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Synthesis and Anticancer Activity of Novel Indole-Trimethoxyphenyl Conjugates

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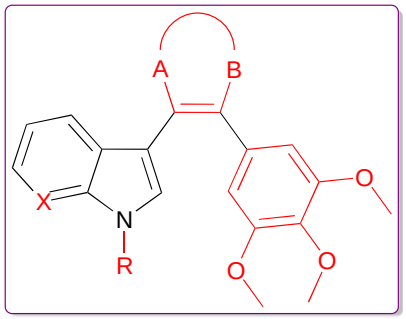
Synthesis and Anticancer Activity of Novel Indole-Trimethoxyphenyl Conjugates

Graphical Abstract

Inhibitor Identification



Chemical Diversification

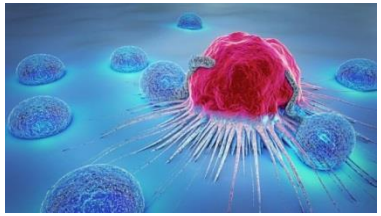
Antiproliferative Activity?

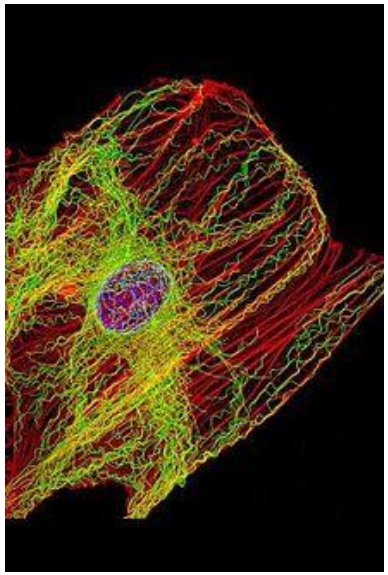
Biological Evaluation

Abstract: The 3,4,5-trimethoxyphenyl moiety is a common motif employed in anticancer drug discovery, due to its prevalence in a variety of important natural products such as Combretastatin. Work undertaken by our group and others has demonstrated that structural diversification of this template can lead to potent anticancer activity. The synthesis and biological evaluation of a series of novel indole-trimethoxyphenyl derivatives are described herein. The consolidation of the combretastatin and bisindolyl templates towards the inclusion of a novel heterocyclic headgroup proffered a versatile pharmacophore with which to pursue chemical diversification. Rationalising the enhancement of existing H-bonding interactions or potential exploitation of new contacts, the introduction of substituted maleimides constituted an overarching theme. This allowed for the evaluation of the effects pertaining to oxygen insertion, extended maleimide substitution and *N*-functionalisation. Photo-mediated dehydrogenation of a key synthetic intermediate offered access to trimethoxyphenylcarbazoles, representing the first time a panel of such congeners has been reported with further derivatisation also possible. Subsequent evaluation of anticancer activity of the indole-trimethoxyphenyl conjugates utilising the NCI-60 cell screen showed growth inhibitory profiles towards numerous cell lines including: A498 renal, IGROV1 ovarian, DU-145 prostate, SW-620 colon and MCF-7 breast cancer cell lines. The influence of structure on anticancer activity is described.

Keywords: 3,4,5-trimethoxyphenyl; diarylmaleimide; diaryl-aminopyrazole; drug discovery; NCI anticancer screen

Cancer and Chemotherapy



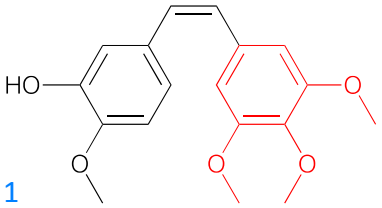


- Cancer refers multitude of disease states which share some common features such as that of uncontrolled, aggressive growth and invasion of other healthy tissues.
- In Ireland, it is estimated that someone gets a cancer diagnosis once every 3 minutes. There are over 40,000 new cancer diagnoses reported on an annual basis in Ireland alone.[1]
- It is projected that, by 2020, 1 in 2 Irish people will get a cancer diagnosis at some point in their lifetime.[1]
- Survival rates for cancer patients vary drastically between the different cancers. There are a multitude of treatments available but a lot of them are, unfortunately, not without their common and well known side effects.
- Many chemotherapeutic agents target all cells indiscriminately and this is a serious issue at the forefront of the clinic.
- There is an urgent need for new, targeted therapies.

1. https://www.cancer.ie/about-us/media-centre/cancer-statistics (accessed October 2018)

2. Pettit, G. R. et al., *Experientia*, **1989**, 45, 209
3. Siemann, D. W. et al., *Expert Opin. Investig. Drug*, **2009**, 18, 189
4. Tron, G. C. et al., *J. Med. Chem.*, **2006**, 49, 3033
5. Griggs, J. et al., *Lancet. Oncol.*, **2001**, 2, 82

The 3,4,5-Trimethoxyphenyl Fragment



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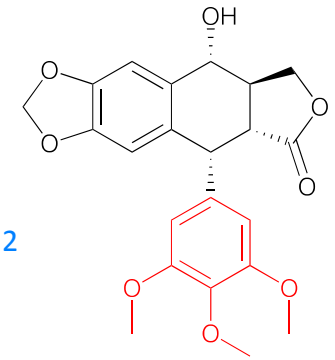

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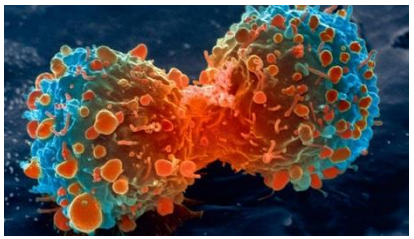
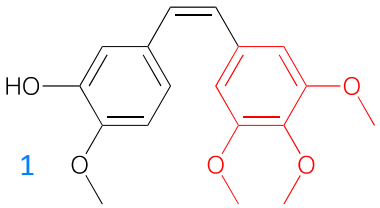


- 3,4,5-TMP fragment commonly used in anticancer drug discovery.
- One example is Combretastatin 1, a potent tubulin and cell growth inhibitor isolated from the African bush willow *Combretum Caffrum*.[2]
- Its water soluble pro-drug, fosbretabulin, has completed twelve clinical trials to date.[3]
- The 3,4,5-TMP pharmacophore (red) is essential for cytotoxicity. It has been found in other natural products with activities against tubulin (such as podophyllotoxin, 2) and also constitutes a common feature of certain topo II inhibitors such as etoposide.[4]
- Inhibition of tubulin disrupts the process of microtubule formation and hence arrests the cell cycle.[5]
- An additional chemotherapeutic effect of combretastatin concerns its ability to disrupt established vasculature within established tumors, while simultaneously rendering normal vascular networks intact.[5]

6. Zavala, F. et al., *J. Med. Chem.*, **1980**, 23, 546
7. LeBlanc, R. et al., *Bioorg. Med. Chem.*, **2005**, 13, 6025
8. Schobert, R. et al., *J. Med Chem*, **2010**, 53, 6595
9. Romagnoli, R. et al., *J. Med. Chem.*, **2012**, 55, 475

