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Quinone-fused pyrazoles through 1,3-dipolar cycloadditions: synthesis of tricyclic scaffolds and *in vitro* cytotoxic activity evaluation on glioblastoma cancer cells

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Abstract: A novel and straightforward synthesis of highly substituted isoquinoline-5,8-dione fused tricyclic pyrazoles is reported. The key step of the synthetic sequence is a regioselective, Ag_2CO_3 promoted, 1,3-dipolar cycloaddition of *C*-heteroaryl-*N*-aryl nitrilimines and substituted isoquinoline-5,8-diones. The broad functional group tolerability and the mild reaction conditions were suitable for the preparation of a small library of compounds. These scaffolds were designed to interact with multiple biological residues and two of them, after brief synthetic elaborations, were analysed by molecular docking studies *in silico* as potential anti-cancer drugs. *In vitro* studies confirmed the potent anti-cancer capability, showing interesting IC_{50} values down to 2.5 μM on three different glioblastoma cell lines. Their cytotoxic activity was finally positively correlated to their ability of inhibiting PI3K/mTOR kinases, which are responsible for the regulation of diverse cellular processes in human cancer cells.

1,3-Dipolar cycloadditions (1,3-DCs) of nitrilimines, reactive species generated *in situ* upon basic treatment of hydrazonoyl halides, with various activated π-systems represent a powerful and general tool for the synthesis of substituted pyrazoles.[1] Both electron-rich and electron-poor double and triple bonds have been widely employed by us as dipolarophiles in the regioselective formation of various pyrazoles.[2] Among these, cyclic systems such as cycloalkenones,[3] α,β-unsaturated lactones, thiolactones and lactams have gained much attention for the preparation of fused structures.[4] Quinones as well would represent a privileged platform for the synthesis of ring-fused pyrazoles, given their wide applications in [4+2] or [3+2] cycloaddition reactions.[5] In 1991, Argyropoulos and Terzis reported a pioneering work in which various 1,4-benzoquinones were reacted with some nitrilimines, proving the process to be feasible.[6] However, the difficulties encountered in the chemoselectivity and the low isolated yields prevented it to represent a useful preparative procedure. To our knowledge, no other report of 1,3-DCs between quinones and nitrilimines has been published. On the other hand, fused quinones would represent an easy alternative to simple 1,4-benzoquinones to introduce molecular diversity and avoid site-selectivity issues. Naphthoquinone-fused pyrazoles were indeed prepared by hydrazones or diazomethane reaction with simple naphthoquinones.[7] However, unsymmetrically substituted substrates represent a regiochemical challenge and undoubtedly provide a much general platform for the synthesis of libraries of compounds. Among them, isoquinolino-5,8-diones could be employed in 1,3-DCs for the synthesis of different 5-membered rings heterocycles. These represent a widely employed substrate for regioselective amination reactions, [8] or Diels-Alder cycloadditions,[9] targeting to biologically active products. On the other hand, their 1,3-DC chemistry is much more limited: only one report disclosed the reaction between *in situ* generated nitriloxides and 6-bromo-isoquinoline-5,8-diones, affording isoxazole ring-fused products with good regioselectivity, mediated by the presence of the bromide on the electrophilic site.[10] Therefore, this class of substrates represents an interesting building block for a 1,3-DCs aiming at the preparation of tricyclic fused pyrazoles, both for the facility of preparation and the interesting biological activities.

Isoquinoline-5,8-diones displayed, indeed, a wide range of biological activities such as antibacterial, antifungal, antimalarial and antitumor agents.[11,12] This moiety is present as an important core in a number of cytotoxic agents, such as naturally occurring Caulibugulones of type I (Figure 1), which exhibited IC_{50} values of 0.03–1.67 μM against murine tumor cells.[13] Moreover, Pixantrone (II), an aza-anthraquinone commercialized under the trade name Pixuvri, is an antineoplastic drug, that has completed phase III clinical trials and stands in the family of antitumor antibiotics for the treatment of different type of cancers.[14] On the other hand, a large number of commercially available drugs containing pyrazoles can be found; among others, they exhibit antispasmodic, anti-inflammatory, antibacterial, antihyperglicemic, antidepressive and antitumor activities.[1] For example, Axitinib (III), an anti-angiogenic drug approved for renal cancer, has been recently discovered to be effective as an inhibitor for ABL1 gatekeeper mutant drug-resistant leukaemia patients.[15] In order to supply phase II clinical trials, Pfizer has developed a scalable process for the preparation of indazol-4-one IV (disclosed by Huang in 2009), an Hsp90 inhibitor exhibiting low nanomolar antiproliferative properties across multiple cancer cell lines.[16]

