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Syntheses and anti-cancer activities of 2-[1-(indol-3-yl-/pyrimidin-5-yl-/pyridine-2-yl-/quinolin-2-yl)-but-3-enylamino]-2-phenyl-ethanols

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Abstract—Schiff bases prepared by the reactions of substituted amines with indole-/, pyrimidine-/, pyridine-/, and quinoline-aldehydes are made to undergo indium mediated allylation whereby a (substituted amine, allyl)methyl group has been introduced at C-3 of indole, C-5 of pyrimidine, and C-2 of pyridine and quinoline. Amongst the 16 compounds investigated for anti-cancer activities at 59 human tumor cell lines **3**, **9**–**12**, and **14** show appreciable activities. The structure–activity relationship studies point that the contribution of phenylglycinol moiety as a part of side chain at C-3 of indole and C-5 of pyrimidine seems to be crucial for exhibiting anti-cancer activities.

1. Introduction

The uncontrolled growth of cells in the body, started due to certain stimuli, lays the foundation of cancer and the complete process of cell multiplication is mediated by various enzymes, some of which have been identified.[1] A large number of anti-cancer compounds available in the NIH database have been classified in accordance with their mechanism of action (target sites).[2] Still the difficulty to diagnose the disease at the early stage, narrow therapeutic indices of anti-cancer compounds, and the problem of multidrug resistance[3] are some of the major hurdles in the successful practice of chemotherapy for cancer.

Heterocycles like indole, pyrimidine, pyridine, quinoline, etc. are an integral part of a huge number of natural and synthetic compounds and play important roles in the biological systems.[4] The structural features of multiple target drugs,[5] which are proven to be more effective and economical, demand the presence of various ligating sites along with the presence of hydrophobic moieties in the molecule. In continuation of our efforts[6] for developing the suitable leads for anti-cancer drugs, in the present contribution, following simple synthetic methodology, we have introduced appropriate substituent at C-3 of indole, C-5 of pyrimidine, and C-2 of pyridine and quinoline. The substituent carries nitrogen and oxygen as two ligating sites along with hydrophobic moieties, the essential requirement for multiple target ligands. The pre-screening of these compounds for their anti-cancer activities at three cell lines was followed by the detailed investigations of selected compounds at 59 human tumor cell lines. Some of these compounds show appreciable anti-cancer activities and it is remarkable that the presence of phenyl glycinol on the side-chain nitrogen of indole and pyrimidine significantly enhances their anti-cancer activities.

2. Chemistry

The imines derived from pyridine-/, pyrimidine-/, indole-aldehydes and appropriate amines on allylation provide a facile route to homoallylic amines.[7] A similar synthetic methodology has been adopted here to procure the

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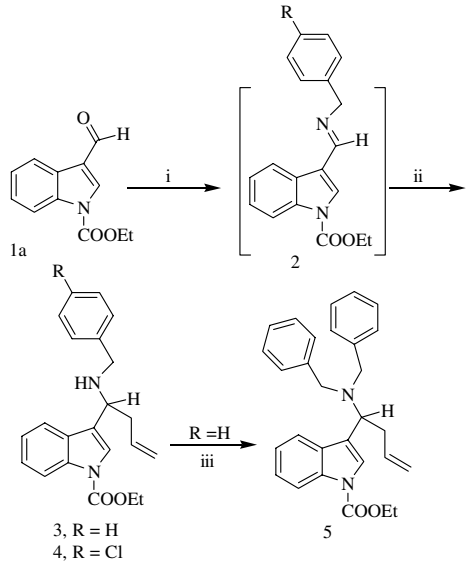
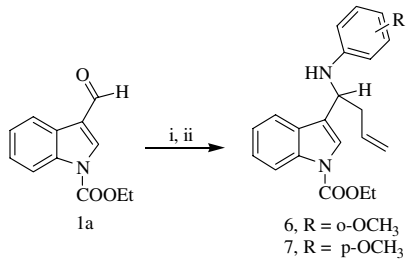


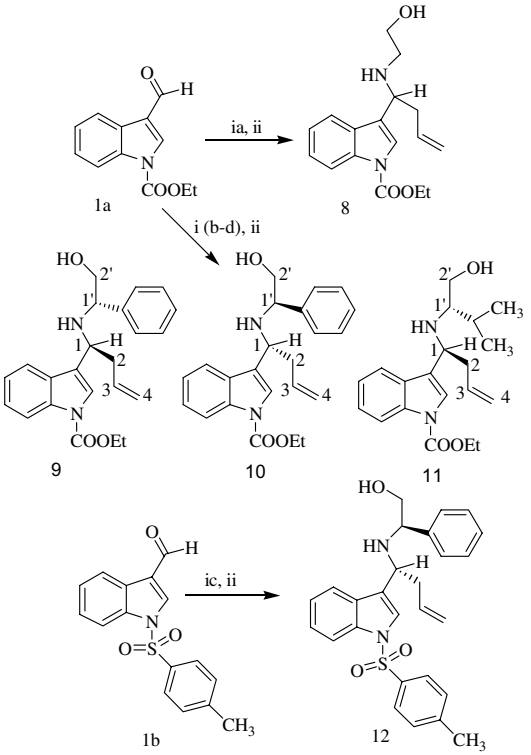
Scheme 1. Reagents and conditions: (i) benzyl-/*p*-Cl-benzyl amine, dry THF, $MgSO_4$, stir, rt; (ii) pre-generated In2(allyl)3Br3, THF/Toluene (1:2), 27 °C; (iii) benzyl chloride, CH_3CN, K_2CO_3, TBA HSO_4, reflux.

desired compounds carrying suitable fragments at the carbon and nitrogen of C=N of imine. 3-Formyl-indole-1-carboxylic acid ethyl ester (**1a**)[8] after reaction with benzyl amine over anhydrous $MgSO_4$ in dry THF was treated with pre-generated $In_2(allyl)_3Br_3$ reagent in THF/Toluene (1:2) to get a thick liquid 83%, [M^+ *m/z* 348] which from its NMR spectral data has been assigned structure **3** (Scheme 1). This reaction (in consonance with three-component reaction) has been proceeded through the initial formation of Schiff base **2** which readily undergoes allylation at C=N to provide compound **3**. Similarly, **1a** on reaction with *p*-chlorobenzyl amine followed by treatment with pre-generated $In_2(allyl)_3Br_3$ reagent provided compound **4**. Reaction of **3** with benzyl chloride under phase transfer catalytic conditions gave compound **5** (Scheme 1).