Analogues of Combretastatin



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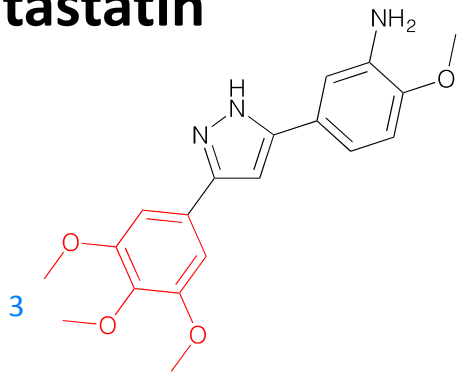
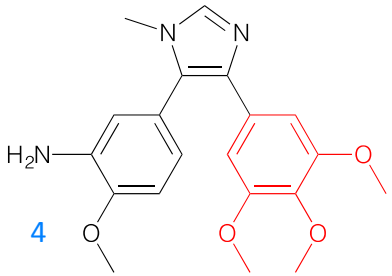


3

IC_{50} = 2.4 µM *vs.* L1210 mouse lymphoma cell line



4

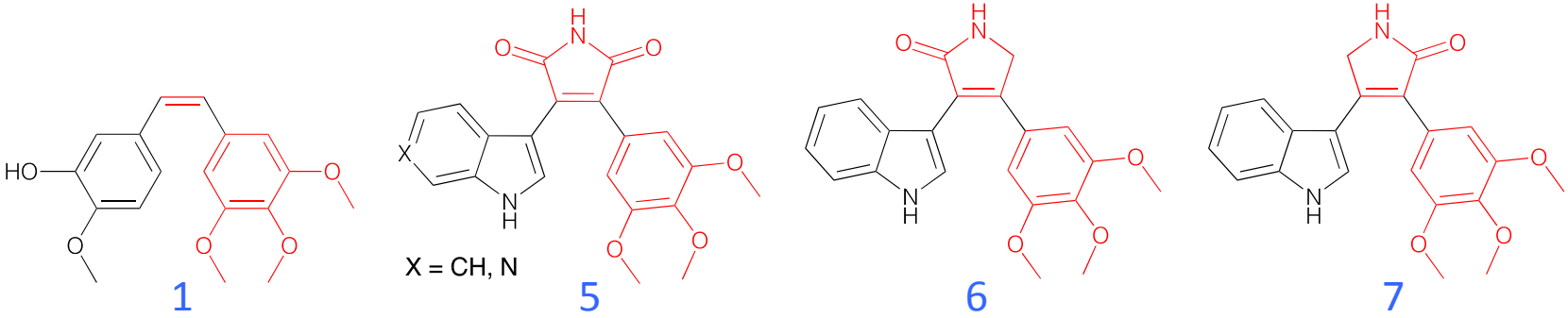
IC_{50} = 64 nM *vs.* HT-29 colon cancer cell line

- 3,4,5-Trimethoxyphenyl moiety in Combretastatin is essential for anticancer activity. This understanding is supported through the isolation of other natural products that contain the same moiety, such as steganacin, a known disruptor of microtubule formation (IC_{50} = 3.5 µM).[6]
- Many chemical modifications to Combretastatin have focused on the ethene double bond and include the assimilation of a pyrazole 3 or imidazole 4 heterocycle.[7, 8]
- In other Combretastatin analogues, replacement of the ethene bond and the 2-methoxyphenol fragment with heterocycles has resulted in the mediation of highly promising chemotherapeutic activity.[9]

10. Peifer, C. et al., *J. Med. Chem.*, **2006**, 49, 7549
11. Ganser, C. et al., *J. Med. Chem.*, **2012**, 55, 9531
12. Peifer, C. et al., *J. Med. Chem.*, **2008**, 51, 3814

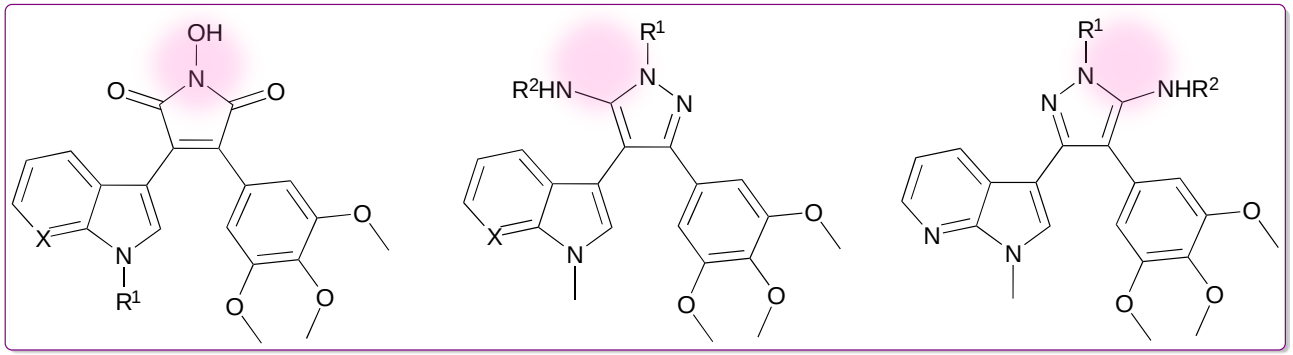
Indole-Trimethoxyphenyl Maleimide Conjugates

Exploring the known space around the headgroup.



- In terms of kinase activity Peifer *et al.* reported a potent VEGF-R2 inhibitor **5** (X = CH) which consolidated combretastatin and bisindolylmaleimide templates (IC_{50} = 2.5 nM *vs.* VEGF-R2) manifesting as a potent anti-angiogenic agent.[10]
- Kinases are enzymes upregulated in cancer cells and, as such, are now the most pursued target in medicinal chemistry.
- 6-Azaindolyl assimilation onto **5** (X = N) gave rise to a potent GSK-3β inhibitor (IC_{50} = 9 nM), which has been described as a selective treatment of colorectal cancer.[11]
- In addition, Peifer *et al.* also unearthed the significant difference between regioisomeric lactams **6** and **7**. It was found that **7** was more potent *vs.* VEGF-R2 (IC_{50} = 31 nM *vs.* **6** IC_{50} = 11 µM), highlighting the profound effect that lactam orientation can have within the target.[12]

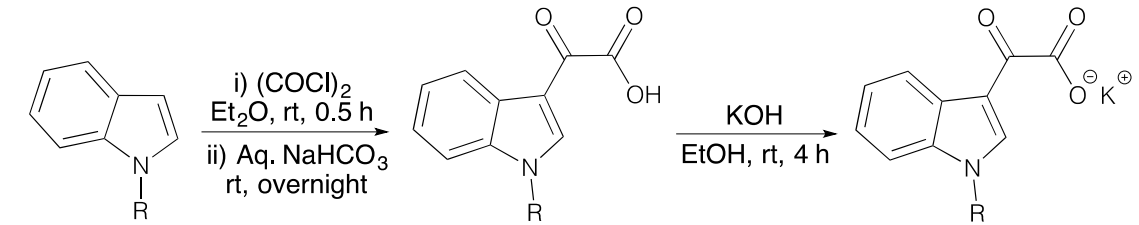
Exploring the Unknown Space around the Headgroup



