4, 130.6, 128.5 (2 × Ar), 122.3, 115.6, 113.1 (2 × Ar), 110.0, 99.9, 98.3, 54.0, 42.5, 12.5;

IR (KBr) cm^{-1}: 3364 (NH), 2214 (CN), 1671 (C═O);

LRMS: (ESI M+1) 297. HRMS: Calcd for $C_{17}H_{16}N_2O_3$; Exact mass: 296.1161, found (ESI M+H) 297.1206.

4.2.27. (*E*)-2-Cyano-3-(5-(hydroxymethyl)furan-2-yl)-*N*-(4-methoxybenzyl)acrylamide (32)

Synthesized using the general procedure as for (**27**), from *N*-(4-methoxybenzyl)propioamide and 5-(hydroxymethyl)furan-2-carbaldehyde to afford (**32**) as a white solid; 45%; 130–132 °C.

^{1}H NMR (Acetone-d_6) (300 MHz): δ 7.98 (s, 1H, CH═O), 7.82 (br, NH), 7.33–7.29 (m, 3H, Ar H2 + Ar H6 + Fur H3), 6.88 (d, J = 8.7 Hz, 2H, Ar H3 + Ar H5), 6.62 (d, J = 3.5 Hz, 1H, Fur H4), 4.65 (s, 2H, CH_2OH), 4.50 (br, OH), 4.49 (d, J = 5.9 Hz, 2H, CH_2NH), 3.77 (s, 3H, OCH_3);

^{13}C NMR (Acetone-d_6) (75 MHz): δ 161.1, 159.8, 158.5, 147.8, 135.7, 130.5, 128.5 (2 × Ar), 121.1, 115.4, 113.2 (2 × Ar), 109.9, 99.6, 56.1, 54.1, 42.6;

IR (KBr) cm^{-1}: 3347 (NH), 3235 (OH), 2215 (CN), 1667 (C═O), 1248 (C–O);

LRMS: (ESI M+1) 313. HRMS: Calcd for $C_{17}H_{16}N_2O_4$; Exact mass: 312.1110, found (ESI M+H) 313.1122.

4.2.28. (*E*)-3-(5-Chlorofuran-2-yl)-2-cyano-*N*-(4-methoxyben zyl)acrylamide (33)

Synthesized using the general procedure as for (**27**), from *N*-(4-methoxybenzyl)propioamide and 5-chlorofuran-2-carbaldehyde to afford (**33**) as a yellow solid; 71%; 164–165 °C.

^{1}H NMR ($CDCl_3$) (300 MHz): δ 7.99 (s, 1H, CH═C), 7.25 (d, J = 8.5 Hz, 2H, Ar H2 + Ar H6), 7.20–7.19 (m, 1H, Fur H3), 6.88 (d, J = 8.5 Hz, 2H, Ar H3 + Ar H6), 6.55 (br, NH), 6.44–6.43 (m, 1H, Fur H4), 4.51 (d, J = 5.6 Hz, 2H, CH_2NH), 3.81 (s, 3H, OCH_3);

^{13}C NMR ($CDCl_3$) (75 MHz): δ 159.3, 158.8, 147.9, 142.5, 135.6, 128.8 (2 × Ar), 128.6, 122.0, 115.8, 113.7 (2 × Ar), 110.1, 99.4, 54.8, 43.5;

IR (KBr) cm^{-1}: 3342 (NH), 2217 (CN), 1666 (C═O), 1251 (C–O);

LRMS: (ESI M+1) 317. HRMS: Calcd for $C_{16}H_{13}ClN_2O_3$; Exact mass: 316.0615, found (ESI M+H) 317.0666.

4.2.29. (*E*)-3-(5-Bromofuran-2-yl)-2-cyano-*N*-(4-methoxyben zyl)acrylamide (34)

Synthesized using the general procedure as for (**27**), from *N*-(4-methoxybenzyl)propioamide and 5-bromofuran-2-carbaldehyde to afford (**34**) as a yellow solid; 84%; 160–162 °C.

^{1}H NMR ($CDCl_3$) (300 MHz): δ 8.01 (s, 1H, CH═C), 7.25 (d, J = 8.6 Hz, 2H, Ar H2 + Ar H6), 7.16 (d, J = 3.7 Hz, 1H, Fur H3), 6.89 (d, J = 8.6 Hz, 2H, Ar H3 + Ar H5), 6.58-6.57 (m, 2H, Fur H4 + NH), 4.51 (d, J = 5.7 Hz, 2H, CH_2NH), 3.80 (s, 3H, OCH_3);

^{13}C NMR ($CDCl_3$) (75 MHz): δ 159.3, 158.7, 150.2, 135.5, 129.1, 128.8 (2 × Ar), 128.6, 122.0, 115.7, 115.1, 113.7 (2 × Ar), 99.5, 54.8, 43.5;

IR (KBr) cm^{-1}: 3348 (NH), 2219 (CN), 1672 (C═O), 1247 (C–O), 807 (Ar–Br);

LRMS: (ESI M+1) 361. HRMS: Calcd for: $C_{16}H_{13}BrN_2O_3$; Exact mass: 360.0110, found (ESI M+H) 361.0145.