Under the same reaction conditions as followed for the formation of compound **3**, the reactions of **1a** with *o*-anisidine and *p*-anisidine gave compounds **6** and **7**, respectively (Scheme 2).



Scheme 2. Reagents and conditions: (i) *o*-/*p*-anisidine, dry THF, $MgSO_4$, stir, rt; (ii) pre-generated $In_2(allyl)_3Br_3$, THF/Toluene (1:2), 27 °C.

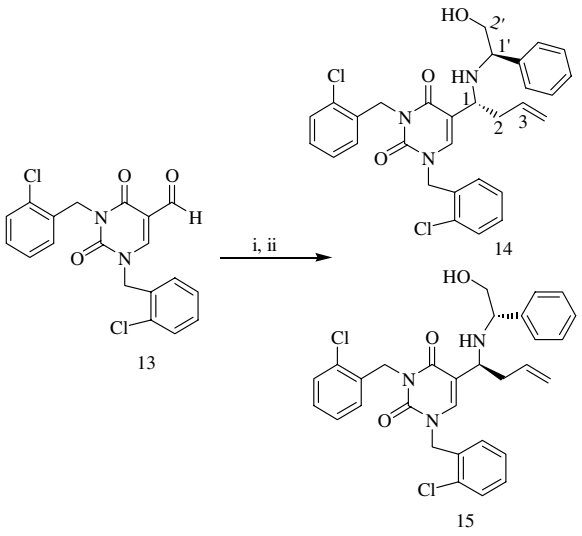


Scheme 3. Reagents and conditions: (i) dry THF, $MgSO_4$, stir, rt; a—2-aminoethanol (for **8**); b—(*S*)-2-phenylglycinol (for **9**); c—(*R*)-2-phenylglycinol (for **10** and **12**); d—(*S*)-2-amino-3-methylbutanol-1 (for **11**); (ii) pre-generated $In_2(allyl)_3Br_3$, THF/Toluene (1:2), 27 °C.

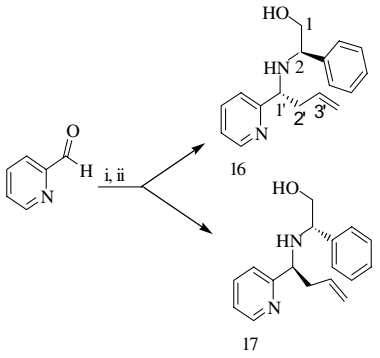
Similarly, the reactions of **1a** with 2-aminoethanol, (*S*)-2-phenylglycinol, (*R*)-2-phenylglycinol, (*S*)-2-amino-3-methyl-1-butanol and reaction of **1b**[8] with (*R*)-2-phenylglycinol followed by allylation gave compounds **8**–**12**, respectively (Scheme 3). In these reactions (except the formation of **8**), the initially formed Schiff bases (analogues of **2**, Scheme 1) undergo diastereoselective allylation (dr > 99:1, ^1H, ^{13}C NMR spectrum) with pre-generated $In_2(allyl)_3Br_2$ reagent to provide enantiomerically pure or highly enriched compounds **9**–**12**. The stereochemistry at C-1 of **9**–**12** has been speculated on the basis of Cram's chelation model where the allyl group approaches to the carbon of C=N from the face anti to phenyl group.[9]

It was found that the benzyl groups at N-1 and N-3 of pyrimidines contribute toward the anti-cancer activities[6] and taking into consideration the electronic contributions of chlorine for interacting with the target enzymes, here, diastereoselective synthesis of compounds **14** and **15** was achieved by the allylation of imines, obtained from **13**[10] and (*R*)-/(*S*)-phenylglycinol, with pre-generated allyl indium reagent (Scheme 4).

Likewise, the diastereoselective synthesis of pyridine derivatives **16** and **17** was achieved by the reaction of pyridine-2-carbaldehyde with (*R*)-2-phenylglycinol and (*S*)-2-phenylglycinol, respectively, followed by the allylation with pre-generated allyl indium reagent (Scheme 5).

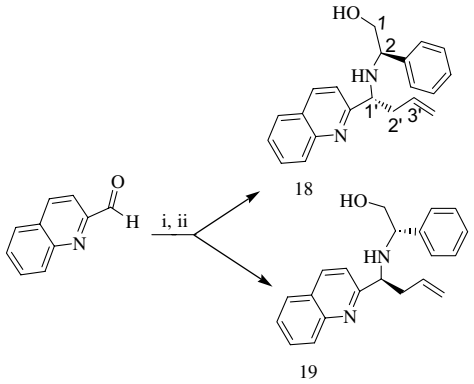


Scheme 4. Reagents and conditions: (i) dry THF, $MgSO_4$, stir, rt; (*R*)-2-phenylglycinol (for **14**), (*S*)-2-phenylglycinol (for **15**); (ii) pre-generated $In_2(allyl)_3Br_3$, THF/Toluene (1:2), stir, 27 °C.



