NJC

Accepted Manuscript

This is an *Accepted Manuscript*, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this *Accepted Manuscript* with the edited and formatted *Advance Article* as soon as it is available.

You can find more information about *Accepted Manuscripts* in the Information for Authors.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard Terms & Conditions and the Ethical guidelines still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this *Accepted Manuscript* or any consequences arising from the use of any information it contains.

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/njc

Journal Name

ARTICLE

A catalyst– and solvent–free multicomponent synthesis and docking study of some new antiproliferative N_5-allyl-quinolylpyrido[2,3-*b*][1,4]benzodiazepinone precursors

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Hitesh A. Barad,[a] Tushar R. Sutariya,[a] Gaurangkumar C. Brahmbhatt,[a] Narsidas J. Parmar,[a*] Irene Lagunes,[b] José M. Padrón,[b] Prashant Murumkar,[c] Mayank Kumar Sharma,[c] Mange Ram Yadav[c]

A multicomponent reaction has been developed incorporating quinoline-3-carbaldehyde, 1,3-cyclohexanedione and 2,3-diaminopyridine into some new quinolylpyrido[2,3-*b*][1,4]benzodiazepinone assemblies under catalyst– and solvent–free conditions at 120 °C. Further reaction of the resulting intermediates with allyl bromide led to the formation of the corresponding N_5–allylated products, *in situ,* with higher yields in the same pot. Many candidates of this new class revealed noticeable activities against the representative human solid tumour cell lines A549 (lung), HBL-100 (breast), HeLa (cervix), SW1573 (lung), T-47D (breast) and WiDr (colon). The most active compounds resemble the standard drug etoposide in antiproliferative activity against HeLa, T-47D and WiDr cell lines. Docking studies in the active site of MDM2 led us to consider this protein a plausible target for the antiproliferative effects of the compounds.

Introduction

Heterocycles with a diazepine nucleus incorporated as one of their fused-ring systems represent noteworthy bioactive molecular assemblies, and so remained highly perused synthetic targets since their introduction in the early 1960s,[1] in both drug discovery and pharmacological investigations. The diazepine nucleus fused with imidazole, pyrazol, pyrimidine, thiazol, pyrrol, indol, benzopyran and triazol units is known to confer a wide variety of biological properties on the resulting heterocycles (Fig. 1).[2] Chlordiazepoxide and diazepam, effective in anxiety;[3] chlozapines, useful in schizophrenia; pirenzepine, a muscarinic receptor M_1 antagonist; and finally apafant, a platelet activating inhibitor, are prominent examples in this context.[4] Practice of isosterism in the synthesis also worked well and effectively in this area. The thieno-fused-benzodiazepine flumezapine (**I**), which holds a thiophene as an isosteric form of the benzene unit, revealed more activity than the similar framework clozapine (**II**), due to the electronegative methyl group at the thiophene heterocycle.[5]

Among the combinations of fused heterocycles discovered so far, those involving a pyridodiazepine fusion led to the generation of many new potential candidates of medicinal interest. Pyridodiazepine fusion conferred the resulting heterocyclic frameworks with a notable neuroleptic property.[6] The prototypical privileged substructure pyridobenzodizepine, known to exhibit high pharmacological properties,[7] is present in the natural product (-)–auranthine (**III**), isolated from *Penicillium aurantiogriseum*. Therapeutic drugs of this group (Fig. 2) include pirenzepine (**IV**) (the first M_1–selective muscarinic receptor antagonist),[8] rispenzepine, propizepine (**V**) and norepinephrine reuptake inhibitor tampramine (**VI**).[9] AF–DX 116 (**VII**) is a selective inhibitor of cardiac muscarinic receptor M_2 and has 10–fold higher *in vitro* affinity over M_1 receptor.[10] The clozapine–like analogues 8-chloro-6-(4'-methyl-l-piperazinyl)-11H-pyrido[2,3-b][1,4]benzodiazepine (**VIII**) and 8-methyl-6-(4'-methyl-1-piperaziny1)-11H-pyrido [2,3-b][1,4]benzodiazepine (**IX**) were reported as effective neuroleptics.[11] Besides, pyridobenzodiazepines are potential modulators of central nervous system and vasopressin V_2 receptor.[12] P. Liu, and others[13] reported pyridobenzodiazepine as sulfonamide–based bombesin receptor subtype 3 agonists. MK–7725 is a potent and selective bombesin receptor subtype–3 agonist, used in the treatment of obesity.[14] M. V. Petrova, et al.[15] reported a two-step synthetic procedure for this compound, in which enaminone intermediate generated in the first step underwent cyclization with an aldehyde. Thus, in view of this, the synthetic effort aimed at the incorporation of a pyridine unit with the diazepine framework represents a vital explorative push towards the development of libraries of bioactive scaffolds with pyridine-fused diazepine containing heterocycles.

[a] *Department of Chemistry, Sardar Patel University, Vallabh Vidyanagar-388120. Dist. Anand, Gujarat, India. Tel.:+91-2692-226858;fax:+91-2692-236475;e-mail:njpchemdeptspu@yahoo.co.in*
[b] *BioLab, Instituto Universitario de Bio-Orgánica "Antonio González" (IUBO-AG), Centro de Investigaciones Biomédicas de Canarias (CIBICAN), Universidad de La Laguna, C/ Astrofísico Francisco Sánchez 2, 38206 La Laguna, Spain*
[c] *, Faculty of Pharmacy, The M.S. University of Baroda, Vadodara, Gujarat, India 390001*

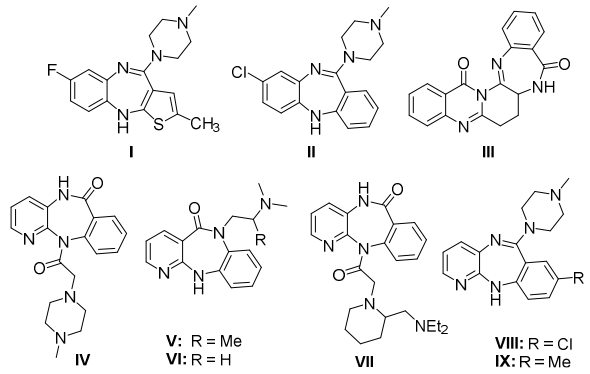


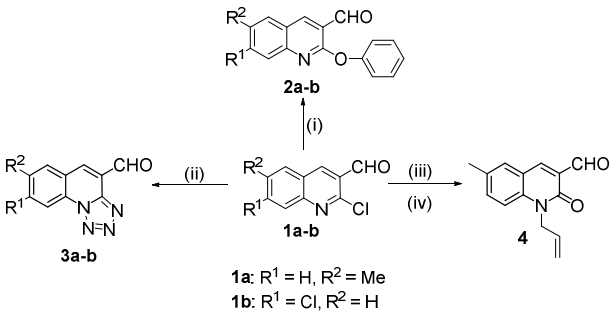
Fig. 1. Pharmacologically relevant benzodiazepine derivatives.

Among various synthetic routes, the cyclization of an enaminone derived from a diketone and *O*-phenylenediamine with an aldehyde is considered to be a widely studied multicomponent domino procedure to achieve diazepine heterocycles. McGowan et. al. and Eduardo et al. reported a two-step method, combining enaminones generated *in situ* with an aldehyde *via* cyclization reaction, catalyzed by acetic acid in refluxing ethanol.[16a-b] Orlov et al.[16c] assembled a Michael adduct generated *in situ* from an aldehyde and a diketone with diamines via a multicomponent reaction (MCR) method. The MCR approach has often provided synthetic chemists with many green and ecological advantages, to achieve synthetic targets. We have reported earlier synthesis of quinolyldibenzo[*b,e*][1,4]diazepinones using MCR strategy.[17] Inspired by the results, we report in the present work the synthesis of new quinolylpyrido[2,3-*b*][1,4]benzodiazepinones via MCR, using pyridine fusion with a diazepine unit successfully. The obtained heterocycles were screened for their antiproliferative activities. Docking studies were performed to predict binding affinity for the MDM2 protein.

Results and discussion

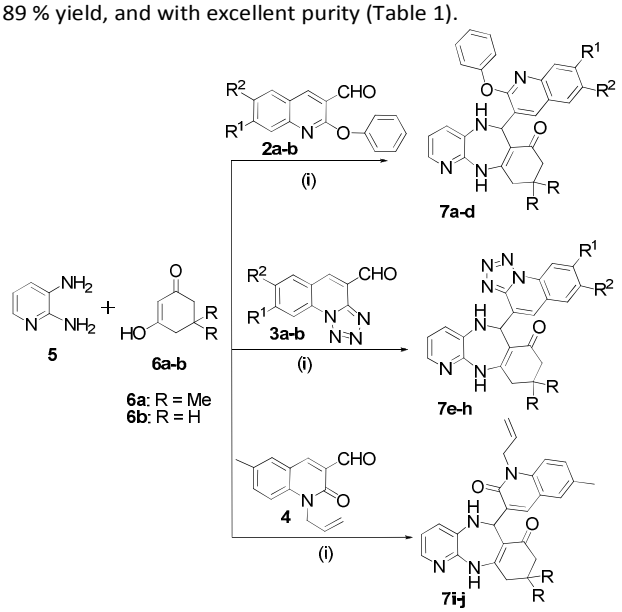
Chemistry

As shown in Scheme 1, all requisite quinoline aldehydes **2**-**3** employed in the present work were prepared according to the reaction between the respective 2-chloroquinoline-3-carbaldehyde **1a**-**b** and phenol in the presence of anhydrous K_2CO_3 in DMF at reflux (to afford **2a**-**b**), or sodium azide in the presence of TBA-HS in DMSO at 45-50 °C (to afford **3a**-**b**). For the synthesis of aldehyde **4**, compound **1a** was heated with 70% AcOH[18] prior to allylation[19] (Scheme 1).