4.2.30. (*E*)-2-Cyano-*N*-(4-methoxybenzyl)-3-(5-phenylfuran-2-yl)acrylamide (35)

Synthesized using the general procedure as for (**27**), from *N*-(4-methoxybenzyl)propioamide and 5-phenylfuran-2-carbaldehyde to afford (**35**) as a yellow solid; 85%; 203–205 °C.

^{1}H NMR (DMSO-d_6) (300 MHz): δ 8.81 (t, J = 5.9 Hz, NH), 7.99 (s, CH=C), 7.90 (d, J = 7.3 Hz, 2H, Ar2 H2 + Ar2 H6), 7.53–7.48 (m, 2H, Ar2 H3 + Ar2 H5), 7.44–7.42 (m, 2H, Ar2 H4 + Fur H3), 7.34–7.33 (m, 1H, Fur H4), 7.23 (d, J = 8.6 Hz, 2H, Ar H2 + Ar H6), 6.88 (d J = 8.6 Hz, 2H, Ar H3 + Ar H5), 4.32 (d, J = 5.9 Hz, 2H, CH_2NH), 3.71 (s, 3H, OCH_3);

^{13}C NMR (DMSO-d_6) (75 MHz): δ 160.9, 158.2, 157.7, 147.7, 135.1, 130.9, 129.5, 129.1 (2 × Ar), 128.7 (2 × Ar), 128.6, 124.7 (2 × Ar), 124.6, 116.6, 113.6 (2 × Ar), 109.6, 99.7, 54.9, 42.6;

IR (KBr) cm^{-1}: 3362 (NH), 2209 (CN), 1666 (C=O), 1607 (Ar), 1247 (C–O);

LRMS: (ESI M+1) 359. HRMS: Calcd for $C_{22}H_{18}N_2O_3$; Exact mass: 358.1317, found (ESI M+H) 359.1489.

4.2.31. (*E*)-3-(4-Bromofuran-2-yl)-2-cyano-*N*-(4-methoxybenzyl)acrylamide (36)

Synthesized using the general procedure as for (**27**), from *N*-(4-methoxybenzyl)propioamide and 4-bromofuran-2-carbaldehyde to afford (**36**) as a white solid; 70%; 169–170 °C.

^{1}H NMR ($CDCl_3$) (300 MHz): δ 8.04 (s, 1H, CH=C), 7.68 (s, 1H, Fur H5), 7.26–7.23 (m, 3H, Ar H2 + Ar H6 + Fur H3), 6.88 (d, J = 8.6 Hz, 2H, Ar H3 + Ar H5), 6.59 (br, NH), 4.51 (d, J = 5.7 Hz, 2H, CH_2NH), 3.80 (s, 3H, OCH_3);

^{13}C NMR ($CDCl_3$) (75 MHz): δ 159.0, 158.8, 148.9, 144.8, 136.1, 128.8 (2 × Ar), 128.5, 121.7, 115.6, 113.7 (2 × Ar), 102.6, 101.1, 54.8, 43.6;

IR (KBr) cm^{-1}: 3332 (NH), 2223 (CN), 1660 (C=O), 1254 (C–O), 926 (Ar–Br);

LRMS: (ESI M+1) 361. HRMS: Calcd for $C_{16}H_{13}BrN_2O_3$; Exact mass: 360.0110, found (ESI M+H) 361.0195.

4.2.32. (*E*)-2-Cyano-3-(furan-3-yl)-*N*-(4-methoxybenzyl)acrylamide (37)

Synthesized using the general procedure as for (**27**), from *N*-(4-methoxybenzyl)propioamide and furan-3-carbaldehyde to afford (**37**) as a brown solid; 60%; 122–124 °C.

^{1}H NMR (Acetone-d_6) (300 MHz): δ 8.32 (s, 1H, Fur H2), 8.21 (s, 1H, CH=C), 7.84 (br, NH), 7.78-7.77 (m, 1H, Fur H5), 7.30 (d J = 8.7 Hz, 2H, Ar H2 + Ar H6), 7.23–7.22 (m, 1H, Fur H4), 6.88 (d, J = 8.7 Hz, 2H, Ar H3 + Ar H5), 4.49 (d, J = 6.0 Hz, 2H, CH_2NH), 3.77 (s, 3H, OCH_3);

^{13}C NMR (Acetone-d_6) (75 MHz): δ 159.7, 158.5, 149.4, 145.0, 141.6, 130.4, 128.5 (2 × Ar), 120.4, 115.8, 113.2, (2 × Ar), 107.3, 103.8, 54.1, 42.5;

IR (KBr) cm^{-1}: 3332 (NH), 2213 (CN), 1661 (C=O), 1611 (Ar), 1513 (Ar), 1251 (C–O). LRMS: (ESI M+1) 283;

HRMS: Calcd for Chemical Formula: $C_{16}H_{14}N_2O_3$; Exact mass: 282.1004, found (ESI M+H) 283.1032.

4.2.33. (*E*)-3-(Benzofuran-2-yl)-2-cyano-*N*-(4-methoxybenzyl)acrylamide (38)

Synthesized using the general procedure as for (**27**), from *N*-(4-methoxybenzyl)propioamide and benzofuran-2-carbaldehyde to afford (**38**) as a white solid; 87%; 150–153 °C.