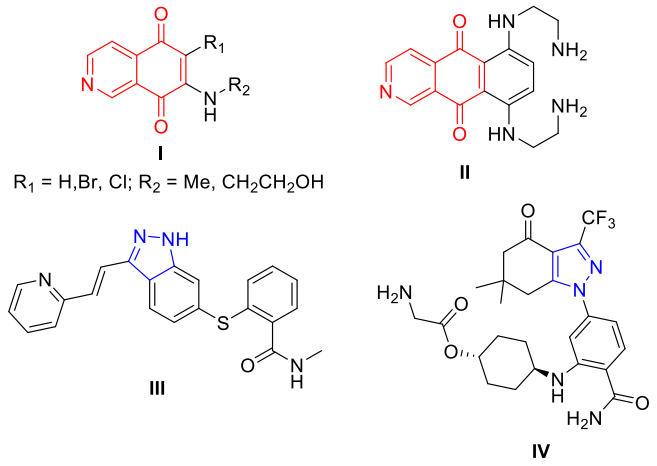
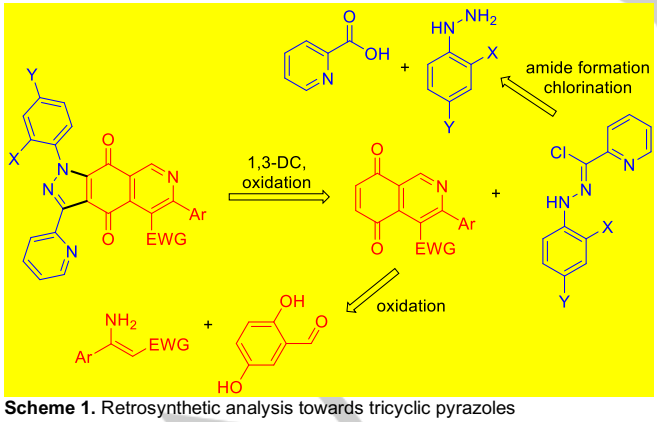


Figure 1. Biologically active structures **I-IV**

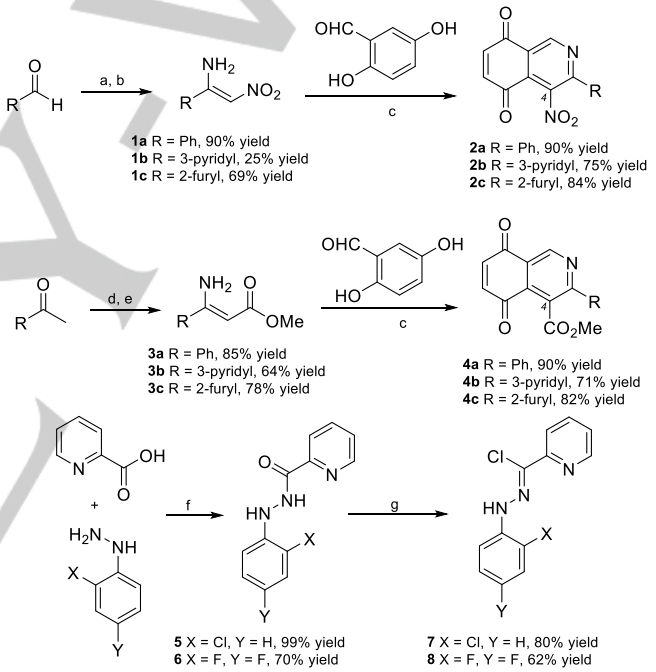
All these features considered, as part of our on-going effort directed towards the preparation of cytotoxic pyrazoles,[17] we decided to develop a new synthetic protocol for the straightforward preparation of some class of isoquinolino-5,8-dione-fused pyrazoles, characterized by a tricyclic core (Scheme 1). A flat polycyclic structure containing the quinone moiety fused with *N*-heterocycles has indeed been found responsible for the potent antitumor activity displayed by compounds such as mytomicin C.[12] Moreover, in order to decorate the structure with some different biologically appealing moieties, we took the opportunity to introduce some halogens as substituents on one of the aryl rings, as this structure itself is frequently recurring in approved drugs and bioactive molecules.[18] Variation of the isoquinolino-5,8-dione was undertaken with different (hetero)aromatic cycles and EWG groups. Finally, to explore the first C-heteroaryl substituted nitrilimine in such 1,3-DCs and to introduce an H-bond acceptor moiety, a 2-pyridyl ring was chosen as the privileged substituent on the pyrazole structure.