Scheme 1. Reagents and conditions: (i) Phenol, K_2CO_3, DMF, reflux, 3.5 h; (ii) NaN_3, TBA–HS, DMSO, 45–50 °C; (iii) 70% acetic acid, reflux (iv) Allyl bromide, K_2CO_3, DMF, rt, 12 h.

Next, MCR was performed in solvent-free environment taking 2,3-diaminopyridine **5**, 1,3-cyclohexadione **6a**-**b** and quinoline-carbaldehyde **2**-**4** in equimolar amounts, at 120 °C, a temperature reported earlier[17] (Scheme 2). The resulting pyrido[2,3-*b*][1,4]benzodiazepinones **7a**-**j** were obtained in 76–89 % yield, and with excellent purity (Table 1).



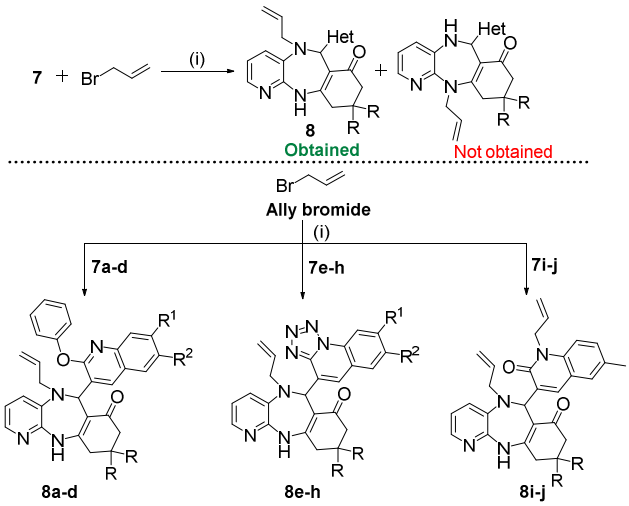
Scheme 2. Reagents and conditions: (i) 120 °C, 2.5-3.5 h.

Table 1. Synthesis of quinolylpyrido[2, 3-*b*][1,4]benzodiazepin-7-ones **7a–j.**

Product	R	R^1	R^2	Time (h)	Yield (%)	M.P. °C [a]
7a	Me	H	Me	2.8	88	296—298
7b	H	H	Me	3.1	85	268—270
7c	Me	Cl	H	3.0	86	252—254
7d	H	Cl	H	3.2	83	247—248
7e	Me	H	Me	2.9	89	288—290
7f	H	H	Me	2.6	88	272—274
7g	Me	Cl	H	3.2	83	231—232
7h	H	Cl	H	3.5	76	236—237
7i	Me	H	Me	2.7	80	242—243
7j	H	H	Me	3.0	78	278—280

[a]Uncorrected

The allylation of heterocycles **7a**-**j**, performed *in situ* in the presence of anhydrous K_2CO_3 in DMF, yielded the corresponding N_5-allylated products **8a**-**j**, after 12 h of stirring of the reaction mass (Scheme 3, Table 2). Spectroscopic data of all allylated compounds **8a**-**j** confirmed the regioselectivity allylation at nitrogen N-5 of the diazepine ring (and not at nitrogen N-10), supported further by the literature.[20]



Scheme 3: Reagents and condition (i) K_2CO_3, DMF, rt, 10-12 h.

Table 2: Synthesis of 5-allylquinolylpyrido[2,3-*b*][1,4] benzodiazepin-7-ones **8a-j.**

Product	R	R^1	R^2	Yield (%)	M.P. °C [a]
8a	Me	H	Me	93	227—228
8b	H	H	Me	89	238—240
8c	Me	Cl	H	90	199—200
8d	H	Cl	H	91	218—219
8e	Me	H	Me	94	207—208
8f	H	H	Me	87	200—201
8g	Me	Cl	H	92	189—190
8h	H	Cl	H	90	232—234
8i	Me	H	Me	93	177—178
8j	H	H	Me	91	248—249

[a]Uncorrected

All of the newly synthesized compounds, **7a-j** and **8a-j**, were characterized by elemental, mass spectrometry, and ^{1}H NMR, ^{13}C NMR, DEPT-135 and IR spectroscopic data, which are summarized in the experimental section. Two ^{1}H NMR singlets; one at δ 1.12–1.21 ppm and second at δ 1.15–1.25 ppm can be attributed to six protons of two methyl groups, three each attached to C–9. Two doublets; one at δ 5.57–5.98 ppm with coupling constant J = 5.2–5.4 Hz, and second in the δ 5.78–6.95 ppm range with J = 4.4–5.2 Hz, can be assigned to NH–5 and methine CH–6 protons respectively, in **7a-j**. The NH–5 proton found in **7a-j** did not appear in allylated products **8a-j**, confirming that NH-5 took part in the allylation. On the other hand, NH–11 proton showed a singlet in the δ 8.86–9.92 ppm range, in all the compounds **8a-j**. IR bands; one in the 2850—3020cm^{-1} range and second in the 3210–3510 cm^{-1} range, can be assigned to ν C–H and ν N–H vibrations, respectively. A band in the 1631–1660 cm^{-1} range confirms C=O carbonyl group in all the heterocycles. Two bands; one in the 1080–1185 cm^{-1} range and second in the 1310–1395 cm^{-1} range confirmed the C–O and C–N bonds respectively.

The antiproliferative activity of all the heterocycles was evaluated using a panel of six representative human tumour cell lines; A549 (lung), HBL-100 (breast), HeLa (cervix), SW1573 (lung), T-47D (breast) and WiDr (colon), employing the SRB assay.[21] The experimental GI_{50} values are summarized in Table 3, and compared with those of the standard drugs (cisplatin, etoposide and camptothecin) after 48 h of treatment. It was observed that each cell line remained a target of minimum one compound considering 50 µM a GI_{50} value. Compounds **7b**, **7d**, **7e**, **7g**, **8a**, **8c**, **8e**, **8g** and **8i**, were found active against HeLa cell line (cervix), with GI_{50} values in the 3.8—43 µM range, fitting into this analogy. Compound **8c**, on the other hand, having the lowest GI_{50} value of 3.8 µM resembled the standard drug etoposide (3.3 µM) in activity, against the same cell line. With GI_{50} values in the same range as those of **8c**, compounds **8g** and **8i** produced similar effect against HeLa cells. T-47D (breast) and WiDr (colon) are other cell lines against which maximum three compounds; **8c**, **8g** and **8i,** registered a notable resistance. While **8g** and **8i** with GI_{50} values of 24 µM and 26 µM against T-47D cells, respectively, were found very near to standard etoposide, **8c** with GI_{50} value of 5.8 µM was comparable to the standard camptothecin in the activity. Furthermore, these compounds registered 26, 15 and 5.5 µM respectively, as the GI_{50} values against WiDr (colon) cell line, which resembled the standard drugs cisplatin, etoposide, and camptothecin, respectively. Furthermore, TGI and LC_{50} values for all the tested compounds **7**-**8** are >100 µM, denoting the absence of cell killing ability of the compounds.

From the results on antiproliferative activity some structure-activity relationships have been formed (Fig. 2). Briefly, the biological activity could be enhanced by replacing the H on *N*-5 with an allyl group (**8** > **7**). The derivatives with two methyl groups at position 9 of the tricycle are more potent than their corresponding analogues bearing only hydrogens (**8e** > **8f**, **8g** > **8h**). Considering the quinolone fragment, either a phenoxy group at position 2 (**8c** > **8g**) or a chloro substituent at position 7 (**8c** > **8a**, **8g** > **8e**) exhibit higher activity. The lead compound **8c** holds all the aforementioned substitutions.

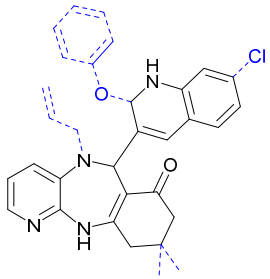


Fig. 2. Structure–activity relationship parameters defined during this study. Functional groups that enhance the antiproliferative activity are depicted with dashed lines.