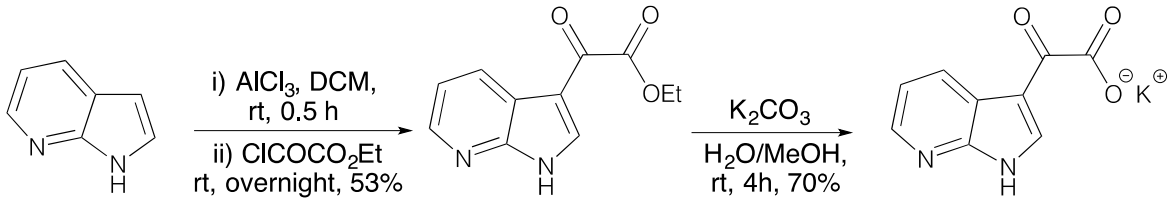
- It is evident that the pharmacophore, incorporating an indole, trimethoxyphenyl and linking headgroup has direct relevance to the disruption of cancer progression.
- Rationalising enhancement of existing H-bonding interactions we propose the synthesis of derivatives of the 3,4-diaryl-1-hydroxymaleimide scaffold in order to probe the effects of oxygen insertion into the maleimide N-H bond and indole *N*-substitution.
- Subsequent replacement of the hydroxymaleimide with structurally related 5-aminopyrazole moiety will aim to validate this approach and explore new chemical spaces.
- Initial evaluation of antiproliferative activity is followed by further investigation of discrete biological mechanism of action through in-house topoisomerase II screening.

Synthesis of the 3,4-Diaryl-1-Hydroxymaleimide Scaffold

Indole is first alkylated under standard conditions to investigate the effect of N-H capping and to incorporate an element of solubility. Indole potassium glyoxylate salts were then synthesised *via* one of two approaches. First approach: oxalyl chloride followed by treatment with aqueous base.



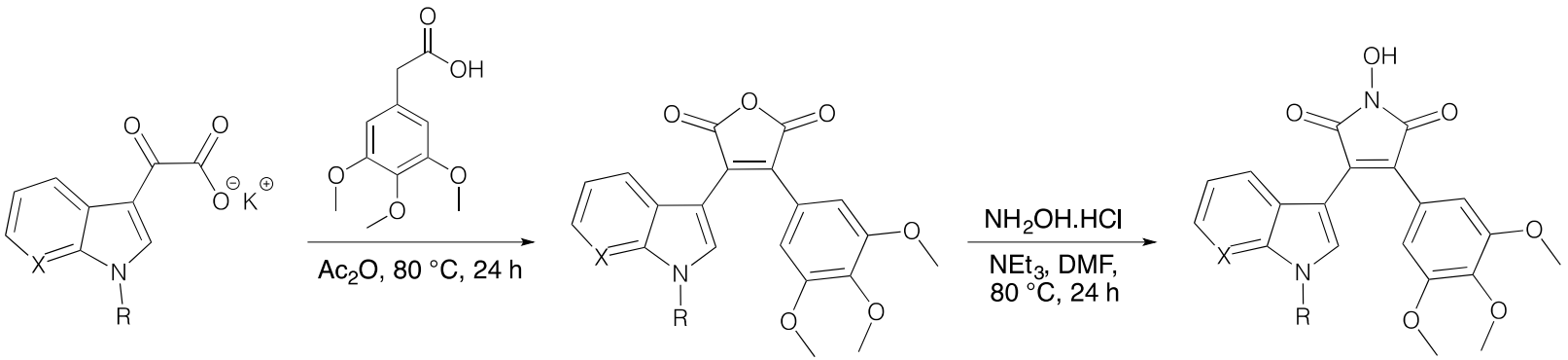
Difficulties of translation to 7-azaindole necessitated the use of the following alternative.



Cahill, M. et al., *Pharmaceuticals*, **2017**, 10, 62

Synthesis of the 3,4-Diaryl-1-Hydroxymaleimide Scaffold

A modified Perkin condensation of the indole potassium glyoxylate salts with 3,4,5-trimethoxyphenylacetic acid furnished the corresponding maleic anhydrides in moderate to low yields. Procession onto the hydroxymaleimides was then effectuated in excellent yield.



X = CH, R = H
X = CH, R = CH_3
X = CH, R = $(CH_2)_5CN$
X = N, R = H

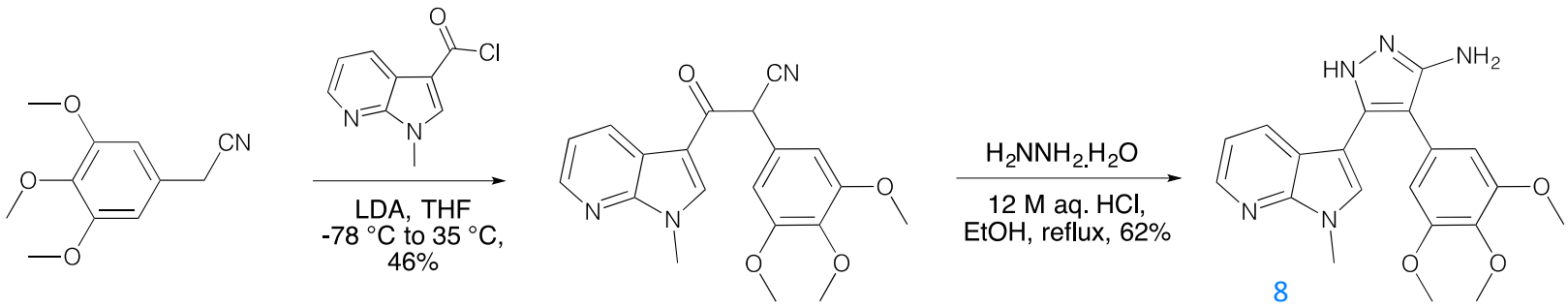
X = CH, R = H, 16%
X = CH, R = CH_3, 13%
X = CH, R = $(CH_2)_5CN$, 44%
X = N, R = H, 27%

X = CH, R = H, 82%
X = CH, R = CH_3, 85%
X = CH, R = $(CH_2)_5CN$, 83%
X = N, R = H, 71%

Cahill, M. et al., *Pharmaceuticals*, **2017**, 10, 62

Synthetic Routes Towards 3,4-Diaryl-5-Aminopyrazoles

Synthesis of novel 3,4-diaryl-5-aminopyrazoles was then effectuated in order to probe the influence of the headgroup on the cytotoxic activity.