Scheme 5. Reagents and conditions: (i) dry THF, $MgSO_4$, stir, rt, (*R*)-2-phenylglycinol (for **16**), (*S*)-2-phenylglycinol (for **17**); (ii) pre-generated $In_2(allyl)_3Br_3$, THF/Toluene (1:2), 27 °C.

The reactions of quinolin-2-carbaldehyde with (*R*)-2-phenylglycinol and (*S*)-2-phenylglycinol with subsequent allylations of Schiff bases result in diastereoselective formation of compounds **18** and **19**, respectively (Scheme 6).



Scheme 6. Reagents and conditions: (i) dry THF, $MgSO_4$, stir, rt; (*R*)-2-phenylglycinol (for **18**), (*S*)-2-phenylglycinol (for **19**); (ii) pre-generated $In_2(allyl)_3Br_3$, THF/toluene (1:2), 27 °C.

Therefore, a simple reaction strategy using three components leads to the synthesis of target compounds. Diastereoselective allylation of Schiff bases (analogues of **2**, Scheme 1) provides enantiomerically pure compounds **9**–**12** and **14**–**19**. All these compounds have been characterized on the basis of NMR spectral data, mass spectra, and elemental analysis, and the stereochemistry at carbon C-1/1′ has been ascertained on the basis of anti addition of allyl group with respect to phenyl group (Cram's chelation model).

3. Anti-cancer activities

All the indole-based compounds were subjected to pre-screening for their anti-cancer activities at three cancer cell lines namely NCI-H460, MCF7, and SF-268 of non-small cell lung cancer, breast cancer, and CNS cancer, respectively. Pre-screening data (Table 1) of 10 compounds showed appreciable anti-cancer activities of compounds **3** and **9**–**12**. On the basis of these data, 11 (nine of them have 2-phenylethanol moiety on amine nitrogen) compounds have been evaluated for their anti-cancer activities against all the 59 human tumor cell lines following the standard procedure[11] at NCI, Bethesda (USA). The results of these studies in terms of 50% growth inhibitory concentrations of respective compounds (GI_{50}) have been given in Table 2.

4. Discussion

The pre-screening anti-cancer data of indole-based compounds **3**–**12** at 10^{-4} M concentration in terms of growth percentage at three cancer cell lines (NCI-H460, MCF7, and SF-268) have been given in Table 1. All these compounds differ from one another in the nature of group present at the nitrogen of C-3 substituent of indole. Compound **3** with benzyl group at nitrogen shows moderate growth inhibition of tumor cells at NCI-H460 and MCF7 cell lines. Substitution of benzyl group of compound **3** with *p*-chloro-benzyl in compound **4** has considerably reduced the growth inhibition of tumor cells at all the three cell lines. Introduction of another benzyl group at nitrogen (compound **5**) has not reduced the growth inhibition of tumor cells rather it promotes the growth. Compounds **6** and **7** with *o*-methoxyphenyl and *p*-methoxyphenyl group, respectively, at nitrogen show very poor growth inhibition of tumor cells at all the three cell lines. The presence of hydroxy ethyl chain on nitrogen in case of compound **8** leads to moderate inhibition of tumor cells. Compounds **9** and **10** with respective (*S*)- and (*R*)-phenylgly-

Table 1. Growth percentage of tumor cells in the presence of compounds **3**–**12** at 10^{-4} M concentration

Cell line	Growth percentage (10^{-4} M)									
Compound:	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
NCI-H460	14	71	105	98	97	68	3	0	1	5
MCF7	27	46	118	55	60	58	21	0	35	21
SF-268	73	81	81	111	116	95	42	16	50	35

Table 2. Concentrations of compounds resulting in growth inhibitions of 50% (log GI_{50}) of in vitro human tumor cell lines