^{1}H NMR (DMSO-d_6) (300 MHz): δ 8.96 (t, J = 5.8 Hz, NH), 8.14 (s, 1H, CH=C), 7.83–7.80 (m, 1H, Ar2 H4), 7.76 (s, 1H, Ar2 H3), 7.68–7.65 (m, 1H, Ar2 H7), 7.54–7.49 (m, 1H, Ar2 H6), 7.38–7.32 (m, 1H, Ar2 H5), 7.25 (d, J = 8.5 Hz, 2H, Ar H2 + Ar H6), 6.88 (d, J = 8.5 Hz, 2H, Ar H3 + Ar H5), 4.34 (d, J = 5.8 Hz, 2H, CH_2NH), 3.72 (s, 3H, OCH_3);

^{13}C NMR (DMSO-d_6) (75 MHz): δ 160.4, 158.2, 155.3, 149.6, 136.3, 130.7, 128.8 (2 × Ar), 128.5, 127.3, 124.1, 123.0, 117.3, 115.7, 113.6 (2 × Ar), 111.6, 104.1, 55.0, 42.6;

IR (KBr) cm^{-1}: 3342 (NH), 2225 (CN), 1672 (C=O), 1513 (Ar), 1251 (C–O);

LRMS: (ESI M+1) 333. HRMS: Calcd for $C_{20}H_{16}N_2O_3$; Exact mass: 322.1161, found (ESI M+H) 333.1231.

4.2.34. (*E*)-2-Cyano-*N*-(4-methoxybenzyl)-3-phenylacrylamide (39)

Synthesized using the general procedure as for (**27**), from *N*-(4-methoxybenzyl)propioamide and benzaldehyde to afford (**39**) as a white solid; 63%; 117–118 °C.

^{1}H NMR (Acetone-d_6) (300 MHz): δ 8.27 (s, 1H, CH=C), 8.00 (m, 32H, Ar2 H2 + Ar2 H6, NH), 7.57 (m, 3H, Ar2 H3 + Ar2 H4 + Ar2 H5), 7.32 (d, J = 8.7 Hz, 2H, Ar H2 + Ar H6), 6.89 (d, J = 8.7 Hz, 2H, Ar H3 + Ar H5), 4.52 (d, J = 5.9 Hz, 2H, CH_2NH), 3.78 (s, 3H, OCH_3);

^{13}C NMR (Acetone-d_6) (75 MHz): δ 159.7, 158.5, 150.7, 131.8 (2 × Ar), 130.9, 130.3, 129.7 (2 × Ar), 128.6 (2 × Ar), 115.6, 113.2 (2 × Ar), 105.4, 104.4, 54.0, 42.6;

IR (KBr) cm^{-1}: 3336 (NH), 2223 (CN), 1663 (C=O), 1259 (C–O);

LRMS: (ESI M+1) 293. HRMS: Calcd for $C_{18}H_{16}N_2O_2$; Exact mass: 292.1212, found (ESI M+H) 293.1215.

4.2.35. (*E*)-2-Cyano-*N*-(4-methoxybenzyl)-3-p-tolylacrylamide (40)

Synthesized using the general procedure as for (**27**), from *N*-(4-methoxybenzyl)propioamide and 4-methylbenzaldehyde to afford (**40**) as a yellow solid; 70%; 115–117 °C.

^{1}H NMR (Acetone-d_6) (300 MHz): δ 8.22 (s, 1H, CH=C), 7.90 (d, J = 8.2 Hz, 2H, Ar2 H2 + Ar 2 H6), 7.38 (d, J = 8.2 Hz, 2H, Ar 2 H3 + Ar2 H5), 7.32 (d, J = 8.8 Hz, 2H, Ar H2 + Ar H6), 6.88 (d, J = 8.8 Hz, 2H, Ar H3 + Ar H5), 4.51 (d, J = 5.9 Hz, 2H, CH_2NH), 3.77 (s, 3H, OCH_3), 2.41 (s, 3H, CH_3);

^{13}C NMR (Acetone-d_6) (75 MHz): δ 159.9, 158.4, 150.7, 142.8, 130.4, 129.9 (2 × Ar), 129.3 (2 × Ar), 129.1, 128.6 (2 × Ar), 115.7, 113.2 (2 × Ar), 103.9, 54.0, 42.6, 20.2;

IR (KBr) cm^{-1}: 3339 (NH), 2220 (CN), 1662 (C=O), 1259 (C–O);

LRMS: (ESI M+1) 307. HRMS: Calcd for $C_{19}H_{18}N_2O_2$; Exact mass: 306.1368, found (ESI M+H) 307.1435.

4.2.36. (*E*)-3-(4-Chlorophenyl)-2-cyano-*N*-(4-methoxybenzyl)acrylamide (41)

Synthesized using the general procedure as for (**27**), from *N*-(4-methoxybenzyl)propioamide and 4-chlorobenzaldehyde to afford (**41**) as a yellow solid; 28%; 134–135 °C.