8

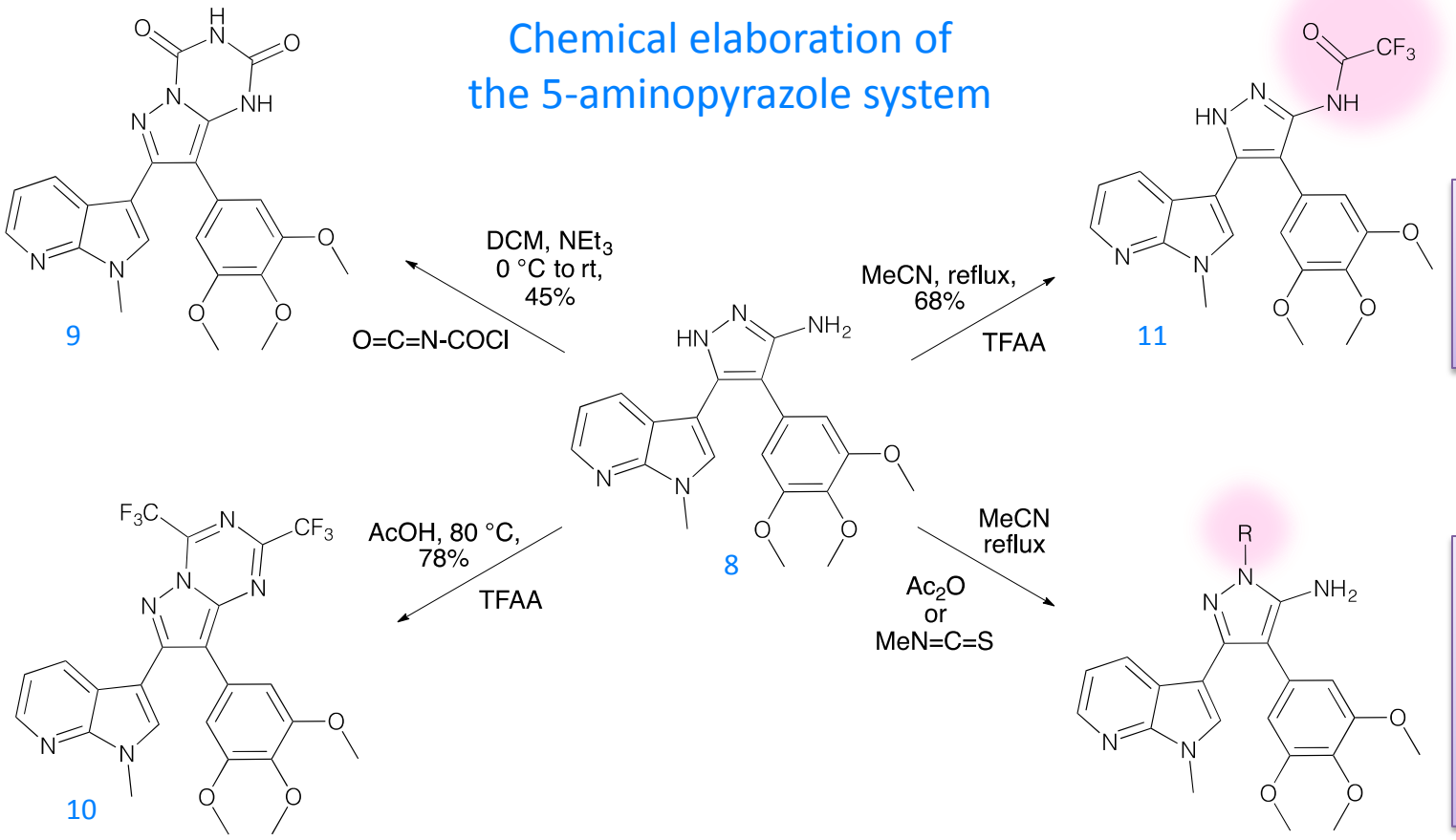
This synthesis was achieved following the reaction of the relevant β-ketonitrile with hydrazine hydrate, using an acid catalyst. The β-ketonitrile was fashioned from the reaction of the 3,4,5-trimethoxyphenylacetonitrile with *N*-methyl-7-azaindole-3-acyl chloride.

Versatility of the 5-aminopyrazole 8 lends itself to further chemical elaboration of the headgroup space. Treatment with bidentate electrophiles lead to the formation of bicyclic systems.

Pierce, L. T. et al., *Tetrahedron*, **2011**, 67, 4601
Cahill, M. et al., *Pharmaceuticals*, **2017**, 10, 62

Synthetic Routes Towards 3,4-Diaryl-5-Aminopyrazoles

Chemical elaboration of the 5-aminopyrazole system



Exocyclic NH_2 substitution confirmed through presence of two broad singlets at 11.37 and 13.30 ppm in the ^1H NMR spectrum.

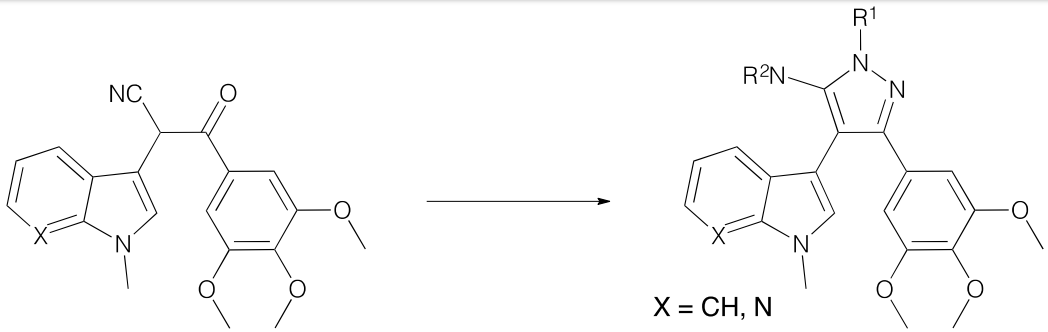
In contrast to 11, both 12 and 13 were substituted at the N(1) position. This was confirmed by ^1H NMR by the presence of a 2H broad singlet in each case (corresponding to the unsubstituted NH_2 moiety).

Cahill, M. et al., *Pharmaceuticals*, **2017**, 10, 62

13. Nie, Z. et al. *Bioorg. Med. Chem. Lett.*, **2007**, 17, 4191.

Synthetic Routes Towards 3,4-Diaryl-5-Aminopyrazoles

Adapting the starting materials and reacting a functionalised indole-3-acetonitrile with 3,4,5-trimethoxyphenyl acid chloride resulted in an opposing 5-aminopyrazole system.

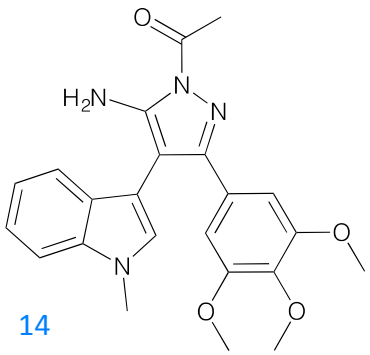


- Reaction of this β-ketonitrile with a range of mono- and bi-dentate electrophiles resulted in mono- and bicyclic structures of the general form shown above.
- In order to confirm the existence of monosubstitution and the bicyclic templates, X-ray crystallographic studies were undertaken on a select panel of aminopyrazoles.
- Nie *et al.* previously described substituted 5-aminopyrazoles with ethoxycarbonyl isocyanate and found substitution was dependent on reaction conditions and nature of ring at C-4 position.[13]

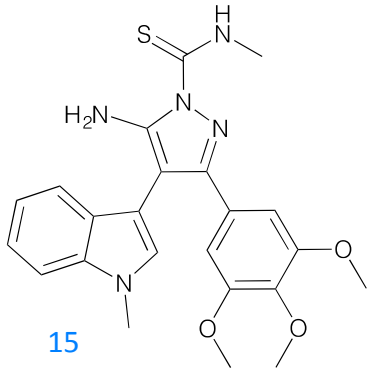
Pierce, L. T. et al., *Tetrahedron*, **2011**, 67, 4601

Single Crystal Analysis of Substituted 3,4-Diaryl-5-Aminopyrazoles

Reaction with acetic anhydride and methyl isothiocyanate resulted in N(1) substitution i.e. 14 and 15. Similar to 12 and 13, the presence of a 2H broad singlet, corresponding to the unsubstituted NH_2 moiety confirmed this in all cases.