About 50% of all human tumours express wild-type p53, which is one of the most potent tumour suppressor proteins in human cancers. The ability of p53 to bind to

Journal Name

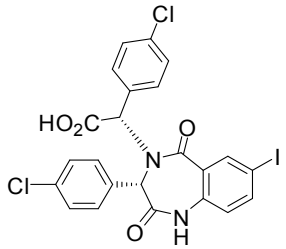
ARTICLE

Table 3. Antiproliferative activity (GI_{50}) against human solid tumour cells.

Compound	Cell line *(origin)*[a]					
	A549 *(lung)*	*HBL-100 (breast)*	HeLa *(cervix)*	SW1573 *(lung)*	T-47D *(breast)*	WiDr *(colon)*
7a	—	—	—	—	—	—
7b	97 (±4.5)	84 (±22)	27 (±3.7)	>100	>100	>100
7c	>100	>100	>100	>100	>100	>100
7d	93 (±10)	62 (±7.4)	43 (±11)	>100	96 (±7.7)	96 (±5.9)
7e	82 (±25)	65 (±20)	25 (±0.2)	>100	89 (±16)	93 (±10)
7f	—	—	—	—	—	—
7g	31 (±14)	48 (±17)	26 (±6.4)	77 (±3.2)	38 (±5.3)	41 (±0.9)
7h	—	—	—	—	—	—
7i	—	—	—	—	—	—
7j	>100	>100	>100	>100	>100	>100
8a	37 (±6.6)	62 (±24)	25 (±4.5)	>100	36 (±0.6)	69 (±15)
8b	—	—	—	—	—	—
8c	5.3 (±2.4)	21 (±0.8)	3.8 (±0.3)	29 (±2.1)	5.8 (±0.6)	5.5 (±1.0)
8d	>100	>100	>100	>100	>100	>100
8e	34 (±15)	52 (±5.5)	33 (±5.7)	>100	56 (±18)	83 (±20)
8f	>100	>100	>100	>100	>100	>100
8g	19 (±7.5)	23 (±8.4)	8.4 (±3.4)	52 (±4.5)	24 (±0.2)	26 (±1.4)
8h	>100	>100	>100	>100	>100	>100
8i	22 (±9.0)	28 (±4.9)	5.6 (±0.5)	61 (±3.3)	26 (±1.2)	15 (±7.9)
8j	—	—	—	—	—	—
[A]	—	1.9 (±0.2)	2.0 (±0.3)	3.0 (±0.4)	15 (±2.3)	26 (±5.3)
[B]	—	1.4 (±0.1)	3.3 (±1.6)	14 (±1.5)	22 (±5.5)	23 (±3.1)
[C]	—	0.23 (±0.05)	0.6 (±0.4)	0.25 (±0.12)	2.0 ±(0.5)	1.8 (±0.7)

[A]: Cisplatin, [B]: Etoposide, [C]: Camptothecin. [a] Values are given in µM and are means of two to four experiments; standard deviation is given in parentheses.

DNA can be inhibited by the human murine double minute 2 (MDM2) oncoprotein which activates transcription and promotes rapid degradation of p53. Benzodiazepine-like compounds, such as TDP222669 (Fig. 3), have been reported in the literature having the ability to inhibit p53-MDM2 interactions.[22] The study of the antiproliferative activity of TDP222669 gave IC_{50} (72 h) values of 33-58 µM and >132 µM in human tumour cell lines expressing wt p53 and mutant/null p53, respectively.[22d]



TDP222669

Fig. 3. Structure of MDM2 inhibitor TDP222669.

Based on the structure similarities between TDP222669 and our benzodiazepinones, it was thought reasonable to predict the interactions of the synthesized compounds **7a-j** and **8a-j** with the p53-binding domain of MDM2. Thus, all the compounds were docked in the active site of human MDM2 (PDB ID: 1T4E). To validate the docking protocol, reference compound TDP222669 was also docked in the active site and its orientation was studied. The docking scores of the compounds are shown in Table 4. The lead compound **8c** showed a glide score of -6.90 which was found to be comparable to that of the reference compound TDP222669 (-6.92). From the series of benzodiazepinones, two compounds **8a** and **8g** displayed better glide scores than the lead **8c**. However, they showed reduced antiproliferative activity than **8c**.

The binding interactions of p53-MDM2 are mediated by hydrophobic surface pockets, namely F19, W23 and L26 (p53 numbering). These pockets are surrounded by various hydrophobic residues i.e. M50, L54, L57, G58, I61, M62, Y67, H73, V75, F91, V93, H96, I99 and Y100. The iodophenyl group of TDP222669 fitted well into the F19 pocket (Fig. 4A),

whereas the 4-chlorobenzyl group attached to the nitrogen occupied the W23 pocket and the 4-chlorophenyl ring fitted into the L26 pocket. The hydroxyl part of the carboxylic acid formed a hydrogen bond with the residue V93 indicating that TDP222669 is well fitted into the defined hydrophobic pockets. Good contacts of TDP222669 were observed with L54, L57, I61, M62, Y67, V93 and I99 residues. The chlorophenyl group of the quinoline ring of compound **8c** was oriented towards the F19 pocket, the cyclohexanone group attached to diazepine fitted into the W23 pocket and the propenyl group attached to the nitrogen of diazepine scaffold fitted well into the L26 pocket indicating that compound **8c** was accommodated nicely into the active site of MDM2 (Fig 4B). The NH part of the diazepine ring formed a hydrogen bond with residue L54. Good contacts of compound **8c** with L54, F55, I61, M62, F91, V93, H96 and I99 residues might explain in part of its antiproliferative activity. The orientation of compound **7j** was different from compound **8c**. The pyridobenzodiazepine scaffold of compound **7j** was oriented outside the active site of MDM2 as shown in Fig. 4C. It does not form any hydrogen bond with the active site residues and this might be one of the reasons for its lack of activity.

Table 4. Docking scores of compounds 7-8 and TDP222669.

Compound ID	G-score	Compound ID	G-score
7a	-5.98	8a	-7.50
7b	-5.55	8b	-5.29
7c	-5.80	8c	-6.90
7d	-6.54	8d	-5.54
7e	-5.07	8e	-5.61
7f	-4.82	8f	-5.72
7g	-5.71	8g	-7.00
7h	-4.71	8h	-6.40
7i	-4.69	8i	-6.21
7j	-4.20	8j	-4.45
		TDP222669	-6.92

Conclusions

In conclusion, we have demonstrated the multicomponent synthesis of 20 new quinolylpyrido[2,3-*b*][1,4]benzodiazepine-7-ones by heating quinoline-carbaldehyde, 2,3-diaminopyridine and 1,3-cyclohexadione under solvent-free conditions and in the absence of catalyst at 120 °C. Many of these newer diazepine-heterocycles displayed noticeable biological activities against human solid tumour cell lines HeLa (cervix), T-47D (breast) and WiDr (colon). Compound **8c** registered excellent resistivity against HeLa (cervix) cell line comparable that of the standard drug etoposide, and against T-47D (breast) and WiDr (colon) cell lines comparable to that of the standard drug camptothecin. Compounds having etoposide–equivalent potential include **8g** and **8i** against the same cell lines. Docking studies helped us to predict the binding pattern of the compounds in the active site of MDM2 and could explain their observed antiproliferative activity. Further experiments will be necessary in order to confirm MDM2 as the cellular target of the lead compound **8c**.

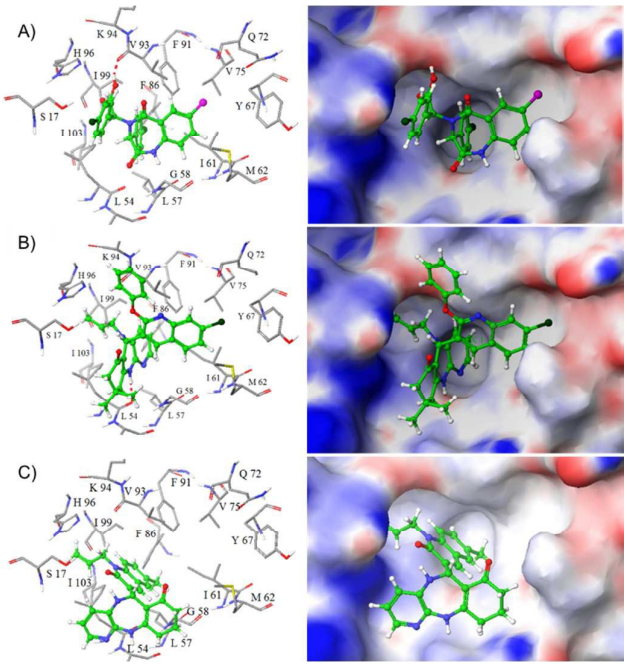


Fig. 4. Binding modes of compounds A) TDP222669, B) **8c** and C) **7j** into the active site of MDM2 (PDB ID: 1T4E). Left: docked pose; right: electrostatic surface.