^{1}H NMR (Acetone-d_6) (300 MHz): δ 8.25 (s, 1H, CH=C), 8.01 (d, J = 8.8 Hz, 2H, Ar2 H2 + Ar2 H6), 7.60 (d, J = 8.8 Hz, 2H, Ar2 H3 + Ar2 H5), 7.31 (d, J = 8.7 Hz, 2H, Ar H2 + Ar H6), 6.89 (d, J = 8.7 Hz, 2H, Ar H3 + Ar H5), 4.51 (d, J = 5.9 Hz, 2H, CH_2NH), 3.77 (s, 3H, OCH_3);

^{13}C NMR (Acetone-d_6) (75 MHz): δ 159.5, 158.5, 149.3, 137.1, 131.3 (2 × Ar), 130.5, 130.3, 128.8 (2 × Ar), 128.6 (2 × Ar), 115.4, 113.2 (2 × Ar), 106.0, 54.1, 42.6;

IR (KBr) cm^{-1}: 3361 (NH), 2216 (CN), 1664 (C=O), 1252 (C–O), 819 (Ar–Cl);

LRMS: (ESI M+1) 327. HRMS: Calcd for $C_{18}H_{15}ClN_2O_2$; Exact mass: 326.0822, found (ESI M+H) 327.0846.

4.2.37. (*E*)-2-Cyano-3-(4-hydroxyphenyl)-*N*-(4-methoxybenzyl)acrylamide (42)

Synthesized using the general procedure as for (**27**), from *N*-(4-methoxybenzyl)propioamide and 4-hydroxybenzaldehyde to afford (**42**) as a light yellow solid; 20%; 197–198 °C.

^{1}H NMR (Acetone-d_6) (300 MHz): δ 8.16 (s, 1H, CH=C), 7.94 (d, J = 8.8 Hz, 2H, Ar H3 + Ar H5), 7.81 (br, NH), 7.31 (d, J = 8.6 Hz, 2H, Ar2 H2 + Ar2 H6), 7.00 (d, J = 8.8 Hz, 2H, Ar H2 + Ar H6), 6.88 (d, J = 8.6 Hz, 2H, Ar2 H3 + Ar2 H5), 4.50 (d, J = 5.9 Hz, 2H, CH_2NH), 3.77 (s, 3H, OCH_3);

^{13}C NMR (Acetone-d_6) (75 MHz): δ 161.0, 160.2, 150.5, 132.5 (2 × Ar), 130.6, 128.5 (2 × Ar), 123.4, 116.4, 115.6 (2 × Ar), 113.1 (2 × Ar), 102.8, 100.8, 54.0, 42.5;

IR (KBr) cm^{-1}: 3342 (NH), 3153 (OH), 2212 (CN), 1645 (C=O), 1172 (C–O);

LRMS: (ESI M+1) 309. HRMS: Calcd for $C_{18}H_{16}N_2O_3$; Exact mass: 308.3312, found (ESI M+H) 309.1234.

4.2.38. (*E*)-2-Cyano-*N*-(4-methoxyphenyl)-3-(4-methoxybenzyl) acrylamide (43)

Synthesized using the general procedure as for (**27**), from *N*-(4-methoxybenzyl)propioamide and 4-methoxybenzaldehyde to afford (**43**) as a yellow solid; 34%; 138–139 °C.

^{1}H NMR (Acetone-d_6) (300 MHz): δ 8.19 (s, 1H, CH=C), 8.01 (d, J = 8.9 Hz, 2H, Ar2 H2 + Ar2 H6), 7.84 (br, NH), 7.31 (d, J = 8.5 Hz, 2H, Ar H2 + Ar H6), 7.10 (d, J = 8.9 Hz, 2H, Ar2 H3 + Ar2 H5), 6.89 (d, J = 8.5 Hz, 2H, Ar H3 + Ar H5), 4.50 (d, J = 6.0 Hz, 2H, CH_2NH), 3.91 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3);

^{13}C NMR (Acetone-d_6) (75 MHz): δ 162.7, 160.2, 158.5, 150.3, 132.1 (2 × Ar), 130.5, 128.5 (2 × Ar), 124.3, 116.5, 114.1 (2 × Ar), 113.1 (2 × Ar), 101.6, 54.6, 54.0, 42.5;

IR (KBr) cm^{-1}: 3420 (NH), 2200 (CN), 1667 (C=O), 1250 (C–O), 1178 (C-O);

LRMS: (ESI M+1) 323. HRMS: Calcd for $C_{19}H_{18}N_2O_3$; Exact mass: 322.1317, found (ESI M+H) 323.1378.

4.2.39. (*E*)-2-Cyano-*N*-(4-methoxybenzyl)-3-(naphthalen-2-yl) acrylamide (44)

Synthesized using the general procedure as for (**27**), from *N*-(4-methoxybenzyl)propioamide and 2-naphthaldehyde to afford (**44**) as a yellow solid; 45%; 143–144 °C.