Scheme 1. Retrosynthetic analysis towards tricyclic pyrazoles

For the synthesis of isoquinolino-5,8-diones **2** and **4** we sought to employ a literature procedure by Valderrama et al.,[19] involving a cyclocondensation-oxidation reaction between 2,5-dihydroxybenzaldehyde and electron-poor enamines, promoted by silver oxide. In order to synthesize a small library of substituted compounds, we decided to engage three different (hetero)aryl substituted β-amino nitroolefins **1a-c** and β-enaminoesters **3a-c** in the abovementioned isoquinolino-5,8-diones formation reaction (scheme 2, top and middle). Synthesis of **1a-c**[20] and **3a-c**[21] was straightforward, following known literature procedures. Thus, we prepared six new isoquinolino-5,8-diones **2a-c** and **4a-c** in good yields (71-90%), proving that such unprecedented substitutions, (phenyl, 3-pyridyl and 2-furyl) were well tolerated in the protocol disclosed by Valderrama, originally limited to ketones and esters as EWGs at the C-4 position, and methyl as R substituent. [19]

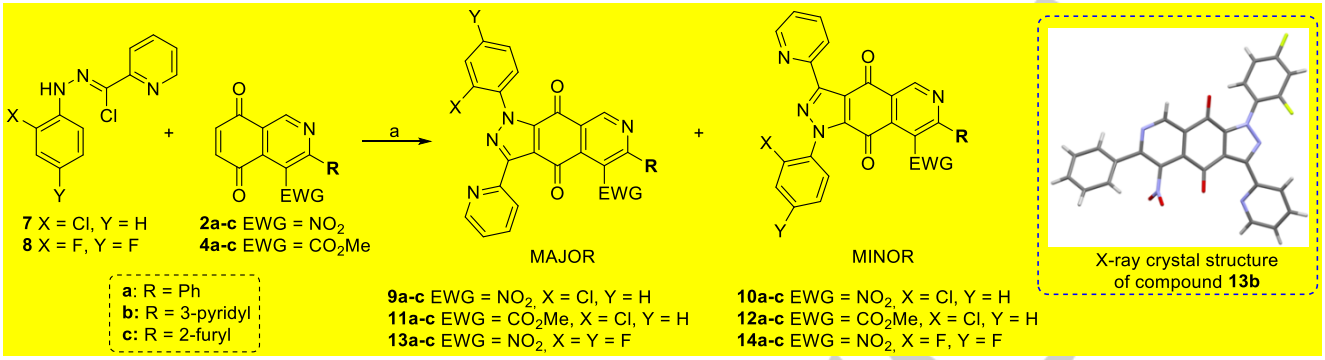
For the synthesis of hydrazonoyl chlorides **7** and **8**, we employed a methodology already reported by us.[2] Coupling of picolinic acid with suitable phenylhydrazines was undertaken by DCC-NHS activation: a milder method, more suitable for the presence of the basic pyridine moiety.[22] Chlorination of hydrazides **5** and **6** under Appel conditions gave the respective hydrazonoyl chlorides **7** and **8** in 80% and 62% yield respectively, representing the first example of *C*-heteroaryl substitution of these substrates (Scheme 2, bottom).