Experimental

Materials and methods

All solvents and reagents were used as supplied from the commercial sources. Recorded all melting points are uncorrected. IR spectra were recorded on Shimadzu FT-IR 8401 spectrometer using KBr discs, and are expressed as wave numbers (cm^{-1}). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 400 spectrometer operating at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR as solutions in DMSO, unless and otherwise indicated. Chemical shifts are expressed in parts per million (ppm, δ) and referenced to the residual protic solvent. Coupling constants are expressed in Hertz (Hz). Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. The degree of substitution (C, CH, CH_2, and CH_3) was determined by the APT method. The ESI mass spectra were measured on Shimadzu LCMS-2010 spectrometer. TLC was performed on Merck 60 F254 pre-coated silica plates, and spots were detected either by means of UV (254 nm, 366 nm) or permanganate solution [$KMnO_4$ (3 g), K_2CO_3 (20 g), NaOH (5 mL, 5% in H_2O), H_2O (300 mL)] or 2,4 dinitrophenylhydrazoine solution [2,4-DNP (12 g), Conc. H_2SO_4 (6 mL), Water (8 mL), EtOH (20 mL)].

All the computational studies were performed using Maestro 9.0 molecular modelling software.[23] Structures of the compounds were sketched and cleaned using 'building tools' option in Maestro 9.0 software. Energy minimization was carried out using OPLS 2005 force field in standard option "Ligprep 2.3". TDP222669 (benzodiazepinedione MDM2

antagonists) was used as reference compound which was also minimized as per the same protocol mentioned above. Minimized structures were used for performing molecular docking using "Glide 5.5". The crystal structures of MDM2 (PDB ID 1T4E) was downloaded from RCSB.[24] The crystal structure was refined by removing water molecules and heteroatoms in standard option "protein preparation wizard" [25]. Receptor grid was prepared by using default setting in standard option "Receptor Grid Generation" in Maestro 9.0. The van der Waals radii of the ligands were scaled to 0.8 with partial charge cut off 0.25. All the minimized structures were docked with a flexible docking option by extra precision method[26].

General procedure for synthesis of quinolylpyrido [2, 3-*b*][1,4] benzodiazepin-7-ones, 7a-j.

A mixture containing 2,3-diaminopyridine **5**, 1,3-cyclohexadione **6a-b** and quinolone-carbaldehyde **2-4** in equimolar amount (2 mmol) was heated at 120 ˚C under solvent-free conditions. The progress of the reactions was monitored by the TLC and it was found out that the reaction got finished entirely in 2.5-3.5 h. The solid products separated out of the reactions were washed with ethanol and dried at room temperature. The entire products **7a-j** were received quantitatively with an excellent purity.

General Procedure for synthesis of 5-allylquinolylpyrido[2,3-*b*][1,4] benzodiazepin-7-ones, 8a-j

Respective quinolylpyrido[2,3-b][1,4]benzodiazepine-7-one **7a-j** crude products were mixed thoroughly with 15 mL K_2CO_3 (3 mmol) suspended in DMF, and added drop-wise 5 mL of allyl bromide (2 mmol) solution in DMF. The resulting mass was then stirred at room temperature to complete the reaction as confirmed by the TLC (10–12 h). The reaction mixture was poured into crushed ice with constant stirring. The solid so separated out was filtered, washed with three 10 mL cold water portions and dried. Further, purification by aqueous ethanol as re-crystallizing solvent, gave pure product. All products **8a–j** were obtained quantitatively with an excellent purity.

Spectroscopy data of compounds:

6-(6-Methyl-2-phenoxyquinolin-3-yl)-9,9-dimethyl-5,6,8,9,10,11-hexahydro-7H-pyrido[2,3-b][1,4]benzodiazepin-7-one (7a):
IR (KBr): ν_{max} = 817, 1002, 1138, 1360, 1422, 1572, 1656, 2958, 3155, 3310 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 1.14 (s, 3H, 9–CH_3), 1.16 (s, 3H, 9–CH_3), 2.17 (s, 2H, 8–H), 2.35 (s, 3H, 15–CH_3), 2.66 (d, 1H, *J* = 16.0 Hz, 10–Ha), 2.79 (d, 1H, *J* = 16.8 Hz, 10–Hb), 5.89 (d, 1H, *J* = 5.2 Hz, 5–H), 6.15 (d, 1H, *J* = 4.8 Hz, 6–H), 6.57–7.54 (m, 12H, Ar–H), 9.01 (s, 1H, 11–H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ_C = 21.15, 28.54, 32.39, 44.61, 49.96, 52.63, 108.82, 120.91, 121.13, 122.75, 123.47, 125.16, 125.53, 126.61, 126.88, 127.86, 129.69, 129.89, 130.06, 131.62, 131.99, 134.53, 138.53, 143.02, 153.99, 156.44, 159.62, 192.61 ppm; Anal. Calcd for $C_{30}H_{28}N_4O_2$: C, 75.61; H, 5.92; N, 11.76; Found: C, 75.68; H, 5.95; N, 11.72

6-(6-Methyl-2-phenoxyquinolin-3-yl)-5,6,8,9,10,11-hexahydro-7Hpyrido[2,3-b][1,4]benzodiazepin-7-one (7b):
IR (KBr): ν_{max} = 790, 1012, 1145, 1358, 1438, 1580, 1645, 2975, 3202cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 2.10 (m, 2H, 3–H), 2.21 (m, 2H, 8–H), 2.37 (s, 3H, 15–CH_3),2.69 (m, 2H, 10–H), 5.80 (d, 1H, *J* = 5.2 Hz, 5–H), 6.21 (d, 1H, *J* = 4.8 Hz, 6–H), 6.70–7.64 (m, 12H, Ar–H), 8.92 (s, 1H, 11–H)ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ_C = 21.15, 32.40, 44.78, 50.02, 52.22, 108.82, 120.91, 121.13,122.88, 123.57, 125.26, 125.53, 126.61, 126.88, 127.86,129.69, 129.89, 130.06, 131.62, 131.99, 134.53, 138.80,143.25, 153.99, 156.44, 160.22, 193.08ppm; Anal. Calcd for $C_{28}H_{24}N_4O_2$: C, 74.98; H, 5.39; N, 12.49; Found: C, 74.91; H, 6.36; N, 12.52

6-(7-Chloro-2-phenoxyquinolin-3-yl)-9,9-dimethyl-8,9,10,11-tetrahydro-7H-pyrido[2,3-b][1,4]benzodiazepin-7-one (7c):
IR (KBr): ν_{max} = 756, 1140, 1336, 1392, 1523, 1631, 2940, 3239, 3315, 3439cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 1.17 (s, 3H, 9–CH_3), 1.19 (s, 3H, 9–CH3), 2.22 (s, 2H, 8–CH_2), 2.70 (d, 1H, J = 16.0 Hz, 10–Ha), 2.82 (d, 1H, *J* = 16.8Hz, 10–Hb), 5.84 (d, 1H, *J* = 5.2 Hz, 5–H), 6.07 (d, 1H, J =4.8 Hz, 6–H), 6.62–7.80 (m, 12H, Ar–H), 8.86 (s, 1H, 11–H)ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ_C = 28.85, 32.32, 44.71, 50.16, 52.85, 108.63, 120.87, 121.25, 122.86, 123.43, 125.34, 125.57, 126.57, 126.67, 127.84,129.78, 129.98, 130.75, 131.64, 132.21, 134.53, 138.53,143.02, 153.89, 156.87, 159.54, 193.18ppm; Anal. Calcd for $C_{29}H_{25}ClN_4O_2$: C, 70.08; H, 5.07; N, 11.27; Found: C, 69.00; H, 5.03; N, 11.31

6-(7-Chloro-2-phenoxyquinolin-3-yl)-5,6,8,9,10,11-hexahydro-7Hpyrido[2,3-b][1,4] benzodiazepin-7-one (7d):
IR (KBr): ν_{max} = 790, 1012, 1145, 1358, 1438, 1580, 1645, 2975, 3202cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 1.90 (m, 2H, 9–CH_2), 2.20 (s, 2H, 8–CH_2), 2.78 (m, 2H, 10– CH_2), 5.75 (d, 1H, *J* = 5.2 Hz, 5–H), 5.95 (d, 1H, *J* = 4.8 Hz, 6–H), 6.71–7.75 (m, 12H, Ar–H), 8.90 (s, 1H, 11–H)ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ_C = 32.40, 44.61, 50.12, 52.77, 108.23, 120.22, 121.55, 122.95, 123.50, 125.02, 125.78, 126.22, 126.85, 127.82, 129.78, 130.18, 130.75, 131.64, 134.22, 134.53, 138.53, 143.02, 153.89, 156.87, 159.68, 193.25ppm; Anal. Calcd for $C_{27}H_{21}N_4O_2$: C, 69.15; H, 4.51; N, 11.95; Found: C, 69.22; H, 4.48; N, 11.91.