^{1}H NMR (Acetone-d_6) (300 MHz): δ 8.49 (s, 1H CH=C), 8.43 (s, 1H, Ar2 H1), 8.20 (dd, J = 1.7, 8.7 Hz, 1H, Ar2 H8), 8.09–7.99 (m, 4H, Ar2 H5 + Ar2 H4 + Ar2 H6 + NH), 7.70–7.60 (m, 2H, Ar2 H5 + Ar2 H3), 7.34 (d, J = 8.7 Hz, 2H, Ar H2 + Ar H6), 6.90 (d, J = 8.7 Hz, 2H, Ar H3 + Ar H5), 4.54 (d, J = 5.9 Hz, 2H, CH_2NH), 3.78 (s, 3H, OCH_3);

^{13}C NMR (DMSO-d_6) (75 MHz): δ 160.9, 158.2, 150.5, 134.2, 132.6, 132.3, 130.7, 129.4, 128.9 (2 × Ar), 128.8, 128.7, 128.6, 127.7, 127.2, 124.5, 116.4, 113.6 (2 × Ar), 106.1, 55.0, 42.6;

IR (KBr) cm^{-1}: 3371 (NH), 2212 (CN), 1676 (C=O), 1253 (C–O);

LRMS: (ESI M+1) 343. HRMS: Calcd for $C_{22}H_{18}N_2O_2$; Exact mass: 342.1368, found (ESI M+H) 343.1527.

4.2.40. (*E*)-2-Cyano-*N*-(4-methoxybenzyl)-3-(naphthalen-1-yl) acrylamide (45)

Synthesized using the general procedure as for (**27**), from *N*-(4-methoxybenzyl)propioamide and 1-naphthaldehyde to afford (**45**) as a clear oil; 70%.

^{1}H NMR (Acetone-d_6) (300 MHz): δ 9.03 (s, 1H, CH=C), 8.14–8.07 (m, 4H, Ar2 H5 + Ar2 H8 + Ar2 H4 + NH), 8.02–7.99 (m, 1H, Ar2 H2), 7.67–7.58 (m, 3H, Ar2 H3 + Ar H6 + Ar2 H7), 7.37 (d, J = 8.7 Hz, 2H, Ar H2 + Ar H6), 6.90 (d, J = 8.7 Hz, 2H, Ar H3 + Ar H5), 4.57 (d, J = 6.0 Hz, 2H, CH_2NH), 3.77 (s, 3H, OCH_3);

^{13}C NMR (Acetone-d_6) (75 MHz): δ 159.7, 158.6, 148.7, 133.1, 131.6, 130.9, 130.3, 128.7 (2 × Ar), 128.4, 127.0, 126.7, 126.2, 125.3, 124.8, 122.8, 115.3, 113.2 (2 × Ar), 109.3, 54.1, 42.7;

IR (KBr) cm^{-1}: 3357 (NH), 2227 (CN), 1676 (C=O), 1237 (C–O);

LRMS: (ESI M+1) 343. HRMS: Calcd for $C_{22}H_{18}N_2O_2$; Exact mass: 342.1368, found (ESI M+H) 343.1448.

4.2.41. (*E*)-2-Cyano-*N*-(3,4-dichlorobenzyl)-3-phenylacrylamide (46)

Synthesized using the general procedure as for (**27**), from *N*-(3,4-dichlorobenzyl)propioamide and benzaldehyde to afford (**46**) as a yellow solid; 57%; 159–160 °C.

^{1}H NMR (Acetone-d_6) (300 MHz): δ 8.29 (s, 1H, CH=C), 8.22 (br, NH), 8.02–7.99 (m, 2H, Ar2 H2 + Ar2 H6), 7.61–7.51 (m, 5H, Ar2 H3 + Ar2 H4 + Ar2 H5 + Ar H1 + Ar H5), 7.38 (dd, J = 2.0, 8.3 Hz, 1H, Ar H6), 4.60 (d, J = 6.0 Hz, 2H, CH_2NH);

^{13}C NMR (Acetone-d_6) (75 MHz): δ 160.2, 151.2, 139.6, 131.9, 131.7, 131.1, 129.9, 129.8 (2 × Ar), 129.5, 129.3 (2 × Ar), 128.6, 127.3, 115.5, 104.9, 42.1;

IR (KBr) cm^{-1}: 3364 (NH), 2215 (CN), 1678 (C=O), 679 (Ar–Cl);

LRMS: (ESI M−1) 329. HRMS: Calcd for $C_{17}H_{12}Cl_2N_2O$; Exact mass: 330.0327, found (ESI M−H) 329.0273.

4.2.42. (*E*)-2-Cyano-*N*-(3,4-dichlorobenzyl)-3-p-tolylacrylamide (47)

Synthesized using the general procedure as for (**27**), from *N*-(3,4-dichlorobenzyl)propioamide and 4-methylbenzaldehyde to afford (**47**) as a light yellow solid; 62%; 161–162 °C.

^{1}H NMR (DMSO-d_6) (300 MHz): δ 8.99 (t, J = 5.8 Hz, NH), 8.16 (s, 1H, CH=C), 7.85 (d, J = 8.1 Hz, 2H. Ar2 H2 + Ar2 H6), 7.59–7.56 (m, 2H, Ar H5 + Ar H1), 7.36 (d, J = 8.1 Hz, 2H, Ar2 H3 + Ar2 H6), 7.31 (dd, J = 1.9, 8.3 Hz, 1H, Ar H6), 4.40 (d, J = 5.8 Hz, 2H, CH_2NH), 2.37 (s, 3H, OCH_3);

^{13}C NMR (DMSO-d_6) (75 MHz): δ 161.2, 150.9, 143.0, 140.1, 130.8, 130.4, 130.1, 129.8 (2 × Ar), 129.7 (2 × Ar), 129.4, 129.1, 127.8, 116.4, 104.5, 42.1, 21.1;

IR (KBr) cm^{-1}: 3366 (NH), 2217 (CN), 1681 (C=O), 813 (Ar–Cl);

LRMS: (ESI M−1) 343. HRMS: Calcd for $C_{18}H_{14}Cl_2N_2O$; Exact mass: 344.0483, found (ESI M−H) 343.0446.