Scheme 2. Preparation of isoquinolino-5,8-diones **2** and **4** and hydrazonoyl chlorides **7** and **8**. Reaction conditions: a) NH_4OAc, $MeNO_2$, reflux, 18h. b) $MeONH_2$ hydrochloride, TEA, DMF, 0 °C, 15 min; then *t*-BuOK, DMF, 0 °C to RT, 1 h. c) Ag_2O (3 equiv), $MgSO_4$, DCM, RT, 18h. d) $(MeO)_2CO$, NaH, PhMe, reflux, 3h. e) NH_4OAc, MeOH, reflux, 18h. f) DCC, NHS, THF, 0 °C to RT, 18 h. g) CCl_4, PPh_3 CH_3CN, 50 °C to 30 °C, 18 h. [TEA, triethylamine; DMF, *N*,*N*'-dimethylformamide; DCM, dichloromethane; DCC, *N*,*N*'-dicyclohexylcarbodiimide; NHS, *N*-hydroxysuccinimide; THF, tetrahydrofurane.]

With the dipolarophiles and the precursors of the 1,3-dipoles in hand, we moved to the cycloaddition-oxidation reaction taking **7** and **2a** as model reactive partners; the first step renders, in fact, two regioisomeric pyrazolines that, upon oxidative treatment, afford the corresponding regioisomeric pyrazoles. While the second step was rather trivial and always accomplished by treatment of the crude first-step mixture with cerium(IV) ammonium nitrate (CAN) in a THF/H_2O mixture at 0 °C, the

Table 1. Scope of the 1,3-DC reaction followed by oxidation [a].



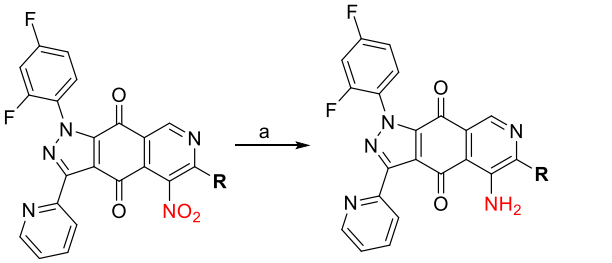
Entry [	Dipolarophile	Precursor of 1,3-dipole	Major Product	Minor Product	Yield (%)[b]	Ratio[c]
1[d]	**2a**	**7**	**9a**	**10a**	67	80:20
2[d]	**2b**	**7**	**9b**	**10b**	55	83:17
3[d]	**2c**	**7**	**9c**	**10c**	72	86:14
4[e]	**4a**	**7**	**11a**	**12a**	54	86:14
5[e]	**4b**	**7**	**11b**	**12b**	45	86:14
6[e]	**4c**	**7**	**11c**	**12c**	61[f]	75:25
7[d]	**2a**	**8**	**13a**	**14a**	58	85:15
8[d]	**2b**	**8**	**13b**	**14b**	70	83:17
9[d]	**2c**	**8**	**13c**	**14c**	61	83:17

[a] Reaction conditions: **2** (or **4**) (1 mmol), **7** (or **8**) (1.2 mmol, 0.2 equiv added hourly), Ag_2CO_3 (2.0 mmol), 1,4-dioxane (5.0 mL, 0.2 M), 50 °C or reflux, 6h; then the mixture is filtered over a Celite® pad, evaporated in vacuo and treated with: CAN (2.5 mmol), THF/H_2O (4:3, 21 mL), 0 °C, 2h. [b] Isolated yield of the major regioisomer (minor regioisomer impurity below 10%) after column chromatography. [c] Determined on the crude mixture by ^{1}H-NMR spectroscopy. [d] Reaction run at 50 °C. [e] Reaction run at 100 °C. [f] Yield of the inseparable mixture of regioisomers.

cycloaddition step required some optimization (see Supporting Information for an extensive reaction scheme and optimization table). When the reaction was run in 1,4-dioxane at 50 °C, Ag_2CO_3 was employed as the base and the total amount of hydrazonoyl chloride **7** was added portionwise, we obtained an optimal satisfactory yield of 67% and a good regioisomeric ratio (80:20 in favour of **9a**, Table 1, entry 1). The structure of major regioisomer **13b** was assesed by means of single crystal X-ray analysis and extended for analogy to all compounds **9**, **11** and **13** (see Supporting Information for more details).