14



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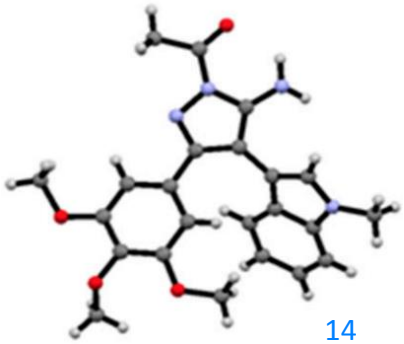
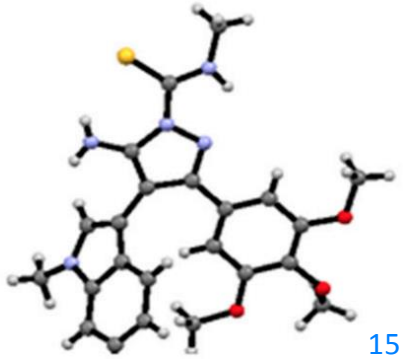
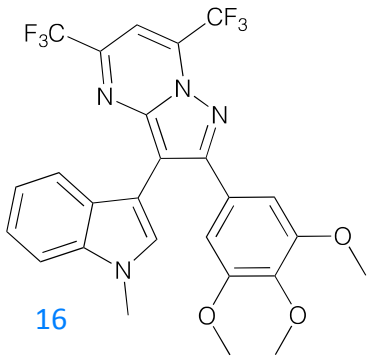


14



15

In contrast, pyrazolo[1,5-*a*]pyrimidine 16 is consistent with the proposed structure. This confirms the reactivities of both the exocyclic amine and the N(1) position of the parent aminopyrazole.



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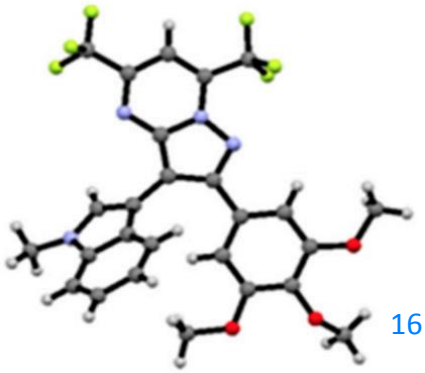
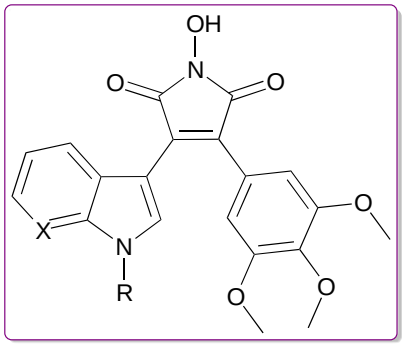


16

- The planarity of the 3,4,5-trimethoxyphenyl and aminopyrazole fragments are worth remarking in each of the three crystal structures.
- The lack of planarity associated with the indole fragment is also evident in each case and it is likely that this will contribute to the bioactivity.

Antiproliferative Activity of Selected 3,4-Diaryl-1-Hydroxymaleimides

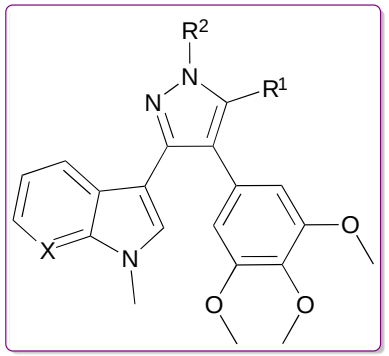


- Antiproliferative activities were assessed in collaboration with NCI and derivatives were tested at a single dose (10 µM) *vs.* 60 cell lines representing a multitude of malignancies.
- Evident lack of antiproliferative activity in this series.
- UO-31 appears to be the most susceptible cell line.
- Limited effect on HOP-92.
- No activity change following indole substitution or 7-azaindole incorporation.

No. (NSC)	Substituents		Mean (%)	Selected Cells (% Growth)				Renal Cells Mean (%)
	X	R		HOP-92	SNB-75	CAKI-1	UO-31	
17 (776698)	CH	H	95.8	89.6	91.0	103.3	71.5	94.9
18 (776695)	CH	CH_3	95.4	-	77.9	100.4	66.4	93.4
19 (776696)	CH	$(CH_2)_5CN$	96.8	69.1	96.3	106.4	77.3	94.9
20 (776697)	N	H	98.4	83.4	94.0	101.9	86.1	97.3

Cahill, M. et al., *Pharmaceuticals*, **2017**, 10, 62

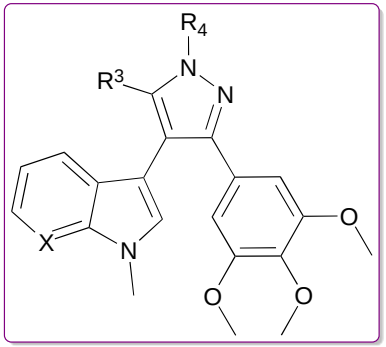
Antiproliferative Activity of Selected 3,4-Diaryl-5-Aminopyrazoles



- Appreciable selectivity for HOP-92 (lung), SNB-75 (CNS), UO-31 and CAKI-1 (renal) cancer cell lines. <50% growth after 48 h incubation.
- Extension to bicyclic systems lead to a decrease in overall growth inhibition.
- However, in the case of **12** and **13** increases in potency were noted together with more selectivity *vs.* UO-31, CAKI-1 and SNB-75. This may point to an alternative mechanism of biological effect.