Panel/cell line	Compound										
	3	**9**	**10**	**11**	**12**	**14**	**15**	**16**	**17**	**18**	**19**
Leukemia											
CCRF-CEM	−4.71	−4.72	−4.36	−4.65	−4.65	−4.97	>−4.0	>−4.0	4.13	>−4.0	−4.34
HL-60 (TB)	nd	−4.62	nd	nd	nd	−5.23	>−4.0	−4.41	−4.62	−4.31	−4.91
K-562	−5.63	−4.65	−5.07	−4.95	−5.57	−5.17	>−4.0	>−4.0	−4.47	>−4.0	−4.44
MOLT-4	−5.0	−4.81	−4.75	−4.81	−4.82	nd	nd	>−4.0	nd	nd	nd
RPMI-8226	−4.88	−4.75	−4.15	−4.88	−5.16	−5.43	>−4.0	>−4.0	−4.49	>−4.0	−4.52
SR	nd	nd	nd	nd	nd	nd	>−4.0	nd	−4.74	>−4.0	−4.77
Non-small cell lung cancer											
A549/ATCC	−4.50	−4.46	−4.88	−4.60	−4.90	−4.82	>−4.0	>−4.0	>−4.0	>−4.0	>−4.0
EKVX	−4.68	−4.45	−4.76	−4.64	−4.60	−4.79	>−4.0	>−4.0	−4.13	>−4.0	>−4.0
HOP-62	−4.61	−4.69	−4.84	−4.54	−4.77	−4.92	>−4.0	>−4.0	>−4.0	>−4.0	>−4.0
HOP-92	−4.86	−4.78	−4.74	−4.85	−4.60	−5.41	>−4.0	>−4.0	nd	nd	nd
NCI-H226	nd	−4.64	−4.82	nd	nd	−4.86	>−4.0	>−4.0	>−4.0	>−4.0	>−4.0
NCI-H23	−4.75	−4.69	−4.80	−4.72	−4.69	−4.71	>−4.0	>−4.0	−4.22	>−4.0	>−4.0
NCI-H322M	−4.48	−4.69	−4.86	−4.60	−4.95	−4.57	>−4.0	>−4.0	>−4.0	Nd	>−4.0
NCI-H460	>−4.0	−4.58	−4.43	−4.49	>−4.0	−4.74	>−4.0	>−4.0	nd	nd	nd
NCI-H522	−4.70	−4.66	−4.82	−4.75	−4.73	−4.84	>−4.0	>−4.0	−4.59	>−4.0	−4.19
Colon cancer											
COLO 205	−4.55	−4.70	−4.71	−4.60	−4.45	−4.83	>−4.0	>−4.0	>−4.0	>−4.0	>−4.0
HCC-2998	−4.85	−4.79	−4.80	−4.77	−4.80	−4.97	>−4.0	>−4.0	>−4.0	>−4.0	>−4.0
HCT-116	−4.89	−4.81	−4.83	−4.62	−4.77	−5.19	>−4.0	>−4.0	>−4.0	>−4.0	>−4.0
HCT-15	−4.68	−4.72	−4.73	−4.49	−4.63	−5.03	>−4.0	>−4.0	>−4.0	>−4.0	>−4.0
HT29	−4.53	−4.63	−4.51	−4.44	−4.51	−4.96	>−4.0	>−4.0	>−4.0	>−4.0	>−4.0
KM12	−4.55	−4.82	−4.78	−4.66	−4.70	−4.76	>−4.0	>−4.0	>−4.0	>−4.0	>−4.0
SW-620	−4.74	−4.54	4.59	−4.55	−4.50	−4.61	>−4.0	>−4.0	>−4.0	>−4.0	>−4.0
CNS cancer											
SF-268	>−4.0	−4.64	−4.49	−4.48	>−4.0	−4.73	>−4.0	>−4.0	nd	nd	nd
SF-295	−4.66	−4.68	−4.81	−4.80	−5.09	−5.09	>−4.0	>−4.0	>−4.0	>−4.0	>−4.0
SF-539	−5.26	−4.69	−4.73	−4.55	−4.67	−4.82	>−4.0	>−4.0	>−4.0	>−4.0	>−4.0
SNB-19	−4.19	nd	−4.65	−4.22	−4.22	−4.45	>−4.0	>−4.0	nd	nd	nd
SNB-75	−4.37	nd	−4.64	−4.16	−4.18	−4.78	>−4.0	>−4.0	>−4.0	>−4.0	>−4.0
U251	−4.72	−4.75	−4.75	−4.56	−4.75	−4.95	>−4.0	>−4.0	>−4.0	>−4.0	>−4.0
Melanoma											
LOX IMVI	−4.77	−4.78	−4.80	−4.71	−4.86	−5.20	>−4.0	>−4.0	>−4.0	>−4.0	>4.0
MALME-3M	>−4.0	−4.77	nd	nd	nd	−4.46	>−4.0	>−4.0	>−4.0	>−4.0	−4.05
M14	−4.73	−4.74	4.84	−4.67	−4.84	−5.21	>−4.0	>−4.0	>−4.0	>−4.0	>−4.0
SK-MEL-2	−4.88	−4.47	4.74	−4.37	−4.49	−4.72	>−4.0	>−4.0	>−4.0	>−4.0	>−4.0
SK-MEL-28	−4.38	−4.47	−4.55	−4.27	−4.38	−4.70	>−4.0	>−4.0	>−4.0	>−4.0	>−4.0
SK-MEL-5	−4.86	−4.85	−4.76	−5.00	−4.58	−4.83	>−4.0	>−4.0	−4.25	nd	nd
UACC-257	−4.62	−4.64	<−8.0	−4.74	−4.97	−4.63	>−4.0	>−4.0	−4.13	>−4.0	−4.49
UACC-62	−4.65	−4.52	−4.79	−4.64	−4.82	−5.12	>−4.0	>−4.0	>−4.0	>−4.0	>−4.0
Ovarian cancer											
IGROV1	−4.73	−4.64	−5.07	−5.11	−4.84	−4.87	nd	>−4.0	>−4.0	−4.34	−4.53
OVCAR-3	−4.76	−4.80	−4.94	−4.78	>−4.0	−5.06	>−4.0	>−4.0	>−4.0	>−4.0	−4.24
OVCAR-4	−4.29	−4.09	−4.43	−4.30	−4.13	−4.57	>−4.0	>−4.0	−4.59	>−4.0	>−4.0
OVCAR-5	−4.80	−4.63	−4.79	−4.31	>−4.0	−4.59	>−4.0	>−4.0	>−4.0	>−4.0	>−4.0
OVCAR-8	−4.62	−4.50	−4.87	−4.66	−4.97	−4.82	>−4.0	>−4.0	>−4.0	>−4.0	>−4.0
SK-OV-3	−4.35	−4.31	−4.50	−4.09	−4.22	−4.20	>−4.0	>−4.0	nd	>−4.0	>−4.0
Renal cancer											
786-0	−4.73	−4.74	−4.82	−4.55	>−4.0	−4.90	>−4.0	>−4.0	>−4.0	>−4.0	>4.0
A498	nd	−4.59	nd	nd	nd	−4.96	−4.87	>−4.0	−4.33	−4.53	−4.03
ACHN	−4.73	−4.62	−4.79	−4.49	−4.74	−5.32	>−4.0	>−4.0	>−4.0	>−4.0	>−4.0
CAKI-1	−4.73	−4.87	−4.91	−4.86	−4.94	−5.35	−4.13	>−4.0	>−4.0	>−4.0	>−4.0
RXF 393	−4.72	−4.64	−6.01	−4.72	nd	−5.07	>−4.0	>−4.0	>−4.0	>−4.0	>−4.0
SN12C	−4.59	−4.67	−4.74	−4.71	−4.77	−4.84	>−4.0	>−4.0	−4.64	>−4.0	−4.17
TK-10	−4.78	−4.63	−4.78	−4.86	−5.44	−4.33	>−4.0	>−4.0	>−4.0	>−4.0	>4.0
UO-31	−4.52	−4.49	−4.79	−4.34	−4.02	−5.16	>−4.0	>−4.0	−4.03	>−4.0	−4.05
Prostate cancer											
PC-3	−4.64	−4.65	−4.63	−4.80	−4.75	−5.39	−4.08	>−4.0	>4.0	>−4.0	>−4.0