With the optimal conditions in hand, we subjected dipolarophiles **2** and **4** to the cycloaddition-oxidation protocol with precursor **7**, obtaining fused pyrazoles **9a-c** and **11a-c** as major regioisomers (**10a-c** and **12a-c** respective minor isomers), with overall useful synthetic yields and moderate to good regioselectivities, proving the disclosed protocol to be of some robustness. Moreover, isoquinolino-5,8-diones **2a-c** were also reacted with hydrazonoyl halide **8**, allowing the preparation of a library of nine novel, tricyclic-fused, fully substituted pyrazoles (Table 1).

Finally, in order to obtain the desired targets **15a** and **15b**, products **13a** and **13b** were hydrogenated with ammonium formate and catalytic Pd/C in MeOH at 50 °C (Scheme 3).



Scheme 3. Preparation of targets **15a** and **15b**. Reaction conditions: a) $HCOONH_4$, Pd/C, MeOH, 50 °C, 18h.

We then underwent an "in silico" study to predict the potential affinity of the novel tricyclic fused pyrazole derivatives **15a** and **15b** to the catalytic active site of PI3K and mTOR kinases, involved in the crucial pathway to many antitumor processes (cell growth, proliferation, survival and apoptosis).[23] These targets have been chosen on the basis of the mode of action of

the below described antitumor drugs, pertaining to the category of pyrazole derivatives. Docking simulations were performed to characterize the binding pose of our tricyclic pyrazoles derived inhibitor candidates to the pocket site of the above indicated PI3K and mTOR. Our tricyclic fused pyrazole derivatives were found to have the minimum requirements for tight binding at the pocket active site of both the PI3K and mTOR domains. The selected target proteins for the docking evaluation of the proposed compounds were retrieved from the Protein Data Bank (http:/www.rcsb.org/pdb/) and were: PI3K (PDB: 4HVB) and mTOR (PDB: 4JT6). Binding modes and binding affinities of the evaluated compounds within the catalytic pocket site of the selected macromolecules were calculated using the Autogrid 4.0 and Autodock 4.2 programs. [24]

We analyzed the location and orientation of the evaluated compounds and the interactions into the binding site of the selected PI3K and mTOR above indicated. The predicted binding free energy (BE, that includes intermolecular energy and torsional free energy) was used as the criterion for ranking. The conformation with the lowest ranking docked binding energy (BE) was considered to be the best docking result.

Satisfactory docking results with good affinity parameters were observed for both compounds (**15a** and **15b**) either for the PI3K and mTOR; virtual constants of inhibition (Ki) at micromolar concentration were contextually calculated (1.65 μM and 1.21 μM for **15a** and **15b** with PI3K; 73.27 μM and 43.55 μM for **15a** and **15b** with mTOR). Both compounds were docked and nicely fitted into the active pocket site of the examined PI3K and mTOR kinases, as indicated from binding free energy and from analysis of ligand binding pose inside the active binding sites.

Better docking results were observed for the examined PI3K than with mTOR, for both compounds; the best poses into active binding sites of compounds **15a** and **15b** exhibit slight better values of binding free energies to PI3K with an estimated binding free energy of -7.89 kcal/mol and -8.07 kcal/mol, respectively. Both compounds showed lower, although still satisfying results for the examined mTOR kinase (-5.64 kcal/mol and -5.89 kcal/mol for **15a** and **15b** respectively).

The binding conformation to PI3K showed a superimposable pose for both **15a** and **15b**, where the molecules of the tricyclic fused pyrazoles are entirely inserted and retained inside the active site. Differently, the binding conformations to mTOR, are characterized by the tricyclic fused pyrazole of both molecules entering the active site and pyridine/phenyl groups retained along the rime region of the pocket (with superimposable conformation).

Only compound **15a** is stabilized inside the catalytic site of the selected PI3K by two hydrogen bonds between the amino group of ASP (ASP964) and the amino group of the tricyclic pyrazole and between the amino group of ALA (ALA885) and the 3F of fluorobenzene moiety. At distances within 5 Å, a possible different set of polar interactions are observed between the pyridine moiety (connected to pyrazole) of both **15a** and **15b**, and the polar residues THR887 and LYS890.