No. (NSC)	Substituents (X = N)		Mean (%)	Selected Cells (% Growth)				Renal Cells Mean (%)	Regioisomer Correlation
	R^1	R^2		HOP-92	SNB-75	CAKI-1	UO-31		
8 (763892)	NH_2	H	79.8	47.9	34.4	48.9	49.6	76.4	0.791
9 (763893)	-NHCONHCO-		101.5	87.7	67.2	89.8	94.2	100.7	0.366
10 (763894)	$-NC(CF_3)CHC(CH_3)-$		95.4	-	73.2	82.3	71.2	92.6	0.632
12 (763896)	NH_2	$COCH_3$	76.6	-	8.5	39.7	33.1	68.7	0.475
13 (763895)	NH_2	$CSNHCH_3$	78.6	-	26.5	34.1	35.9	71.1	0.805

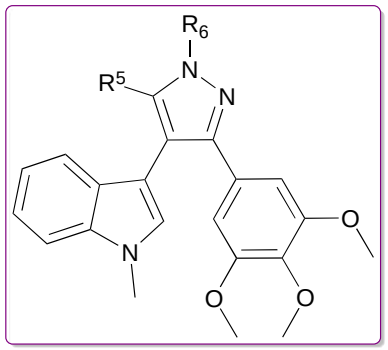
Antiproliferative Activity of Selected 3,4-Diaryl-5-Aminopyrazoles



- **21** and **25** also display considerable selectivity *vs.* SNB-75, UO-31 and CAKI-1. Surprisingly **24** is inactive by comparison.
- Conversion of **21** to **22** and **23** resulted in an increase in mean growth in both cases but led to greater selectivity *vs.* HOP-92.
- This was particularly evident in the case of **23**, demonstrating a degree of cytotoxicity *vs.* HOP-92.
- High regioisomeric correlation suggests likelihood of common mechanism of action. Scope for further SAR.

No. (NSC)	Substituents (X = N)		Mean (%)	Selected Cells (% Growth)				Renal Cells Mean (%)	Regioisomer Correlation
	R^3	R^4		HOP-92	SNB-75	CAKI-1	UO-31		
21 (754616)	NH_2	H	75.1	30.9	38.1	50.0	51.7	70.8	0.791
22 (754617)	-NHCONHCO-		104.3	53.5	99.7	118.4	94.8	101.4	0.366
23 (754618)	$-NC(CF_3)CHC(CH_3)-$		94.0	-3.1	67.2	-	73.7	92.5	0.632
24 (763899)	NH_2	$COCH_3$	104.2	86.4	101.9	81.0	92.8	97.6	0.475
25 (763898)	NH_2	$CSNHCH_3$	66.5	-	39.7	18.2	25.3	61.5	0.805

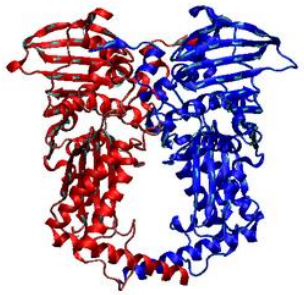
Antiproliferative Activity of Selected 3,4-Diaryl-5-aminopyrazoles

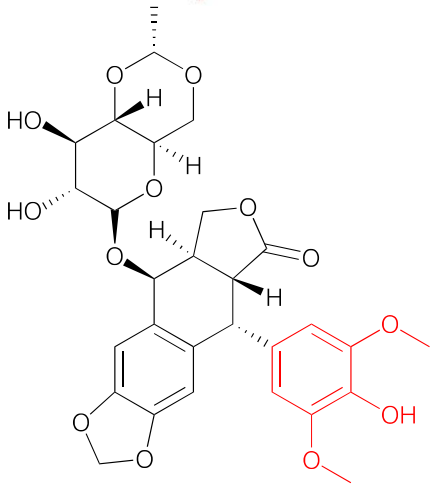


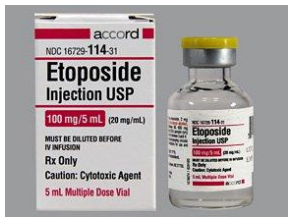
- Assimilation of an *N*-methylindolyl nucleus in place of *N*-methyl-7-azaindolyl one resulted in notable increases in potency.
- Parent aminopyrazole **26** and monosubstituted derivatives **14** and **15** are more potent than the corresponding bicyclic derivatives.
- **15** almost completely arrests growth in the HOP-92 cell line in addition to excellent selectivity *vs.* SNB-75, UO-31 and CAKI-1.
- Of great interest is the fact that **26**, **14** and **15** exhibit a highly similar level of growth inhibition against renal cancer cells UO-31 and CAKI-1

No. (NSC)	Substituents		Mean (%)	Selected Cells (% Growth)				Renal Cells Mean (%)
	R^5	R^6		HOP-92	SNB-75	CAKI-1	UO-31	
26 (763905)	NH_2	H	70.6	-	4.8	18.8	24.6	65.0
27 (763910)	-NHCONHCO-		75.1	-	47.2	52.9	43.9	80.3
16 (763909)	$-NC(CF_3)CHC(CH_3)-$		92.9	48.6	56.3	55.2	61.4	87.5
14 (763906)	NH_2	$COCH_3$	69.4	-	40.3	18.1	23.7	60.6
15 (763907)	NH_2	$CSNHCH_3$	59.3	0.3	27.8	16.3	17.9	53.2

Topoisomerase II Decatanation Assay





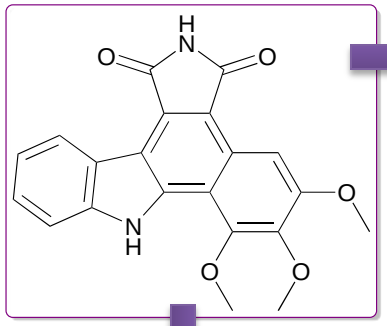


- Etoposide is a known topoisomerase II inhibitor/poison which contains a dimethoxyphenol moiety.
- In light of this, interaction with topoisomerase II was also investigated as a potential mechanism of action.
- Topo II is an enzyme that helps to modulate DNA processes *via* transient double-strand breaks in the DNA helix.
- There is a notably higher expression of Topo II in proliferating cells than inactive cells and is a clinical target for apoptosis in cancer cells. One such chemotherapeutic agent that acts in this way is etoposide.
- Candidates **9 – 19** were screened for their ability to inhibit Topo II activity.
- From the assay it was clear that there was lack of activity associated with all derivatives.
- Lack of activity is proposed due to lack of a core planar region, which would serve to disrupt intercalation.

Q: Could we therefore rationalise derivatives that bridge this gap and work towards more potent, planar derivatives?

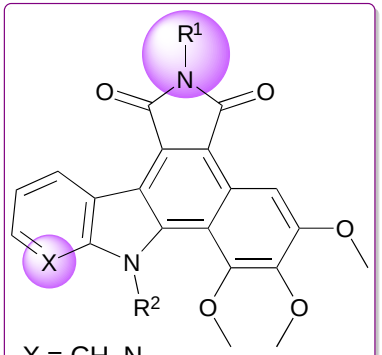
A: Yes, through the synthesis of bridged 3,4,5-trimethoxyphenylcarbazoles.

3,4,5-Trimethoxyphenylcarbazoles

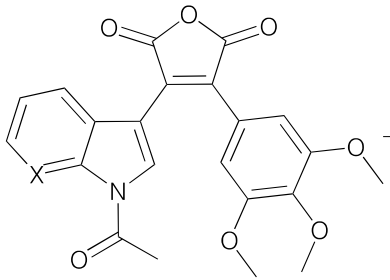


- Previously isolated by Peifer.
- Found to result in 16% residual activity of VEGF-R2 at a 10 μM dose.
- Represents a unique construct with surprising paucity within the literature.