(*continued on next page*)

Table 2 (*continued*)

Panel/cell line	Compound										
	3	**9**	**10**	**11**	**12**	**14**	**15**	**16**	**17**	**18**	**19**
DU-145	−4.68	−4.56	−4.71	−4.52	−4.57	−4.63	>−4.0	>−4.0	>−4.0	>−4.0	>−4.0
Breast cancer											
MCF7	−4.29	−4.53	−4.45	−4.46	>−4.0	−4.79	>−4.0	>−4.0	>−4.0	nd	nd
NCI/ADR-RES	−4.67	−4.72	−4.80	−4.66	−4.72	−5.03	>−4.0	>−4.0	>−4.0	>−4.0	>−4.0
MDA-MB-2321/ATCC	−4.74	−4.69	−4.80	−4.88	−4.97	−5.43	>−4.0	>−4.0	>−4.0	>−4.0	−4.34
HS 578T	−4.70	−4.68	−4.71	−4.64	−4.61	−4.59	>−4.0	>−4.0	>−4.0	−4.65	>−4.0
MDA-MB-435	−4.69	−4.64	−4.74	−4.69	−4.72	−4.80	>−4.0	>−4.0	>−4.0	>−4.0	>−4.0
BT-549	−4.67	−4.48	−4.70	−4.61	−4.69	<−8.0	>−4.0	>−4.0	nd	>−4.0	>−4.0
T-47D	−4.48	−4.59	−4.60	−4.40	−4.25	>−4.0	>−4.0	>−4.0	>−4.0	>−4.0	−4.21

nd, not done (the evaluation has not been performed at this cell line).

cinol moieties at nitrogen, that is, possessing both benzyl and ethanol units show best growth inhibition of tumor cells at all the three cell lines. Compound **11**, with iso-propyl group in place of phenyl group in **9**, exhibits less growth inhibition in comparison to **9**. The replacement of ester moiety at N-1 of indole in compound **10** with *p*-toluenesulfonyl does not improve the growth inhibitory property of compound **12**.

Therefore, it was found that amongst the 10 compounds subjected to pre-screening anti-cancer investigations, compounds **9** and **10** possessing (*S*)- and (*R*)-phenylglycinol give best results in terms of growth inhibition of tumor cells and were chosen for further detailed studies at 59 human tumor cell lines along with compounds **3**, **11**, and **12**. Moreover, based upon these results six more compounds with the same substituent as present at C-3 of **9** and **10** but at C-5 of pyrimidine (**14** and **15**), C-2 of pyridine (**16** and **17**), and C-2 of quinoline (**18** and **19**) were included for studying anti-cancer activities at 59 cancer cell lines.

All the 11 compounds subjected to 59 Human tumor cell lines carry a similar side chain of but-3-enylamino-2-hydrogen-/phenyl-/isopropyl-ethanol on indole, pyrimidine, pyridine, and quinoline heterocyclic moiety except for compound **3**. It is evident from the data of anti-cancer activities given in Table 2 that almost all the compounds are active against the 59 Human tumor cell lines assays. Some of the compounds are more specific for certain cell lines and show inhibitory activities at sub-micromolar concentrations. Compounds **9**–**11** show average GI_{50} over the entire cell lines in the range 1.58×10^{-5} to 2.27×10^{-5} M which is quite similar to the anti-cancer activity shown by 5-fluorouracil (average GI_{50} 1.77×10^{-5} M). Amongst compounds **3**–**10**, remarkable anti-cancer activity of **10** has been observed against UACC-257 cell line of melanoma cancer ($GI_{50} < 10^{-8}$ M). Change of ester group present at N-1 of indole in compound **10** with tosyl group in compound **12** results in decrease in the anti-cancer activities (average GI_{50} 2.83×10^{-5} M). Significantly, in contrast to the preliminary investigations where **3** shows poor activity in comparison to **9**–**11** (Table 1), the detailed investigations over 59 tumor cell lines show the anti-cancer activity of **3** (average GI_{50} 2.29×10^{-5} M) quite similar to those of compounds **9**–**11**. The effect of *R*/*S*-configuration of phenylglycinol is quite significant in case of pyrimidine derivatives **14** and **15**. Compound **14** (average GI_{50} 1.16×10^{-5} M) with same side chain as in compounds **10** and **12** but on the pyrimidine moiety shows better anti-cancer activity than its analogue **15** ($GI_{50} > 10^{-4}$ M) with *S*-configuration on the chiral carbon carrying phenyl group (C-1′). Compound **14** inhibits 50% growth of BT-549 cell line of breast cancer at $<10^{-8}$ M concentration. The replacement of pyrimidine moieties of compounds **14** and **15** with pyridine in compounds **16** and **17** or with quinoline in compounds **18** and **19** leads to considerable decrease in their anti-cancer activities.