4.2.43. (*E*)-3-(4-Chlorophenyl)-2-cyano-*N*-(3,4-dichlorobenzyl)acrylamide (48)

Synthesized using the general procedure as for (**27**), from *N*-(3,4-dichlorobenzyl)propioamide and 4-chlorobenzaldehyde to afford (**48**) as a yellow solid; 30%; 156–158 °C.

^{1}H NMR (Acetone-d_6) (300 MHz): δ 8.27 (s, 1H, CH=C), 8.24 (br, NH), 8.02 (d, J = 8.5 Hz, 2H, Ar2 H2 + Ar2 H6), 7.63–7.60 (m, 3H, Ar2 H3 + Ar2 H5 + Ar H5), 7.53 (d, J = 8.3 Hz, 1H, Ar H1), 7.38 (dd, J = 2.0, 8.3 Hz, 1H, Ar H6), 4.60 (d, J = 6.1 Hz, 2H, CH_2NH);

^{13}C NMR (Acetone-d_6) (75 MHz): δ 159.9, 149.7, 139.5, 138.3, 137.2, 131.3 (2 × Ar), 131.1, 130.5, 129.9, 129.3, 128.8, 127.3 (2 × Ar), 124.6, 115.3, 42.2;

IR (KBr) cm^{-1}: 3384 (NH), 2212 (CN), 1673 (C=O);

LRMS: (ESI M−1) 363. HRMS: Calcd for $C_{17}H_{11}Cl_3N_2O$; Exact mass: 363.9937, found (ESI M−H) 363.9459.

4.2.44. (*E*)-2-Cyano-*N*-(3,4-dichlorobenzyl)-3-(4-hydroxyphenyl)acrylamide (49)

Synthesized using the general procedure as for (**27**), from *N*-(3,4-dichlorobenzyl)propioamide and 4-hydroxybenzaldehyde to afford (**49**) as a yellow solid; 61%; 230–232 °C.

^{1}H NMR (DMSO-d_6) (300 MHz): δ 10.57 (br, OH), 8.86 (t, J = 5.8 Hz, NH), 8.08 (s, 1H, CH=C), 7.87 (d, J = 8.7 Hz, 2H, Ar2 H2 + Ar2 H6), 7.58–7.54 (m, 2H, Ar H1 + Ar H5), 7.29 (dd, J = 2.0, 8.3 Hz, 1H, Ar H6), 6.92 (d, J = 8.7 Hz, 2H, Ar H3 + Ar H5), 4.38 (d, J = 5.8 Hz, 2H, CH_2NH);

^{13}C NMR (DMSO-d_6) (75 MHz): δ 161.8, 161.7, 150.8, 140.3, 132.9 (2 × Ar), 130.7, 130.4, 129.4, 129.3, 127.7, 122.8, 117.0, 116.1 (2 × Ar), 100.6, 42.1;

IR (KBr) cm^{-1}: 3350 (NH), 3140 (OH), 2217 (CN), 1642 (C=O), 837 (Ar–Cl);

LRMS: (ESI M−1) 345. HRMS: Calcd for $C_{17}H_{12}Cl_2N_2O_2$; Exact mass: 346.0276, found (ESI M−H) 345.0249.

4.2.45. (*E*)-2-Cyano-*N*-(3,4-dichlorobenzyl)-3-(4-methoxyphenyl)acrylamide (50)

Synthesized using the general procedure as for (**27**), from *N*-(3,4-dichlorobenzyl)propioamide and 4-methoxybenzaldehyde to afford (**50**) as a light yellow solid; 58%; 169–170 °C.

^{1}H NMR (DMSO-d_6) (300 MHz): δ 8.91 (t, J = 5.8 Hz, 1H, NH), 8.14 (s, 1H, CH=C), 7.96 (d, J = 8.9 Hz, 2H, Ar2 H2 + Ar2 H6), 7.59–7.56 (m, 2H, Ar H1 + Ar H5), 7.30 (dd, J = 1.9, 8.2 Hz, 1H, Ar H6), 7.11 (d, J = 8.9 Hz, 2H, Ar2 H3 + Ar2 H5), 4.39 (d, J = 5.8 Hz, 2H, CH_2NH), 3.84 (s, 3H, OCH_3);

^{13}C NMR (DMSO-d_6) (75 MHz): δ 162.6, 161.5, 150.5, 140.2, 132.5 (2 × Ar), 130.7, 130.4, 129.4, 129.4, 127.7, 124.3, 116.8, 114.7 (2 × Ar), 102.1, 55.5, 42.1;

IR (KBr) cm^{-1}: 3368 (NH), 2208 (CN), 1673 (C=O), 1182 (C–O), 832 (Ar–Cl);

LRMS: (ESI M−1) 359. HRMS: Calcd for $C_{18}H_{14}Cl_2N_2O_2$; Exact mass: 360.0432, found (ESI M−H) 359.0397.