6-(7-Methyltetrazolo[1,5-a]quinolin-4-yl)-9,9-dimethyl-5,6,8,9,10,11-hexahydro-7H-pyrido[2,3-b][1,4]benzodiazepin-7-one (7e):
IR (KBr): ν_{max} = 761, 980, 1175, 1310, 1385, 1580, 1645, 3220, 3340, 3510cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 1.21 (s, 3H, 9–CH_3), 1.25 (s, 3H, 9–CH_3), 2.32 (s, 2H, 8– CH_2), 2.45 (s, 3H, 15–CH_3), 2.79 (d, 1H, *J* = 16.0 Hz, 10–Ha), 2.85 (d, 1H, *J* = 16.8 Hz, 10–Hb), 5.98 (d, 1H, *J* = 5.0 Hz, 5–H), 6.33 (d, 1H, *J* = 4.4 Hz, 10–H), 6.34–8.36 (m, 7H, Ar–H), 8.88 (s, 1H, 11–H)ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ_C = 26.53, 28.88, 32.33, 42.92, 44.61, 54.08, 107.58, 115.02, 116.37, 118.60, 120.70, 121.10, 122.73, 123.30, 130.84, 131.59, 133.55, 134.46, 135.04, 138.45, 139.13, 156.27, 161.14, 192.76ppm; Anal. Calcd for $C_{24}H_{23}N_7O$: C, 67.75; H, 5.45; N, 23.04; Found: C, 67.70; H, 5.48; N, 23.00.

6-(7-Methyltetrazolo[1,5-a]quinolin-4-yl)-5,6,8,9,10,11-hexahydro-7H-pyrido[2,3-b][1,4]benzodiazepin-7-one (7f):
IR (KBr): ν_{max} = 770, 968, 1160, 1330, 1390, 1595, 1660, 2910, 3225, 3380, 3490 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 1.98 (m, 2H, 9–H), 2.28 (m, 2H, 8–H), 2.35 (S, 3–H, 15–CH_3), 2.72 (m, 2H, 10–H), 5.64 (d, 1H, *J* = 5.2 Hz, 5–H), 5.76 (d, 1H, *J* = 5.0 Hz, 6–H), 6.52–7.34 (m, 7H, Ar–H), 8.94 (s, 1H, 11–H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ_C = 21.02, 22.11, 31.33, 36.62, 58.19, 117.92, 120.65, 122.25, 123.15, 123.63, 123.99, 127.50, 128.05, 129.28, 136.55, 136.48, 138.82, 147.79, 158.91, 193.22 ppm; Anal. Calcd for $C_{22}H_{19}N_7O$: C, 66.49; H, 4.82; N, 24.67; Found: C, 66.55; H, 4.85; N, 24.63.

6-(8-Chlorotetrazolo[1,5-a]quinolin-4-yl)-9,9-dimethyl-5,6,8,9,10,11-hexahydro-7H-pyrido[2,3-b][1,4]benzodiazepin-7-one (7g):
IR (KBr): ν_{max} = 761, 980, 1175, 1310, 1385, 1580, 1645, 2917, 3220, 3340, 3510cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 1.15 (s, 3H, 9–CH_3), 1.18 (s, 3H, 9–CH_3), 2.18 (s, 2H, 8–CH_2), 2.63 (d, 1H, *J* = 16.0 Hz, 10–Ha), 2.92 (d, 1H, *J* = 16.4 Hz, 10– Hb), 5.98 (d, 1H, *J* = 5.0 Hz, 5–H), 6.02 (d, 1H, *J* = 5.2 Hz, 6–H), 6.81–7.57 (m, 7H, Ar–H), 9.82 (s, 1H, 11–H)ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ_C = 28.85, 32.32, 44.71, 44.88, 50.16, 52.85, 106.08, 120.87, 121.25, 122.86, 125.57, 127.84, 128.22, 129.78, 129.98, 130.70, 131.64, 134.53, 138.53, 139.58, 153.89, 159.54, 193.18ppm; Anal. Calcd for $C_{23}H_{20}ClN_7O$: C, 61.95; H, 4.52; N, 21.99; Found: C, 61.99; H, 4.49; N, 22.03.

6-(8-Chlorotetrazolo[1,5-a]quinolin-4-yl)-5,6,8,9,10,11-hexahydro-7Hpyrido[2,3-b][1,4] benzodiazepin-7-one (7h):
IR (KBr): ν_{max} = 780, 915, 1181, 1330, 1393, 1588, 1638, 2830, 3240, 3340cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 1.18 (s, 2H, 9–H), 2.22 (m, 2H, 8–CH_2), 2.80 (m, 2H, 10–H), 5.62 (d, 1H, *J* = 5.4 Hz, 5–H), 5.95 (d, 1H, *J* = 5.2 Hz, 6–H), 6.75–7.82 (m, 7H, Ar–H), 9.62 (s, 1H, 11–H)ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ_C = 44.88, 45.08, 50.25, 52.90, 106.18, 120.77, 121.35, 123.02. 125.57, 127.72, 128.28, 129.83, 130.10, 130.65, 131.78, 134.45, 138.85, 139.58, 153.95, 159.22, 193.45ppm; Anal. Calcd for $C_{21}H_{16}ClN_7O$: C, 60.36; H, 3.86; N, 23.46; Found: C, 60.40; H, 3.83; N, 23.40.

6-(1-Allyl-6-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-9,9-dimethyl-5,6,8,9,10,11-hexahydro-7H-pyrido[2,3-b][1,4]benzodiazepin-7-one (7i):
IR (KBr): ν_{max} = 787, 933, 1116, 1285, 1392, 1444, 1519, 1572, 1607, 1653, 2917, 2975, 3051, 3215, 3368cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 1.12 (s, 3H, 9–CH_3), 1.15 (s, 3H, 9–CH_3), 2.120 (s, 2H, 8–H), 2.26 (s, 3H, 15–CH_3), 2.61 (d, 1H, *J* = 16.0 Hz, 10–Ha), 2.75 (d, 1H, *J* = 16.0 Hz, 10–Hb), 4.71 (m, 2H, 22–H), 5.02 (m, 2H, 20–H), 5.57 (d, 1H, J = 5.2 Hz, 5–H), 5.78 (d, 1H, J = 5.2 Hz, 6–H), 5.88 (s, 1H, 21–H), 6.43–7.84 (m, 7H, Ar–H), 8.92 (s, 1H, 11–H)ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ_C = 20.34, 20.38, 28.24, 28.68, 28.84, 32.31, 44.15, 44.61, 49.97, 54.17, 107.80, 115.18, 119.72, 120.48, 120.99, 123.24, 128.73, 131.51, 131.61, 132.73, 133.72, 133.95, 136.26, 138.52, 156.16, 161.14, 192.74ppm; Anal. Calcd for $C_{27}H_{28}N_4O_2$: C, 73.61; H, 6.41; N, 12.72; Found: C, 73.50; H, 6.45; N, 12.69.

6-(1-Allyl-6-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-5,6,8,9,10,11-hexahydro-7H-pyrido[2,3-b][1,4]benzodiazepin-7-one (7j):
IR (KBr): ν_{max} = 782, 940, 1126, 1278, 1395, 1444, 1580, 1653, 2895, 2975, 3051, 3210cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 2.18 (m, 2H, 9–H), 2.21 (m, 2H, 8–H), 2.30 (s, 3H, 15–CH_3), 2.68 (m, 2H, 10–H), 4.75 (m, 2H, 22–H), 5.52 (m, 2H, 20–H), 5.52 (d, 1H, *J* = 5.2 Hz, 5–H), 5.92 (d, 1H, *J* = 4.8 Hz, 6–H), 6.03 (s, 1H, 21–H), 6.82–7.75 (m, 7H, Ar–H), 9.52 (s, 1H, 11– H)ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ_C = 20.34, 28.75, 28.95, 32.22, 44.88, 44.98, 50.07, 54.53, 107.65, 115.25, 119.85, 120.77, 121.10, 123.35, 128.73, 131.51, 131.61, 132.73, 133.72, 133.90, 136.53, 138.22, 156.88, 161.22, 192.80ppm; Anal. Calcd for $C_{25}H_{24}N_4O_2$: C, 72.60; H, 5.86; N, 13.55; Found: C, 72.80; H, 5.86; N, 13.58.

5-Allyl-6-(6-methyl-2-phenoxyquinolin-3-yl)-9,9-dimethyl-5,6,8,9,10,11-hexahydro-7H-pyrido[2,3-b][1,4]benzodiazepin-7-one (8a):
IR (KBr): ν_{max} = 780, 850, 980, 1085, 1368, 1450, 1588, 1645, 2940, 3210cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 1.12 (s, 3H, 9–CH_3), 1.15 (s, 3H, 9–CH_3), 2.25 (s, 2H, 8–H), 2.45 (s, 3H, 15–CH_3), 2.65 (d, 1H, *J* = 16.0 Hz, 10–Ha), 2.72 (d, 1H, *J* = 16.0 Hz, 10–Hb), 3.89 (m, 2H, 22–H), 5.13 (d, 1H, *J* = 10 Hz, 20–Ha), 5.29 (d, 1H, *J* = 16.4 Hz, 20–Hb), 5.78 (m, 1H, 21–H), 6.05 (s, 1H, 6–H), 6.70–7.82 (m, 12H, Ar–H), 8.89 (s, 1H, 11–H)ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ_C = 20.35, 28.56, 28.74, 32.68, 44.52, 51.04, 56.51, 56.54, 109.49, 117.36, 120.70, 122.16, 123.01, 123.72, 125.12, 125.45, 126.54, 126.74, 127.62, 130.18, 131.70, 134.54, 136.68, 136.81, 136.87, 140.94, 143.22, 154.38, 156.31, 159.87, 192.50ppm; Anal. Calcd for $C_{33}H_{32}N_4O_2$: C, 76.72; H, 6.24; N, 10.84; Found: C, 76.65; H, 6.28; N, 10.87.