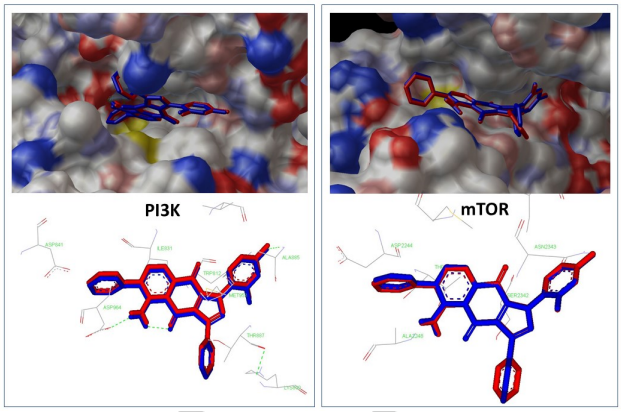


Figure 2. Low energy conformations of molecules **15a** and **15b** into the PI3K and mTOR binding sites. Top: best docking binding poses of compound **15a** (blue) and **15b** (red) are shown into the pocket binding site of PI3K (on the left) and mTOR (on the right) and - in the bottom part - the amino acid residues of the PI3K (on the left) and mTOR (on the right) binding sites within 5 A° from the compound **15a** (blue) and **15b** (red) are displayed.

Additional polar interactions between the pyridine or the benzene group of **15a** and **15b** respectively and ASP841, between the sulphanyl of MET953 and the pyrazole ring, between the carboxylate of VAL882 and the difluorobenzene moiety, stabilize the molecules inside the active site. The examined compounds revealed a common binding mode in the hydrophobic cleft, through a complementary apolar interaction surface with the hydrophobic chain of ILE831.

The best poses of both molecules, obtained after docking to PI3K and mTOR PDB structures, suggest that these are typical of aspecific kinase inhibitors. In all the cases, the synthesized molecules fitted and entered into the pocket binding site with good binding affinity. These docking results on the two above described structures encouraged us to continue the investigation by testing the synthesized compounds as PI3K/mTOR inhibitors *in vitro*.

The PI3K/AKT/mTOR pathway regulates diverse cellular processes, including cell growth, proliferation, survival, and metabolism [23] and, indeed, it is activated in a large percentage of human cancers through a variety of mechanisms including Ras mutation, loss of PTEN, activation of growth factor receptors such as EGFR, and mutations in PIK3CA.[25]

On the basis of our results demonstrating promising molecular docking of compounds **15a** and **15b** to PI3K and mTOR proteins, we next studied the ability of the drugs of affecting viability of glioblastoma (GBM) cells. Indeed, amplification of the EGFR gene, mutation and deletion of the PTEN gene, and mutations of the PIK3CA gene are among the most frequent alterations observed in primary GBM.[26] Specifically, we choose a panel of three cell lines, U251, DBTRG, and U87MG and demonstrated, in all of them, that the most active compound, in terms of cytotoxicity, was **15b**, with an IC_{50} value of ~2.5 μM after 72h, while the other compound (**15a**) resulted less active with IC_{50} values higher than 10 μM (Figure 3). While these differences in the cytotoxicity of the two compounds against GBM cell lines may be surprising, these data suggest that, although predicted common binding modes by docking analysis, their ability of effectively interfering with kinases activity may differ, explaining observed biological consequences.

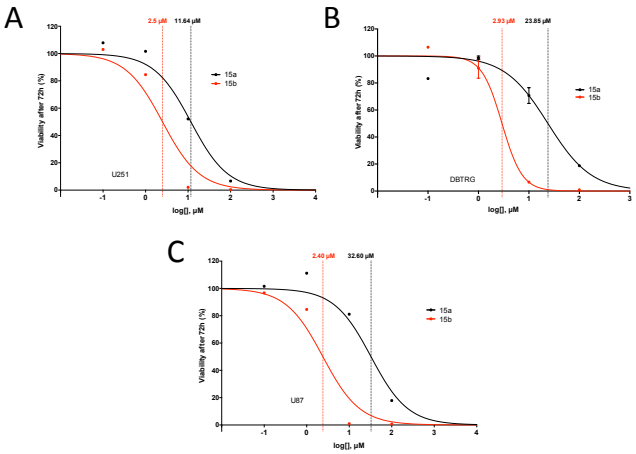


Figure 3. Cytotoxicity evaluation in different GBM cell lines. IC_{50} evaluation, after 72h treatment of U251, DBTRG, and U87MG cells, of compounds **15a** and **15b**, at different concentrations, obtained by cell counting through a Z2 coulter counter. The results shown are averages of triplicate samples from a typical experiment.