Therefore, amongst the 11 compounds investigated over all the 59 human tumor cell lines, compounds with indole and pyrimidine as the central core exhibit better anti-cancer activities than those with pyridine and quinoline moieties as the central part of the molecule.

5. Conclusions

Schiff bases formed from indole-/, pyrimidine-/, pyridine-/, quinoline-aldehydes and substituted amines on indium mediated allylation provide a versatile synthetic methodology for incorporating hydrophilic as well as hydrophobic groups at the respective heterocyclic system. Out of the 16 compounds studied here, six (**3**, **9**–**12**, and **14**) compounds show appreciable anti-cancer activities which are quite similar to anti-cancer activity of 5-fluorouracil and out of these compounds **10** and **14** bearing (*R*)-2-phenylglycinol as part of side chain at C-3 of indole and C-5 of pyrimidine show best anti-cancer activities.

6. Experimental

6.1. General details

Melting points were determined in capillaries and are uncorrected. ^{1}H and ^{13}C NMR spectra were run on JEOL 300 and 75 MHz NMR spectrometer, respectively, using $CDCl_3$ as solvent. Chemical shifts are given in parts per million with TMS as an internal reference. *J* values are given in Hertz. Chromatography was

performed with silica 100–200 mesh and reactions were monitored by thin layer chromatography (TLC) with silica plates coated with silica gel HF-254. Indole-3-carbaldehyde, pyridine-2-carbaldehyde, and quinoline-2-carbaldehyde were obtained form Aldrich.

6.2. General procedure for the synthesis of compounds 3, 4, and 6–12

The solution of 3-formyl-indol-1-carboxylic acid ethyl ester [1-(toluene-4-sulfonyl)-1*H*-indole-3-carbaldehyde for **12** (1 mmol)] and appropriate amine (1.2 mmol) in dry THF was stirred at 27 °C over anhydrous $MgSO_4$ for 24 h. After completion of the formation of imine (TLC), the suspended $MgSO_4$ was filtered and the solvent was removed under vacuum. The imine thus obtained was taken in THF/toluene (1:2) and transferred to the cooled solution of allylindium reagent obtained by refluxing a solution of allyl bromide (5 mmol) and indium (2 mmol) in dry THF (2 ml) for 1 h. The reaction mixture was stirred at 27 ± 2 °C. The progress of the reaction was monitored by TLC. On completion, the reaction mixture was diluted with 5 ml of water and extracted with $CHCl_3$ (3× 25 ml). The organic phase was dried over Na_2SO_4. The removal of solvent provided a dark yellow brown liquid. The crude reaction mixture was column chromatographed over silica gel to isolate the pure homoallylic amine.

6.2.1. 3-(1-Benzylamino-but-3-enyl)-indole-1-carboxylic acid ethyl ester (3). Yield 83%, liquid, ^{1}H NMR (300 MHz): δ 1.45 (t, J = 7.2 Hz, 3H, CH_3), 1.94 (br s, 1H, NH, exchanges with D_2O), 2.51–2.71 (m, 2H, CH_2), 3.79 (d, J = 13.2 Hz, 2H, NCH_2), 4.03 (t, J = 6.6 Hz, 1H, CH), 4.48 (q, J = 7.2 Hz, 2H, OCH_2), 5.04–5.24 (m, 2H, =CH_2), 5.69–5.87 (m, 1H, =CH), 7.24–7.36 (m, 7H, ArH), 7.58 (s, 1H, indole H-2), 7.73 (d, J = 7.8 Hz, 1H, InH), 8.19 (d, J = 6.9 Hz, 1H, InH); ^{13}C NMR (normal/DEPT-135) (75 MHz): δ 14.39 (+ve, CH_3), 40.79 (−ve, CH_2), 51.47 (−ve, CH_2), 54.04 (+ve, CH), 63.03 (−ve, CH_2), 115.28 (+ve, CH), 117.65 (−ve, CH_2), 119.97 (+ve, CH), 122.56 (+ve, CH), 122.85 (+ve, CH), 123.32 (ab, C), 124.49 (+ve, CH), 126.82 (+ve, CH), 128.11 (+ve, CH), 128.29 (+ve, CH), 129.35 (ab, C), 135.29 (ab, C), 135.96 (+ve, CH), 140.43 (ab, C), 150.97 (ab, C). FAB mass (M^+) m/z 348, 307 (M^+-allyl). Anal. Calcd for $C_{22}H_{24}N_2O_2$: C, 75.83%; H, 6.94; N, 8.04. Found: C, 75.60%; H, 6.72%; N, 8.25%.

6.2.2. 3-[1-(4-Chlorobenzylamino)-but-3-enyl]-indole-1-carboxylic acid ethyl ester (4). Yield 86%, liquid, ^{1}H NMR (300 MHz): δ 1.47 (t, J = 7.2 Hz, 3H, CH_3), 1.64 (br s, 1H, NH, exchanges with D_2O), 2.53–2.65 (m, 2H, CH_2), 3.74 (d, J = 13.2 Hz, 2H, NCH_2), 3.99 (t, J = 6.9 Hz, 1H, CH), 4.49 (q, J = 7.2 Hz, 2H, CH_2), 5.01–5.07 (m, 2H, =CH_2), 5.69–5.82 (m, 1H, =CH), 7.17–7.37 (m, 6H, ArH), 7.55 (s, 1H, InH-2), 7.72 (d, J = 7.8 Hz, 1H, InH), 8.19 (d, J = 7.8 Hz, 1H, InH); ^{13}C NMR (normal/DEPT-135) (75 MHz): δ 14.41 (+ve, CH_3), 40.78 (−ve, CH_2), 50.71 (−ve, CH_2), 54.10 (+ve, CH), 63.10 (−ve, CH_2), 115.34 (+ve, CH), 117.76 (−ve, CH_2), 119.94 (+ve, CH), 122.60 (+ve, CH), 122.91 (+ve, CH), 123.10 (ab, C), 124.57 (+ve, CH), 128.38 (+ve, CH), 129.28 (+ve, CH), 129.47 (ab, CH), 132.50 (ab, C), 135.13 (+ve, CH), 136.00 (ab, C), 138.92 (ab, C), 150.97 (ab, C); FAB mass (M^+) m/z 382, 384 (3:1), 341, 343 (M+-allyl). Anal. Calcd for $C_{22}H_{23}ClN_2O_2$: C, 69.01%; H, 6.05%; N, 7.32%. Found: C, 69.30%; H, 6.18%; N 7.48%.