- Indolocarbazoles (ICZs) obtained previously within our group through a photo-mediated dehydrogenation proceeding the modified Perkin condensation.
- Deacylation of starting anhydrides was found to increase the yield of ICZ.
- We aimed to apply this route to synthesise related trimethoxyphenylcarbazoles (TMPCs).

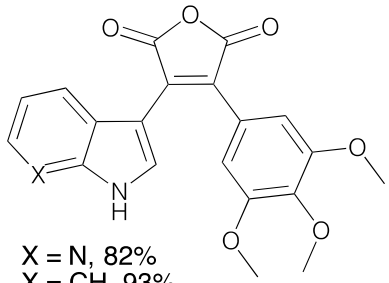


X = CH, N
R^1 = H, Substituted Amine
R^2 = H, CH_3



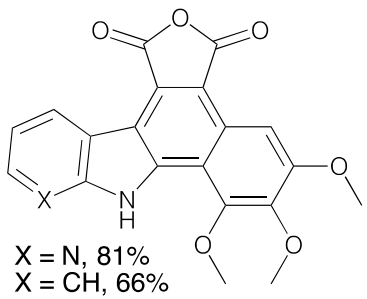
From modified Perkin Condensation

K_2CO_3
Aq. MeOH



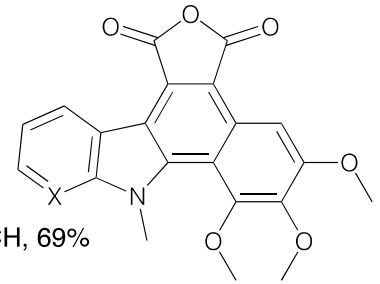
X = N, 82%
X = CH, 93%

$h\nu$, I_2
MeCN



X = N, 81%
X = CH, 66%

i) NaH
ii) MeI
DMF
0 °C to rt

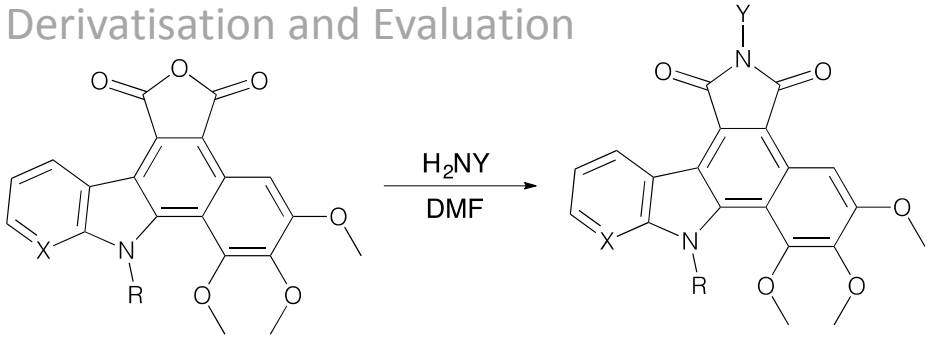


X = CH, 69%

- Successful dehydrogenation indicated by collapse of H-2, H-2' proton resonances together with a collective downfield shift.
- *N*-Substitution achieved on indole congener in a 69% yield.
- Anhydrides could then be further derivatised.

3,4,5-Trimethoxyphenylcarbazoles

Derivatisation and Evaluation



Compound	R	X	Y	Yield
28	CH_3	CH	OH	91%
29	H	CH	OH	57%
30	H	N	OH	93%

- TMP carbazole derivatised in good to excellent yields.
- Single dose biological results suggest planarity is slightly beneficial.
- Little to no benefit with azaindole assimilation or *N*-alkylation. Hydroxymaleimide **29**, however, is cytotoxic *vs.* A498 renal cancer cell line.
- Two tables are presented. One showing mean growths and stand out cell lines, another with selected activities as a comparison with **18** – **20**.

No.	NSC	R	X	Y	Mean Growth (%)	Stand Out Cell Line (%)
28	802077	CH_3	CH	OH	**89.9**	SR (Leukemia), 38.8
29	783505	H	CH	OH	**44.4**	**A498 (Renal), -16.8**
30	799295	H	N	OH	**90.9**	MOLT-4 (Leukemia), 56.7

No.	Selected Cells (% Growth)			
	HOP-92	SNB-75	CAKI-1	UO-31
28	82.4	102.3	90.3	68.1
29	78.4	72.6	36.0	10.0
30	72.2	82.4	78.4	91.9

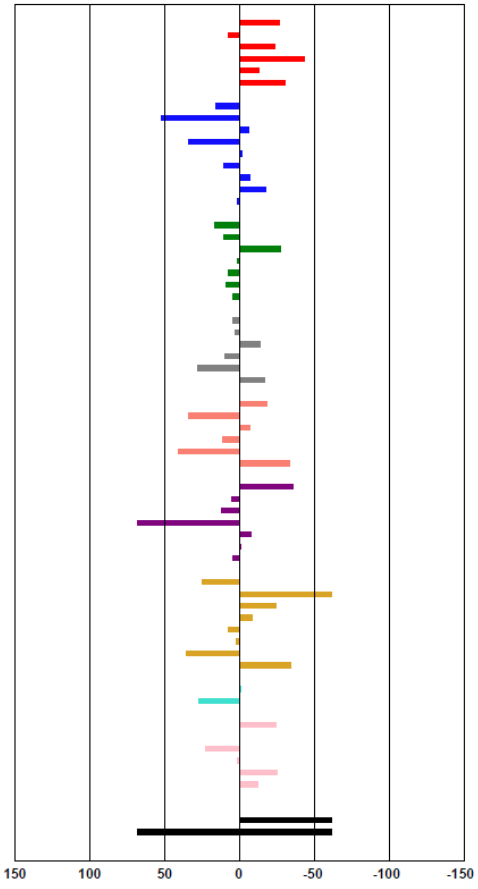
Full One Dose Data for TMP carbazole 29 as assessed by NCI at 10μM

Developmental Therapeutics Program
One Dose Mean Graph

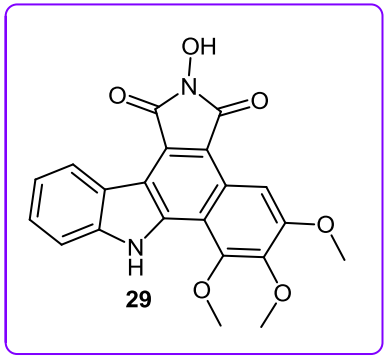
NSC: D-783505 / 1	Conc: 1.00E-5 Molar	Test Date: Mar 09, 2015
Experiment ID: 1503OS44		Report Date: Nov 07, 2018