5-Allyl-6-(6-methyl-2-phenoxyquinolin-3-yl)-5,6,8,9,10,11-hexahydro- 7H-pyrido[2,3-b][1,4]benzodiazepin-7-one (8b):
IR (KBr): ν_{max} = 748, 921, 1196, 1329, 1390, 1501, 1530, 1582, 1614, 2923, 3147, 3311cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 1.74 (m, 2H, 9–H), 2.10 (m, 2H, 8–H), 2.34 (s, 3H, 15–CH_3), 2.62 (m, 2H, 10–H), 3.97 (m, 2H, 22–H), 5.06 (d, 1H, *J* = 10 Hz, 20–Ha), 5.19 (d, 1H, *J* = 16.8 Hz, 20–Hb), 5.80 (m, 1H, 21– H), 6.20 (s, 1H, 6–H), 6.67–7.52 (m, 12H, Ar–H), 9.00 (s, 1H, 11–H)ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ_C = 22.15, 32.47, 44.40, 50.04, 56.51, 56.54, 109.49, 117.36, 120.68, 122.16, 123.01, 123.72, 124.91, 125.52, 126.56, 126.74, 127.59, 130.05, 131.70, 134.43, 136.68, 136.81, 136.87, 139.94, 142.96, 154.38, 156.11, 159.76, 192.68ppm; Anal. Calcd for $C_{31}H_{28}N_4O_2$: C, 76.21; H, 5.78; N, 11.47; Found: C, 76.15; H, 5.82; N, 11.50.

5-Allyl-6-(7-chloro-2-phenoxyquinolin-3-yl)-9,9-dimethyl-5,6,8,9, 10,11-hexahydro-7H-pyrido[2,3-b][1,4]benzodiazepin-7-one (8c):
IR (KBr): ν_{max} = 770, 890, 1080, 1140, 1345, 1480, 1545, 1650, 2890, 3080, 3250, 3340cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 1.21 (s, 3H, 9–CH_3), 1.28 (s, 3H, 9–CH_3), 2.32 (s, 2H, 8–H), 2.75 (d, 1H, *J* = 16.0 Hz, 10–Ha), 2.85 (d, 1H, *J* = 16.0 Hz, 10– Hb), 3.50 (m, 2H, 22–H), 5.18 (d, 1H, *J* = 10 Hz, 20–Ha), 5.31 (d, 1H, *J* = 16.4 Hz, 20–Hb), 5.75 (m, 1H, 21–H), 6.10 (s, 1H, 6–H), 6.75–7.71 (m, 12H, Ar–H), 8.98 (s, 1H, 11–H)ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ_C = 27.99, 28.83, 32.70, 44.52, 51.16, 56.51, 57.14, 109.57, 114.45, 120.73, 122.25, 123.11, 123.72, 125.22, 125.45, 126.43, 126.74, 127.56, 130.18, 131.70, 134.54, 136.68, 136.81, 136.87, 141.04, 143.22, 154.38, 156.31, 159.68, 192.74ppm; Anal. Calcd for $C_{32}H_{29}ClN_4O_2$: C, 71.57; H, 5.44; N, 10.43; Found: C, 71.52; H, 5.47; N, 10.39.

5-Allyl-6-(7-chloro-2-phenoxyquinolin-3-yl)-5,6,8,9,10,11-hexahydro- 7H-pyrido[2,3-b][1,4]benzodiazepin-7-one (8d):
IR (KBr): ν_{max} = 780, 960, 1055, 1178, 1350, 1410, 1560, 1640, 2896, 3250, 3455cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 1.362.59 (m, 6H, 8, 9 & 10–H), 3.88 (m, 2H, 22–H), 5.15 (d, 1H, *J* = 10 Hz, 20–Ha), 5.22 (d, 1H, *J* = 16.8 Hz, 20–Hb), 5.98 (m, 1H, 21–H), 6.15 (s, 1H, 6–H), 6.62–7.45 (m, 12H, Ar–H), 9.05 (s, 1H, 11–H)ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ_C = 32.58, 44.38, 51.26, 56.65, 57.04, 109.70, 117.34, 120.83, 122.21, 123.31, 123.72, 125.22, 125.45, 126.56, 126.74, 127.43, 130.08, 131.81, 134.40, 136.54, 136.68, 136.87, 141.22, 143.31, 154.38, 156.26, 159.68, 193.68ppm; Anal. Calcd for $C_{30}H_{25}ClN_4O_2$: C, 70.79; H, 4.95; N, 11.01; Found: C, 70.82; H, 4.98; N, 11.05.

5-Allyl-6-(7-methyltetrazolo[1,5-a]quinolin-4-yl)-9,9-dimethyl-5,6,8,9,10,11-hexahydro-7H-pyrido[2,3-b][1,4]benzodiazepin-7-one (8e):
IR (KBr): ν_{max} = 766, 1046, 1393, 1469, 1576, 1660, 2890, 2956, 3217, 3480cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 11.07 (s, 3H, 9–CH_3), 1.12 (s, 3H, 9–CH_3), 2.07 (m, 2H, 8–H), 2.34 (s, 3H, 15–CH_3), 2.56 (d, 1H, *J* = 16.0 Hz, 10–Ha), 2.70 (d, 1H, *J* = 16.0 Hz, 10–Hb), 4.02 (m, 2H, 24–H), 5.08 (d, 1H, *J* = 10 Hz, 22–Ha), 5.28 (d, 1H, *J* = 16.4 Hz, 22–Hb), 5.78 (m, 1H, 23–H), 6.06 (s, 1H, 6–H), 6.53–7.38 (m, 7H, Ar–H), 8.86 (s, 1H, 11–H)ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ_C = 21.15, 27.81, 28.93, 32.45, 44.85, 50.40, 56.77, 58.14, 108.96, 116.14, 117.82, 120.77, 122.09, 122.99, 123.63, 123.83, 127.40, 127.97, 129.12, 129.25, 129.83, 136.24, 136.48, 138.41, 139.57, 158.73, 193.01ppm; Anal. Calcd for $C_{27}H_{27}N_7O$: C, 69.66; H, 5.85; N, 21.06; Found: C, 69.60; H, 5.88; N, 21.02.

5-Allyl-6-(7-methyltetrazolo[1,5-a]quinolin-4-yl)-5,6,8,9,10,11-hexahydro-7H-pyrido[2,3-b][1,4]benzodiazepin-7-one (8f):

IR (KBr): ν_{max} = 750, 990, 1080, 1355, 1425, 1588, 1655, 2890, 3150, 3250, 3388cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 1.25 (m, 2H, 9–H), 2.21 (m, 2H, 8–H), 2.44 (s, 3H, 15–CH_3), 2.66 (m, 2H, 10–H), 4.18 (m, 2H, 24–H), 5.22 (d, 1H, J = 10 Hz, 22–Ha), 5.30 (d, 1H, *J* = 16.4 Hz, 22–Hb), 5.80 (m, 1H, 23–H), 6.02 (s, 1H, 6–H), 6.62–7.75 (m, 7H, Ar–H), 8.98 (s, 1H, 11–H)ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ_C = 21.25, 32.21, 44.85, 50.48, 56.87, 58.14, 108.82, 116.22, 117.96, 120.63, 122.09, 122.83, 123.77, 124.12, 127.40, 127.97, 129.09, 129.25, 129.83, 136.24, 136.48, 138.57, 139.41, 158.73, 192.91ppm; Anal. Calcd for $C_{25}H_{23}N_7O$: C, 68.63; H, 5.30; N, 22.41; Found: C, 68.70; H, 5.35; N, 22.45.

5-Allyl-6-(8-chlorotetrazolo[1,5-a]quinolin-4-yl)-9,9-dimethyl-5,6,8,9,10,11-hexahydro-7H-pyrido[2,3-b][1,4]benzodiazepin-7-one (8g):

IR (KBr): ν_{max} = 810, 978, 1090, 1158, 1345, 1396, 1568, 1660, 2840, 3025, 3180, 3355cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 1.12 (s, 3H, 9–CH_3), 1.18 (s, 3H, 9–CH_3), 2.21 (m, 2H, 8–H), 2.65 (d, 1H, *J* = 16.0 Hz, 10–Ha), 2.78 (d, 1H, *J* = 16.0 Hz, 10– Hb), 4.12 (m, 2H, 24–H), 5.18 (d, 1H, *J* = 10 Hz, 22–Ha), 5.32 (d, 1H, *J* = 16.4 Hz, 22–Hb), 5.80 (m, 1H, 23–H), 6.12 (s, 1H, 6–H), 6.65–7.49 (m, 7H, Ar–H), 9.02 (s, 1H, 11–H)ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ_C = 27.45, 28.32, 32.28, 44.77, 50.56, 56.83, 58.04, 109.06, 116.22, 117.72, 120.97, 122.19, 122.83, 123.63, 123.97, 127.40, 127.58, 129.12, 129.25, 129.83, 136.29, 136.48, 138.57, 139.48, 158.29, 192.71ppm; Anal. Calcd for $C_{26}H_{24}ClN_7O$: C, 64.26; H, 4.98; N, 20.18; Found: C, 64.23; H, 5.01; N, 20.13.