4.2.46. (*E*)-2-Cyano-*N*-(3,4-dichlorobenzyl)-3-(naphthalen-2-yl)acrylamide (51)

Synthesized using the general procedure as for (**27**), from *N*-(3,4-dichlorobenzyl)propioamide and 2-naphthaldehyde to afford (**52**) as a light yellow solid; 40%; 180–181 °C.

^{1}H NMR (DMSO-d_6) (300 MHz): δ 9.08 (t, J = 5.6 Hz, NH), 8.45 (s, 1H, CH=C), 8.36 (s, 1H, Ar2 H1), 8.14–7.97 (m, 4H, Ar2 H5 + Ar2 H8 + Ar2 H4 + Ar H5), 7.69-7.58 (m, 4H, Ar2 H6 + Ar2 H7 + Ar2 H3 + Ar H1), 7.33 (dd, J = 1.8, 8.3 Hz, 1H, Ar H6), 4.43 (d, J = 5.6 Hz, 2H, CH_2NH);

^{13}C NMR (DMSO-d_6) (75 MHz): δ 161.2, 151.0, 140.0, 134.3, 132.7, 132.3, 130.8, 130.4, 129.5, 129.4, 129.0, 128.8, 128.6, 127.8, 127.8, 127.7, 127.2, 124.5, 116.4, 105.7, 42.2;

IR (KBr) cm^{-1}: 3370 (NH), 2212 (CN), 1686 (C=O), 1257 (C–O), 739 (Ar–Cl);

RMS: (ESI M−1) 379. HRMS: Calcd for $C_{21}H_{14}Cl_2N_2O$; Exact mass: 380.0483, found (ESI M−H) 379.0541.

4.2.47. (*E*)-2-Cyano-*N*-(3,4-dichlorobenzyl)-3-(naphthalen-1-yl)acrylamide (52)

Synthesized using the general procedure as for (**27**), from *N*-(3,4-dichlorobenzyl)propioamide and 1-naphthaldehyde to afford (**52**) as a light yellow solid; 57%; 173–175 °C.

^{1}H NMR (DMSO-d_6) (300 MHz): δ 9.25 (t, J = 5.7 Hz, NH), 8.90 (s, 1H, CH=C), 8.14–8.02 (m, 4H, Ar2 H5 + Ar2 H4 + Ar2 H8 + Ar2 H2), 7.68–7.59 (m, 5H, Ar2 H3 + Ar2 H6 + Ar2 H7 + Ar H1 + Ar H5), 7.37 (dd, J = 1.7, 8.3 Hz, 1H, Ar H6), 5.73 (d, J = 5.7 Hz, 2H, CH_2NH);

^{13}C NMR (DMSO-d_6) (75 MHz): δ 161.0, 148.9, 140.0, 132.9, 131.9, 130.8, 130.7, 130.4, 129.5, 129.4, 129.2, 128.7, 127.8, 127.5, 127.2, 126.8, 125.4, 123.6, 115.9, 110.3, 42.1;

IR (KBr) cm^{-1}: 3370 (NH), 2214 (CN), 1680 (C=O), 779 (Ar–Cl);

LRMS: (ESI M−1) 379. HRMS: Calcd for $C_{21}H_{14}Cl_2N_2O$; Exact mass: 380.0483, found (ESI M−H) 379.0469.

Acknowledgements

This project was funded by the Australian Research Council. MT acknowledges the receipt of scholarship support from the University of Newcastle, Australia.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmc.2012.10.003.