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	17.98
HL-60(TB)	51.74
K-562	20.81
MOLT-4	1.38
RPMI-8226	31.62
SR	14.32
Non-Small Cell Lung Cancer	
A549/ATCC	60.29
EKVX	97.09
HOP-62	38.04
HOP-92	78.40
NCI-H226	42.62
NCI-H23	54.88
NCI-H322M	37.36
NCI-H460	26.95
NCI-H522	45.67
Colon Cancer	
COLO 205	61.12
HCC-2998	55.28
HCT-116	16.83
HCT-15	45.85
HT29	52.09
KM12	53.68
SW-620	49.01
CNS Cancer	
SF-268	49.29
SF-295	47.82
SF-539	30.91
SNB-19	54.53
SNB-75	72.56
U251	28.01
Melanoma	
LOX IMVI	26.30
MALME-3M	78.47
M14	37.51
MDA-MB-435	56.09
SK-MEL-2	85.57
SK-MEL-5	11.07
Ovarian Cancer	
IGROV1	9.03
OVCAR-3	49.50
OVCAR-4	56.59
OVCAR-5	112.48
OVCAR-8	36.83
NCI/ADR-RES	43.80
SK-OV-3	48.80
Renal Cancer	
786-0	69.61
A498	-16.76
ACHN	20.58
CAKI-1	35.95
RXF 393	52.25
SN12C	46.59
TK-10	80.11
UO-31	10.04
Prostate Cancer	
PC-3	43.79
DU-145	71.67
Breast Cancer	
MCF7	20.41
MDA-MB-231/ATCC	44.18
HS 578T	67.40
BT-549	46.23
T-47D	19.50
MDA-MB-468	32.69
Mean	44.43
Delta	61.19
Range	129.24

Mean Growth Percent - Growth Percent



- Inducing planarity to form the TMP carbazole yields most pronounced anticancer effects from the panel with **29** eliciting a mean growth of 44%
- The graph shows the growth percentage variance from the mean (44%) and highlights and particular cell lines that are more or less susceptible to treatment with **29**.



29

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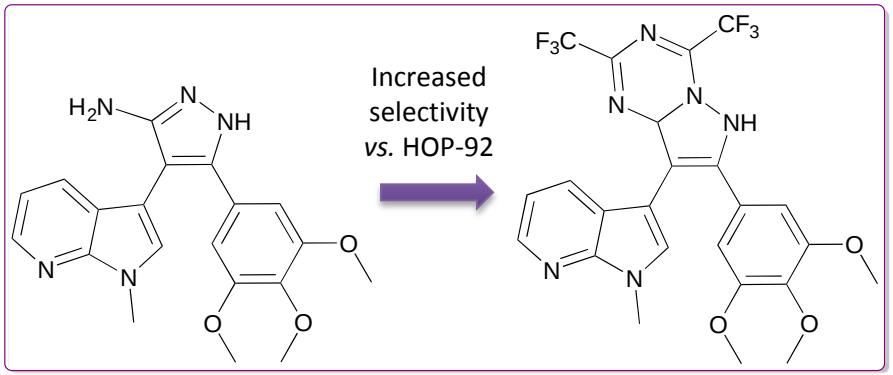
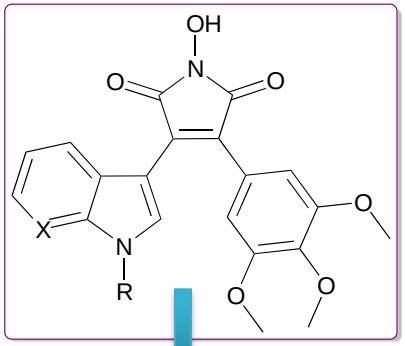
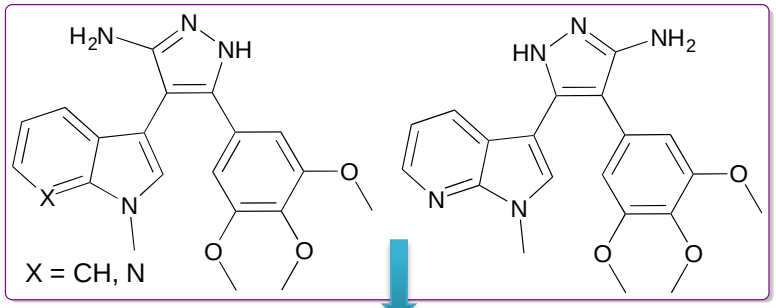
- Significant growth inhibition above the mean seen for leukemia cell lines
- TMP carbazole 29 is cytotoxic towards A498 (renal cancer cell line) but inactive against OVCAR-5 which may point to a molecular target – further work in this area is necessary.
- The TMP carbazoles provide an interesting template for future derivatisation and the potential for assessment of other biological targets.

Conclusions

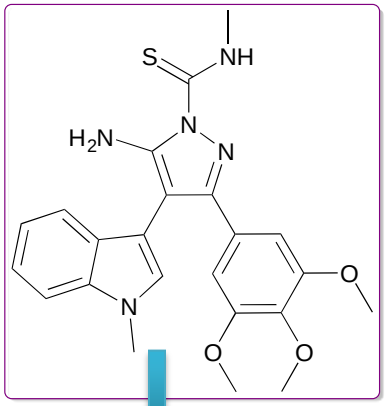




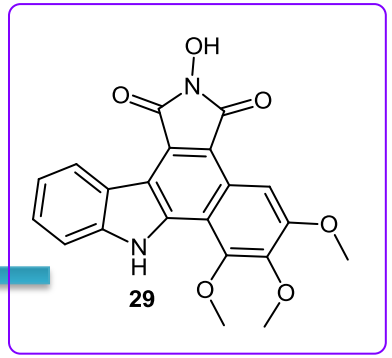
- Disappointing results for raw N-OH potency.
- Cell growth inhibition results indicate possible similar mode of bioactivity.



- Appreciable selectivities noted for the parent aminopyrazoles (AMP).



- Most potent derivative in the AMP series.
- Almost complete growth arrest *vs.* HOP-92.
- Comparative activities of both 7-azaindole derivatives suggest this orientation as the best for activity.



- Inducing planarity causes a slight decrease in mean growths for **28** and **30**. Effect most pronounced for **29** which delivers the lowest mean growth of all derivatives and is cytotoxic towards A498 (renal cancer cell line).
- Huge scope for further derivatisation and the potential for assessment of other biological targets.

- Overall, it is evident that modulation of the connecting headgroup between indole and trimethoxyphenyl can imbue potency and selectivity in some cancer cell lines.
- There exists huge scope for future extension of the structures and molecular targets of the 3,4,5-trimethoxyphenyl conjugates.

Acknowledgments

- The ‘Trimethoxyphenyl’ team: Dr. Larry Pierce and Dr. Michael Cahill.
- The Irish Research Council for funding.
- Staff and personnel of the ABCRF at UCC.
- The National Cancer Institute.

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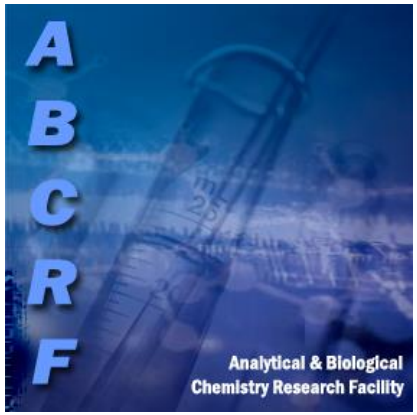

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