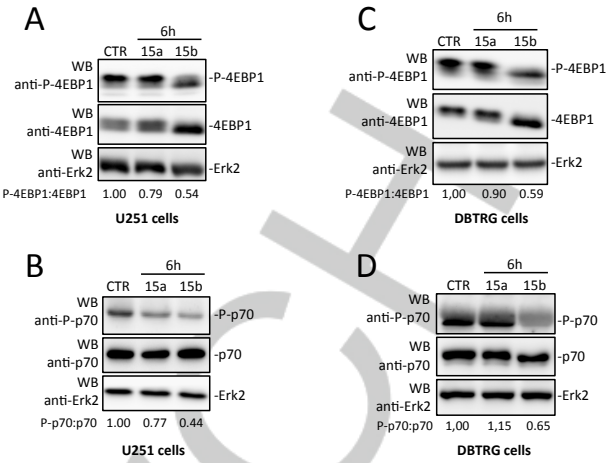


Figure 4. Inhibition of PI3K/mTOR signalling in U251 and DBTRG cells. Cells were incubated 6 h with vehicle (CTR), and compounds **15a** and **15b** (10 μM). Corresponding lysates were next immunoblotted with (**A and C**) anti-phospho-4EBP1 and "total" 4EBP1 antibodies, and (**B and D**) anti-phospho-p70 and "total" p70 antibodies. Equal loading was confirmed by immunoblot with anti-Erk2 antibody. Below each experiment, phospho-4EBP1/4EBP1 or phospho-p70/p70 ratios of intensitometric signals are shown. Anti-Erk2 levels are also shown to confirm equal loading of samples.

Therefore, we next sought to investigate if the cytotoxic activity of these compounds on GBM cells was indeed correlated to their ability of inhibiting PI3K/mTOR kinases. Therefore, upon treatment with **15a** and **15b**, we evaluated phosphorylation of 4EBP1, a well-established substrate of mTOR[27] and of p70 S6 Kinase, which acts predominantly downstream of PI3K,[28] in our GBM cells panel. Interestingly, **15b** was the most effective compound at inhibiting PI3K/mTOR biochemical activities in both U251 and DBTRG cells (Figure 4 and Figures S2A and S2B, see Supporting Information), confirming the consistent higher efficiency of this compound in cytotoxicity studies (see above). Ultimately, the two compounds showed very limited activity on PI3K/mTOR in U87MG cells (Figures S2C and S2D).

In conclusion, products characterized by high molecular complexity and great functional group diversity were easily obtained. The previously described reaction sequence was shown to be a convenient synthetic protocol to afford libraries of substituted compounds, bearing a free amine, an isoquinolino-5,8-dione-fused pyrazole, a terminal pyridine, a halogen substituted aryl ring and a different (hetero)aryl moiety. These scaffolds were designed to interact with multiple biological residues and two of them, after brief synthetic elaborations, were analysed by molecular docking studies *in silico* as potential anti-cancer drugs. Further *in vitro* studies confirmed the potent anti-cancer capability, showing interesting IC_{50} values down to 2.5 μM on three different glioblastoma cell lines. Their cytotoxic activity was finally positively correlated to their ability of inhibiting PI3K/mTOR kinases, which are responsible for the regulation of diverse cellular processes in human cancer cells. Further in vivo experiments using these molecules are still underway and will be released in due course.

Experimental Section

Synthetic procedures, reaction optimization parameters, spectral characterizations and additional biological essays are provided in the Supporting Information. The following preparation (and characterization) of compound **15b** through cycloaddition-oxidation followed by nitro group reduction may be taken as a representative example.