References and notes

1. www.cancer.org.au/Newsmedia/factsfigures.htm accessed 21/9/2011.
2. McCluskey, A.; Bowyer, M. C.; Collins, E.; Sim, A. T. R.; Sakoff, J. A.; Baldwin, M. L. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1687.
3. McCluskey, A.; Ackland, S. P.; Gardiner, E.; Baldwin, M. L.; Bowyer, M. C.; Keane, M. A.; Walkom, C.; Sakoff, J. A. *Anti-Cancer Drug Des.* **2001**, *16*, 291.
4. Sakoff, J. A.; Ackland, S. P.; Baldwin, M. L.; Keane, M. A.; McCluskey, A. *Invest. New Drugs* **2002**, *20*, 1.
5. McCluskey, A.; Ackland, S. P.; Bowyer, M. C.; Baldwin, M. L.; Garner, J.; Walkom, C. C.; Sakoff, J. A. *Bioorg. Chem.* **2003**, *31*, 68.
6. Sakoff, J. A.; Howitt, I. J.; Ackland, S. P.; McCluskey, A. *Cancer Chemother. Pharmacol.* **2004**, *53*, 225.
7. Hart, M. E.; Chamberlin, A. R.; Walkom, C.; Sakoff, J. A.; McCluskey, A. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1969.
8. Hill, T. A.; Stewart, S. G.; Sauer, B.; Gilbert, J.; Ackland, S. P.; Sakoff, J. A.; McCluskey, A. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3392.
9. Hill, T. A.; Stewart, S. G.; Gordon, C. P.; Ackland, S. P.; Gilbert, J.; Sauer, B.; Sakoff, J. A.; McCluskey, A. *ChemMedChem* **2008**, *3*, 1878.
10. Joshi, S.; Gaddipati, S.; Gilbert, J.; Smith, C. M.; Gordon, C. P.; Sakoff, J. A.; McCluskey, A.; Robinson, P. J.; Braithwaite, A. W.; Chircop, M. *Mol. Cancer Ther.* **2010**, *9*, 1995.
11. Chircop, M.; Malladi, C. S.; Lian, A. T.; Zavortink, M.; Gordon, C. P.; McCluskey, A.; Robinson, P. J. *Cell. Mol. Life Sci.* **2010**, *21*, 3725.
12. Chircop, C.; Perera, S.; Mariana, A.; Lau, H.; Ma, M. P. C.; Gilbert, J.; Jones, N. C.; Gordon, C. P.; Young, K. A.; Morokoff, A.; Sakoff, J. A.; O'Brien, T. J.; McCluskey, A.; Robinson, P. J. *Mol. Cancer Ther.* **2011**, *10*, 1553.
13. Tarleton, M.; Robertson, M. J.; Gilbert, J.; McCluskey, A.; Sakoff, J. A. *MedChemCommun* **2011**, *2*, 31.
14. Carta, A.; Sanna, P.; Palomba, M.; Vargiu, L.; La Colla, M.; Loddo, R. *J. Med. Chem.* **2002**, *37*, 891.
15. Carta, A.; Palomba, M.; Boatto, G.; Busonera, B.; Murreddu, M.; Loddo, R. *IL Farmaco* **2004**, *59*, 637–644.
16. Carta, A.; Briguglio, I.; Piras, S.; Boatto, G.; La Colla, P.; Loddo, R.; Tolomeo, M.; Grimaudo, S.; Cristina, A. D.; Pipitone, R. M.; Laurini, E.; Paneni, M. S.; Posocco, P.; Fermeglia, M.; Pricl, S. *Eur. J. Med. Chem.* **2011**, *46*, 4151.
17. Gazit, A.; Osherov, N.; Gilon, C.; Levitzki, A. *J. Med. Chem.* **1996**, *39*, 4905.
18. Ohsumi, K.; Nakagawa, R.; Fukuda, Y.; Hatanaka, T.; Morinaga, Y.; Nihei, Y.; Osishi, K.; Suga, Y.; Akiyama, Y.; Tsuji, T. *J. Med. Chem.* **1998**, *41*, 3022.
19. Quiroga, J.; Cobo, D.; Insuasty, B.; Abonia, R.; Nogueras, M.; Cobo, J.; Vasquez, Y.; Gupta, M.; Derita, M.; Zacchino, S. *Arch. Pharm.* **2007**, *340*, 603.
20. Repicky, A.; Jantova, S.; Cipak, L. *Cancer Lett.* **2009**, *277*, 55.
21. Saczewski, F.; Reszka, P.; Gdaneic, M.; Grunert, R.; Bednarski, P. J. *J. Med. Chem.* **2004**, *47*, 3449.
22. Saczewski, F.; Stencel, A.; Bienczak, A. M.; Langowska, K.; Michaelis, M.; Werel, W.; Halasa, R.; Reszka, P.; Bednarski, P. J. *Eur. J. Med. Chem.* **2008**, *43*, 1847.
23. Yamazaki, R.; Nishiyama, Y.; Furuta, T.; Hatano, H.; Igarashi, Y.; Asakawa, N.; Kodaira, H.; Takahashi, H.; Aiyama, R.; Matsuzaki, T.; Yagi, N.; Sugimoto, Y. *Mol. Cancer Ther.* **2011**, *10*, 1252.
24. Slatt, J.; Bergman, J. *Synthesis* **2004**, *16*, 2760.
25. Alberghina, G.; Amato, M. E.; Bottino, F. A.; Corsaro, A.; Fisichella, S. J. *Heterocycl. Chem.* **1986**, *23*, 1747–1752.
26. Herz, W.; Brasch, J. *J. Org. Chem.* **1958**, *23*, 711.
27. Wang, K.; Kim, D. D.; Dömling, A. *J. Comb. Chem.* **2010**, *12*, 111.
28. Radi, M.; Botta, L.; Casaluce, G.; Bernardini, M.; Botta, M. *J. Comb. Chem.* **2010**, *12*, 200.
29. McCluskey, A.; Robinson, P. J.; Hill, T.; Scott, J. L.; Edwards, J. K. *Tetrahedron Lett.* **2002**, *43*, 3117.
30. Inokuchi, T.; Kawafuchi, H. *J. Org. Chem.* **2006**, *71*, 947.
31. Ryabukhin, R. V.; Plaskon, A. S.; Volochnyuk, D. M.; Pipko, S. E.; Shivanyuk, A. N.; Tolmachev, A. A. *J. Comb. Chem.* **2007**, *9*, 1073.
32. Bergman, A. M.; van Haperen, V. W. R.; Veerman, G.; Kuiper, C. M.; Peters, G. J. *Clin. Cancer Res.* **1996**, *2*, 521.
33. Sakoff, J. A.; Ackland, S. P. *Cancer Chemother. Pharmacol.* **2000**, *46*, 477.