6.2.3. 3-(1-Dibenzylamino-but-3-enyl)-indole-1-carboxylic acid ethyl ester (5). A mixture of **3** (0.001 mol), benzyl chloride (0.0012 mol), K_2CO_3 (0.0012 mol), and TBAH-SO_4 (phase transfer catalyst) in dry CH_3CN was refluxed with stirring. After completion of the reaction (TLC, 15 h), the solid suspension was filtered off and washed twice with chloroform (20 ml). The solvent was removed under reduced pressure and the crude product was column chromatographed and crystallized to isolate pure **5**. Yield 69%, solid, mp 123 °C; ^{1}H NMR (300 MHz): δ 1.51 (t, J = 7.2 Hz, 3H, CH_3), 1.94 (br s, 1H, NH, exchanges with D_2O), 2.63–2.65 (m, 1H, CH_2), 2.92–2.96 (m, 1H, CH_2), 3.53 (d, J = 13.2 Hz, 2H, NCH_2), 3.71 (d, J = 13.2 Hz, 2H, NCH_2), 4.14 (dd, ^3J = 6.0 Hz, ^3J = 8.7 Hz, 1H, NCH), 4.49 (q, J = 7.2 Hz, 2H, OCH_2), 4.99–5.13 (m, 2H, =CH_2), 5.78–5.87 (m, 1H, =CH), 7.15–7.51 (m, 13H, ArH), 7.52 (s, 1H, InH-2), 8.13 (d, J = 7.8 Hz, 1H, InH-2); ^{13}C NMR (normal/DEPT-135) (75 MHz): δ 14.39 (+ve, CH_3), 33.61 (−ve, CH_2), 53.87 (−ve, CH_2), 54.04 (+ve, CH), 63.87 (−ve, CH_2), 115.00 (+ve, CH), 116.37 (−ve, CH_2), 120.51 (+ve, CH), 122.55 (+ve, CH), 123.32 (ab, C), 124.46 (+ve, CH), 126.87 (+ve, CH), 128.16 (+ve, CH), 129.02 (+ve, CH), 129.35 (ab, C), 135.29 (ab, C), 136.39 (+ve, CH), 140.01 (+ve, CH), 140.43 (ab, C), 150.97 (ab, C); FAB mass (M^+) m/z 438. Anal. Calcd for $C_{29}H_{30}N_2O_2$: C, 79.42%; H, 6.89%; N, 6.39%. Found: C, 79.12%; H, 6.64%; N, 6.32%.

6.2.4. 3-[1-(2-Methoxy-phenylamino)-but-3-enyl]-indole-1-carboxylic acid ethyl ester (6). Yield 68%, liquid, ^{1}H NMR (300 MHz): δ 1.43 (t, J = 7.2 Hz, 3H, CH_3), 1.54 (br s, 1H, NH, exchanges with D_2O), 2.70–2.76 (m, 2H, CH_2), 3.86 (s, 3H, OCH_3), 4.40 (q, J = 7.2 Hz, 2H, OCH_2), 4.69 (deformed t, J = 6.6 Hz, 1H, NCH), 5.11–5.23 (m, 2H, =CH_2), 5.73–5.86 (m, 1H, =CH), 6.48 (d, J = 7.5 Hz, 1H, ArH), 6.63 (t, J = 7.5 Hz, 1H, ArH), 6.69 (t, J = 7.5 Hz, 1H, ArH), 6.75 (d, J = 7.5 Hz, 1H, ArH), 7.26 (t, J = 8.0 Hz, 1H, InH), 7.32 (t, J = 8 Hz, 1H, InH), 7.52 (s, 1H, InH-2), 7.64 (d, J = 7.8 Hz, 1H, InH), 8.18 (d, J = 7.8 Hz, 1H, InH); ^{13}C NMR (normal/DEPT-135) (75 MHz): δ 14.43 (+ve, CH_3), 40.57 (−ve, CH_2), 50.21 (+ve, CH), 55.52 (+ve, CH_3), 63.07 (−ve, CH_2), 109.45 (+ve, CH), 110.98 (+ve, CH), 115.46 (+ve, CH), 116.66 (+ve, CH), 118.17 (−ve, CH_2), 119.24 (+ve, CH), 121.18 (+ve, CH), 122.72 (+ve, CH), 123.35 (ab, C), 124.57 (+ve, CH), 128.93 (ab, C), 134.51 (+ve, CH), 136.12 (ab, C), 137.29 (ab, C), 146.91 (ab, C), 150.97 (ab, C); FAB mass (M^+) m/z 364, 323 (M+-allyl). Anal. Calcd for $C_{22}H_{24}N_2O_3$: C, 72.50%; H, 6.64%; N, 7.69%. Found: C, 72.30%; H, 6.62%; N, 7.80%.