In an oven dried Schlenk tube equipped with a magnetic stirring bar and under nitrogen atmosphere, isoquinoline-5,8-dione **2b** (281.2 mg, 1 mmol) and Ag_2CO_3 (441 mg, 1.6 mmol) were suspended in dry dioxane (5 mL) and heated to 50 °C. Then, hydrazonoyl chloride **8** (53.5 mg, 0.2 mmol) was added and the resulting mixture was stirred for 1 h. Then, another portion (53.5 mg, 0.2 mmol) of **8** was added hourly until 1.2 equivalents (320.6 mg, 1.2 mmol) were reached after 5 hours. The reaction was then stirred for 1 additional hour, cooled to room temperature, filtered over a Celite® pad and washed repeatedly with DCM. The filtrate was evaporated *in vacuo* and suspended in 21 mL of a 4:3 THF/H_2O mixture and cooled to 0 °C. Cerium (IV) ammonium nitrate (1.37 g, 2.5 mmol) was added in portions and the resulting slurry was stirred at 0 °C for 2 h. Hereafter, the THF was evaporated *in vacuo*, EtOAc (20 mL) was added and the phases were separated. The organic phase was washed repeatedly with water and once with brine (10 mL), dried over $MgSO_4$, filtered and evaporated *in vacuo*. The crude product was analyzed by means of ^1H NMR spectroscopy to calculate the regioisomeric ratio **13b**/**14b** of the reaction, which was found to be 83:17, and finally purified by column chromatography on silica gel (*n*-hexane/EtOAc 1:1) to afford pure compound **13b** in 70% (357 mg) as a dark yellow solid, which was completely charcterized (see Supporting Information).

In a Schlenk tube equipped with a magneting stirring bar and under nitrogen atmosphere, compound **13b** (50,8 mg, 0.1 mmol) and

ammonium formate (63 mg, 1 mmol) were dissolved in degassed MeOH (1 mL) and heated to 50 °C. Then, 10% wt. Pd/C (3.2 mg, 3 mol%) was added and the reaction mixture was stirred at 50 °C overnight under nitrogen. Hereafter, DCM (5 mL) was added, the resulting suspension was filtered over a Celite® pad and washed repeatedly with DCM. The solvent was evaporated *in vacuo* and the crude product was purified by column chromatography on silica gel (EtOAc/MeOH 10:1) to afford 43 mg of pure product **15b** as an intense cherry-red powder in 90% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (dd, *J* = 2.3, 0.9 Hz, 1H, **pyridine-H**), 8.83 (ddd, *J* = 4.8, 1.8, 0.9 Hz, 1H, **pyridine-H**), 8.77 (s, 1H, **isoquinoline-H**), 8.76 – 8.75 (m, 1H, **pyridine-H**), 8.22 (dt, *J* = 7.9, 1.1 Hz, 1H, **pyridine-H**), 8.04 (ddd, *J* = 7.9, 2.3, 1.7 Hz, 1H, **pyridine-H**), 7.90 (td, *J* = 7.8, 1.8 Hz, 1H, **pyridine-H**), 7.68 (tdd, *J* = 8.2, 5.7, 0.9 Hz, 1H, **Ar^F-H**), 7.50 (ddd, *J* = 7.8, 4.9, 0.9 Hz, 1H, **pyridine-H**), 7.43 (ddd, *J* = 7.6, 4.9, 1.2 Hz, 1H, **pyridine-H**), 7.12 – 6.99 (m, 2H, **Ar^F-H**) overlapped with 7.00 (bs, 2H, **NH_2**) ppm; ^{13}C NMR (101 MHz, $cdcl_3$) δ 182.8, 174.8, 163.5 (dd, *J* = 253.6, 11.2 Hz), 157.4 (dd, *J* = 256.1, 12.8 Hz), 153.0, 151.8, 150.8, 149.9, 149.4, 149.3, 142.6, 139.3, 136.5, 136.4, 136.3, 132.7, 129.3 (d, *J* = 10.2 Hz), 125.2, 125.1, 124.3, 124.0, 123.5 (dd *J* = 12.6, 4.1 Hz), 120.9, 116.9, 111.9 (dd, *J* = 22.9, 3.8 Hz), 105.0 (dd, *J* = 26.7, 23.1 Hz) ppm; ^{19}F NMR (282 MHz, $CDCl_3$) δ -105.33 (qd, *J* = 8.3, 5.6 Hz, 1F), -116.97 (q, *J* = 8.8 Hz, 1F) ppm; ESIMS *m/z* = 481 [M + H$^+$], 503 [M + Na$^+$].

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Keywords: Pyrazole, Quinone, 1,3-Dipolar Cycloaddition, Anticancer Drugs, Molecular Docking

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