5-Allyl-6-(8-chlorotetrazolo[1,5-a]quinolin-4-yl)-5,6,8,9,10,11-hexahydro-7H-pyrido[2,3-b][1,4]benzodiazepin-7-one (8h):

IR (KBr): ν_{max} = 750, 935, 1150, 1345, 1408, 1590, 1658, 2912, 3150, 3330cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 1.21 (m, 2H, 9–H), 2.05 (m, 2H, 8–H), 2.65 (m, 2H, 10–H), 4.25 (m, 2H, 24–H), 5.28 (d, 1H, *J* = 10 Hz, 22–Ha), 5.36 (d, 1H, *J* = 16.4 Hz, 22–Hb), 5.89 (m, 1H, 23–H), 6.07 (s, 1H, 6– H), 6.65–7.82 (m, 7H, Ar–H), 8.89 (s, 1H, 11–H)ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ_C = 30.54, 42.85, 44.65, 54.28, 107.69, 115.42, 116.81, 118.78, 120.85, 121.67, 122.69, 123.72, 130.35, 131.65, 133.88, 134.66, 135.25, 139.15, 139.65, 156.84, 161.73, 192.59ppm; Anal. Calcd for $C_{24}H_{20}ClN_7O$: C, 62.95; H, 4.40; N, 21.41; Found: C, 62.89; H, 4.42; N, 21.39.

5-Allyl-6-(1-allyl-6-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-9,9-dimethyl-5,6,8,9,10,11-hexahydro-7H-pyrido[2,3-b][1,4] benzodiazepin-7-one (8i):

IR (KBr): ν_{max} = 772, 950, 1090, 1278, 1389, 1450, 1526, 1580, 1653, 2918, 3055, 3240cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 1.11 (s, 3H, 9–CH_3), 1.31 (s, 3H, 9–CH_3), 2.12 (s, 2H, 8–H), 2.29 (s, 3H, 15–CH_3), 2.55 (d, 1H, *J* = 16.0 Hz, 10a–H), 2.72 (d, 1H, *J* = 15.6 Hz, 10b–H),4.03 (m, 2H, 22–H), 4.67 (m, 2H, 25–H), 4.96 (m, 4H, 20 & 23–H), 5.73 (m, 2H, 21 & 24–H), 5.93 (s, 1H, 6–H), 6.52–7.24 (m, 7H, Ar–H), 8.89 (s, 1H, 11– H)ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ_C = 20.34, 27.93, 28.94, 32.44, 44.15, 44.35, 50.02, 56.40, 57.23, 109.66, 114.93, 116.05, 116.75, 119.77, 120.40, 121.25, 122.16, 123.48, 131.22, 131.37, 132.98, 133.85, 134.72, 135.95, 136.28, 137.13, 140.48, 156.36, 161.22, 192.17ppm; Anal. Calcd for $C_{30}H_{32}N_4O_2$: C,74.97; H, 6.71; N, 11.66; Found: C, 75.05; H, 6. 68; N, 11.62.

5-Allyl-6-(1-allyl-6-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-5,6,8,9,10,11-hexahydro-7H-pyrido[2,3-b][1,4]benzodiazepin-7-one (8j):

IR (KBr): ν_{max} = 755, 921, 1027, 1147, 1222, 1362, 1466, 1530, 1576, 1642, 1959, 3186, 323, 3373cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 1.99–2.25 (m, 4H, 8 & 9–CH2), 2.29 (s, 3H, 15–CH3), 2.68 (m, 2H, 10–CH2), 4.03 (m, 2H, 22–H), 4.67 (m, 2H, 25–H), 4.96 (m, 4H, 20 & 23–H), 5.73 (m, 2H, 21 & 24–H), 5.93 (s, 1H, 6–H), 6.52–7.24 (m, 7H, Ar–H), 8.89 (s, 1H, 5–H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ_C = 20.35, 22.02, 31.08, 36.57, 44.11, 57.72, 110.73, 115.96, 116.88, 119.82, 120.39, 121.01, 122.07, 123.37, 128.65, 131.08, 131.32, 132.98, 133.64, 134.71, 134.88, 135.77, 136.26, 137.14, 140.36, 158.37, 161.28, 192.53 ppm; Anal. Calcd for C28H28N4O2: C, 74.31; H, 6.24; N, 12.38; Found: C, 74.39; H, 6.28; N, 12.42

Acknowledgements

We express our thanks to the Head, Department of Chemistry, S. P. University for providing required research facilities. We (HAB, TRS & GCB) are grateful to the UGC, New Delhi for financial support under the UGC schemes; RFSMS and the UGC-CAS program.

Notes and references

1 H. Tucker and D. J. Le Count, In Comprehensive Heterocyclic Chemistry II; A. R. Katritzky, C. W. Rees and E. F. V. Scriven, Eds.; Pergamon Press, 1996; pp 151–182.

2 a) A. Kondaskar, S. Kondaskar, J. C. Fishbein, B. A. Carter-Cooper, R. G. Lapidus, M. Sadowska, M. J. Edelman and R. S. Hosmane, *Bioorg. Med. Chem.*, 2013, **21**, 618; b) B. Insuasty, J. Ramírez, D. Becerra, C. Echeverry, J. Quiroga, R. Abonia, S. M. Robledo, I. Darío Velez, Y. Upegui, J. A. Munoz, V. Ospina, M. Nogueras and J. Cobo, *Eur. J. Med. Chem.,* 2015, **93**, 401; c) J. Ramírez, L. Svetaz, J. Quiroga, R. Abonia, M. Raimondi, S. Zacchino and B. Insuasty, *Eur. J. Med. Chem.,* 2015, **92**, 866; d) H. I. El-Subbagha, G. S. Hassanb, A. S. El-Azabb, A. A.-M. Abdel-Azizb, A. A. Kadib, A. M. Al-Obaid, O. A. Al-Shabanah and M. M. Sayed-Ahmed, *Eur. J. Med. Chem.,* 2011, **46**, 5567; e) T. Kaneko, H. Wong, T. W. Doyle, W. C. Rose and W. T. Bradner, *J. Med. Chem.* 1985, **28**, 388; f) V. Lisowski, F. Fabis, A. Pierre, D. H. Caignard, P. Renard and S. J. Rault, *Enzyme Inhib. Med. Chem.,* 2002, **17**, 403; g) J. J. Wang, Y. K. Shen, W. P. Hu, M. C. Hsieh, F. L. Lin, M. K. Hsu and M. H. Hsu, *J. Med. Chem.,* 2006, **49**, 1442; h) M. Kidwai, V. Bansal, P. Mothsra, *J. Mol. Catal. A – Chem.,* 2007, **26**, 643–46; i) M. K. Hussain, M. I. Ansari, R. Kant and K. Hajela, *Org. Lett.* 2014, **16**, 560.

3 a) S. C. Dulawa and R. Hen, *Neurosci. Biobehav. Rev.*, 2005, **29**, 771; b) T. Inada, S. Nozaki, A. Inagaki and T. A. Furukawa, Hum. *Psychopharmacol. Clin. Exp.*, 2003, **18**, 483.

4 a) W. Nawrocka, B. Sztuba, A. Opolski, J. Wietrzyk, M. W. Kowalska and T. Głowiak, *Part II Arch. Pharm. Pharm. Med. Chem.*, 2001, **334**, 3; b) S. Miyanaga, H. Sakurai, I. Saiki, H. Onaka and Y. Igarashi, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 963.

5 J. K. Chakrabarti, L. Horsman, T. M. Hotten, I. A. Pullar, D. E. Tupper and F. C. Wright, *J. Med. Chem.,* 1980, **23**, 878; *Drugs Future*, 1983, **8**, 110.

6 a) F. Savelli, A. Boido, I. Vazzana and F. Sparatore, *J. Heterocycl. Chem.*, 1987, **24**, 1709; b) F. Savelli, A. Boido, M. Satta, A. Peana and C. Marzano, *Farmaco*, 1994, **49**, 259; c) F. Savelli, A. Boido and G. Damonte, *J. Heterocycl. Chem.,* 1996, **33**, 1737.

7 D. A. Horton, G. T. Bourne and M. L. Smythe, *Chem. Rev.* 2003, **103**, 893.

8 B. H. Jaup and G. Dotevall, *Scand. J. Gastroenterol.,* 1981, **16**, 769.

9 a) N. F. Muller and R. P. Dessing, European Society of Clinical Pharmacy. European Drug Index, 1997, Volume 33; b) D. J. Triggle, Dictionary of Pharmacological Agents. Boca Raton: Chapman & Hall/CRC. 1996, p. 1680; c) W. J. Kinnier, R. D. Tabor and L. Y. Norrell, *Biochem. Pharmacol.,* 1984, **33**, 3001.

10 a) W. E. Eberlein, W. W. Engel, G. Trummlitz, G. Schmidt and R. Hammer, *J. Med. Chem.* 1988, **31**, 1169; b) W. G. Eberlein, G. Trummlitz, W. W. Engel, G. Schmidt, H. Pelzer and N. Mayer, *J. Med. Chem.*, 1987, **30**, 1378; c) W. W. Engel, W. G. Eberlein, G. Mihm, R. Hammer and G. Trummlitz, *J. Med. Chem.*, 1989, **32**, 1718.

11 a) J. F. LiBgeois, J. Bruhwyler, J. Damas, T. P. Nguyea, M. G. Eric, C. M. Mercier, F. A. Register and J. E. Delarget, *J. Med. Chem.,*

1993, **36**, 2107; b) J. F. Liegeois, L. Eyrolles, B. A. Ellenbroek, C. Lejeune, P. Carato, J. Bruhwyler, J. Geczy, J. Damas and J. Delarge, *J. Med. Chem.,* 2002, **45**, 5136.

12 a) A. A. Failli, J. S. Shumsky, R. J. Steffan, T. J. Caggiano, D. K. Williams, E. J. Trybulski, X. Ning, Y. Lock, T. Tanikella, D. Hartmann, P. S. Chan and C. H. Park, *Bioorg. Med. Chem. Lett.* 2006, **16**, 954; b) A. A. Failli, J. S. Shumsky and R. J. Steffan, U.S. Patent 6,194,407, July 24, 1998.

13 P. Liu, Jr. T. J. Lanza, M. Chioda, C. Jones, H. R. Chobanian, Y. Guo, L. Chang, T. M. Kelly, Y. Kan, O. Palyha, X. Guan, D. J. Marsh, J. M. Metzger, K. Ramsay, S. Wang, A. M. Strack, R. Miller, J. Pang, K. Lyons, J. Dragovic, J. G. Ning, W. A. Schafer, C. J. Gong, X. Welch, Y. Gao, V. Hornak, R. G. Ball, N. Tsou, M. L. Reitman, M. J. Wyvratt, R. P. Nargund and L. S. Lin, *ACS Med. Chem. Lett.* 2011, **2**, 933.

14 H. R. Chobanian, Y. Guo, P. Liu, M. Chioda, Jr. T. J. Lanza, L. Chang, T. M. Kelly, Y. Kan, O. Palyha, X. Guan, D. J. Marsh, J. M. Metzger, J. N. Gorski, K. Raustad, S. Wang, A. M. Strack, R. Miller, J. Pang, M. Madeira, K. Lyons, J. Dragovic, M. L. Reitman, R. P. Nargund and L. S. Lin, *ACS Med. Chem. Lett.,* 2012, 3, 252.

15 N. N. Tonkikh, A. Strakovs and M. V. Petrova, *Chem. Heterocycl. Compd.* 2004, **40**, 944.

16 a) D. McGowan, O. Nyanguile, M.D. Cummings, S. Vendeville, K. Vandyck, W. V. den Broeck, C.W. Boutton, H. D. Bondt, L. Quirynen, K. Amssoms, J.F. Bonfanti, S. Last, K. Rombauts, A. Tahri, L. Hu, F. Delouvroy, K. Vermeiren, G. Vandercruyssen, L. V. der Helm, E. Cleiren, W. Mostmans, P. Lory, G. Pille, K. V. Emelen, G. Fanning, F. Pauwels, TI. Lin, K. Simmen and P. Raboisson, *Bioorg. Med. Chem. Lett.* 2009, **19**, 2492; b) E. C. Cortes, M. A. Banos and O. G. Cortes, *J. Heterocycl. Chem.*, 2004, **41**, 277; c) N. N. Kolos, E. N. Yurchenko, V. D. Orlov, S. V. Shishkina and O. V. Shishkin, Chem. Heterocycl. Compd. 2004, 40, 1550.

17 N. J. Parmar, H. A. Barad, B. R. Pansuriya, S. B. Teraiya, V. K. Gupta and R. Kant, *Bioorg. Med. Chem. Lett.* 2012, **22**, 3816.

18 A. Srivastava and R. M. Singh, *Indian J. Chem.* 2005, **44B**, 1868.

19 a) M. Y. Onysko and V. G. Lendel, *Chem. Heterocycl. Compd.,* 2007, 43, 1020; b) K. K. Park and J. J. Lee, *Tetrahedron*, 2004, **60**, 2993.

20 a) E. Cortes, O. Collera, P. Mufioz and E. Diaz, *Spectrochim. Acta, Part A*, 1997, **53**, 1825; b) N. Rashed, M. Sayed and E. S. H. El Ashry, *J. Chin. Chem. Soc.* 1993, **40**, 189; c) A. Guidi, T. Dimoulas, D. Gianotti and N. Harmat, *Patentdocs* 20080275023, 2008.

21 P. O Miranda, J. M. Padrón, J. I. Padrón, J. Villar and V. S. Martín, *ChemMedChem*, 2006, **1**, 323.

22 a) B. L. Grasberger, T. Lu, C. Schubert, D. J. Parks, T. E. Carver, H. K. Koblish, M. D. Cummings, L. V. LaFrance, K. L. Milkiewicz, R. R. Calvo, D. Maguire, J. Lattanze, C. F. Franks, S. Zhao, K. Ramachandren, G. R. Bylebyl, M. Zhang, C. L. Manthey, E. C. Petrella, M. W. Pantoliano, I. C. Deckman, J. C. Spurlino, A. C. Maroney, B. E. Tomczuk, C. J. Molloy and R. F. Bone, *J. Med. Chem.* 2005, **48**, 909; b) D. J. Parks, L. V. LaFrance, R. R. Calvo, K. L. Milkiewicz, V. Gupta, J. Lattanze, K. Ramachandren, T. E. Carver, E. C. Petrella, M. D. Cummings, D. Maguire, B. L. Grasberger and T. Lu, *Bioorg. Med. Chem. Lett.,* 2005, **15**, 765; c) D. J. Parks, L. V. LaFrance, R. R. Calvo, K. L. Milkiewicz, J. J. Marugán, P. Raboisson, C. Schubert, H. K. Koblish, S. Zhao, C. F. Franks, J. Lattanze, T. E. Carver, M. D. Cummings, D. Maguire, B. L. Grasberger, A. C. Maroney and T. Lu, *Bioorg. Med. Chem. Lett.,* 2006, **16**, 3310; d) H. K. Koblish, S. Zhao, C. F. Franks, R. R. Donatelli, R. M. Tominovich, L. V. LaFrance, K. A. Leonard, J. M. Gushue, D. J. Parks, R. R. Calvo, K. L. Milkiewicz, J. J. Marugán, P. Raboisson, M. D. Cummings, B. L. Grasberger, D. L. Johnson, T. Lu, C. J. Molloy and Anna C. Maroney, *Mol. Cancer Ther.* 2006, **5**, 160; e) K. Leonard, J. J. Marugan, P. Raboisson, R. Calvo, J. M. Gushue, H. K. Koblish, J. Lattanze, S. Zhao, M. D. Cummings, M. R. Player, A. C. Maroney, T. Lu, *Bioorg. Med. Chem. Lett.,* 2006, **16**, 3463.

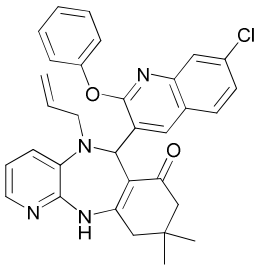
23 Maestro 9.0 version Schrodinger, LLC, New York, NY, USA.

24 www.rcsb.org (assessed on 20.10.2015)

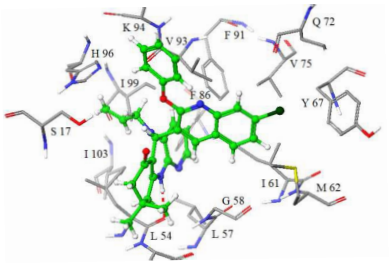
25 S. DasGupta, P. R. Murumkar, R. Giridhar, M. R. Yadav, *Bioorg. Med. Chem*., 2009, **17**, 3604.

26. P. R. Murumkar, M. K. Sharma, R. Giridhar, M. R. Yadav, *Med. Chem. Res., 2015,* **24,** 226.

A series of 20 benzodiazepinones resembling MDM2 inhibitors was synthesized. The antiproliferative activity of these compounds was studied.



Leader, 8c



Binding modes of 8c docked in the active site of MDM2

Cell line	HeLa(cervix)	T-47D(breast)	WiDr(colon)
Leader	**3.8 (±0.3)**	**5.8 (±0.6)**	**5.5 (±1.0)**
Cisplatin	**2.0 (±0.3)**	**15 (±2.3)**	**26 (±5.3)**
Etoposide	**3.3 (±1.6)**	**22 (±5.5)**	**23 (±3.1)**