6.2.5. 3-[1-(4-Methoxy-phenylamino)-but-3-enyl]-indole-1-carboxylic acid ethyl ester (7). Yield 71%, liquid, ^{1}H NMR (300 MHz): δ 1.46 (t, J=7.2 Hz, 3H, CH_3), 1.56

(br s, 1H, NH, exchanges with D_2O), 2.72–2.78 (m, 2H, CH_2), 3.71 (s, 3H, OCH_3), 4.45 (q, J = 7.2 Hz, 2H, OCH_2), 4.61 (t, J = 6.3 Hz, 1H, NCH), 5.13–5.23 (m, 2H, $=CH_2$), 5.71–5.84 (m, 1H, =CH), 6.54 (d, J = 6.6 Hz, 2H, ArH), 6.72 (d, J = 6.6 Hz, 2H, ArH) 7.26 (t, J = 7.8 Hz, 1H, InH-2), 7.35 (t, J = 7.8 Hz, 1H, InH), 7.37 (s, 1H, InH-2), 7.64 (d, J = 7.8 Hz, 1H, InH), 8.17 (d, J = 7.8 Hz, 1H, InH); ^{13}C NMR (normal/DEPT-135) (75 MHz): δ 14.43 (+ve, CH_3), 40.45 (−ve, CH_2), 51.31 (+ve, CH_3), 63.12 (−ve, CH_2), 114.68 (+ve, CH), 115.04 (+ve, CH), 115.43 (+ve, CH), 118.34 (−ve, CH_2), 119.18 (+ve, CH), 122.69 (+ve, CH), 128.57 (ab, C), 134.50 (+ve, CH), 150.97 (ab, C). FAB mass (M^+) m/z 364, 323 (M+-allyl). Anal. Calcd for $C_{22}H_{24}N_2O_3$: C, 72.50%; H, 6.64%; N, 7.69%. Found: C, 72.30%; H, 6.62%; N, 7.80%.

6.2.6. 3-[1-(2-Hydroxy-ethylamino)-but-3-enyl]-indole-1-carboxylic acid ethyl ester (8). Yield 70%, liquid, ^{1}H NMR (300 MHz): δ 1.47 (t, J=7.2 Hz, 3H,CH_3), 1.62 (br s, 1H, NH, exchanges with D_2O), 3.41 (br s, 1H, OH, exchanges with D_2O), 2.62 (m, 2H, CH_2) 2.75 (t, J=5.4 Hz, 2H, NCH_2), 3.41–3.64 (m, 2H, CH_2OH), 4.01 (t, J = 6.6 Hz, 1H, NCH), 4.48 (q, J = 7.2 Hz, 2H, OCH_2), 5.06–5.15 (m, 2H, $=CH_2$), 5.71–5.82 (m, 1H, =CH), 7.25 (t, J = 7.5 Hz, 1H, ArH), 7.33 (t, J = 7.5 Hz, 1H, InH), 7.53 (s, 1H, In H-2), 7.69 (d, J = 7.5 Hz, 1H, InH-2), 8.18 (d, J = 7.5 Hz, 1H, InH-2); ^{13}C NMR (normal/DEPT-135) (75 MHz): δ 14.43 (+ve, CH_3), 40.49 (−ve, CH_2), 48.80 (−ve, CH_2), 54.64 (+ve, CH), 61.32 (−ve, CH_2), 63.17 (−ve, CH_2), 115.45 (+ve, CH), 117.86 (−ve, CH_2), 119.61 (+ve, CH), 122.74 (+ve, CH), 122.80 (ab, C), 123.05 (ab, C), 124.67 (+ve, CH), 129.23 (ab, C), 134.98 (+ve, CH), 150.98 (ab, C). FAB mass (M^++1) m/z 303, 361 (M+-allyl). Anal. Calcd for $C_{17}H_{22}N_2O_3$: C, 67.53%; H, 7.33%; N, 9.26%. Found: C, 67.45%; H, 7.18%; N, 9.35%.

6.2.7. (1*S*,1′*S*)-3-[1-(2-Hydroxy-1-phenyl-ethylamino)-but-3-enyl]-indole-1-carboxylic acid ethyl ester (9). Yield 68%, liquid, $[\alpha]^{25}$ = +19.0 (c 0.70, $CHCl_3$); ^{1}H NMR (300 MHz): δ 1.46 (t, J = 7.2 Hz, 3H,CH_3), 1.62 (br s, 1H, NH, exchanges with D_2O), 2.62–2.67 (m, 2H, CH_2), 3.41 (br s, 1H, OH, exchangeable with D_2O), 3.53 (dd, J = 8.0 Hz, J = 10.8 Hz, 1H, CH_2OH), 3.74 (dd, J = 4.5 Hz, J = 10.8 Hz, 1H, CH_2OH), 3.95 (dd, J = 4.5 Hz, J = 8 Hz, 1H, CH), 4.01 (t, J = 6.6 Hz, 1H, NCH), 4.47 (q, J = 7.2 Hz, 2H, OCH_2), 5.00–5.09 (m, 2H, $=CH_2$), 5.65–5.79 (m, 1H, =CH), 7.15–7.30 (m, 7H, ArH), 7.43 (d, J = 7.2 Hz, 2H, ArH), 8.14 (d, J = 7.8 Hz, 1H, InH-2); ^{13}C NMR (normal/DEPT-135) (75 MHz): δ 14.41 (+ve, CH_3), 39.03 (−ve, CH_2), 51.77 (+ve, CH), 61.58 (+ve, CH), 63.11 (−ve, CH_2), 66.12 (−ve, CH_2), 115.29 (+ve, CH), 117.55 (−ve, CH_2), 119.60 (+ve, CH), 122.59 (+ve, CH), 122.70 (+ve, CH), 123.49 (ab, C), 124.57 (+ve, CH), 127.12 (+ve, CH), 127.53 (+ve, CH), 128.54 (+ve, CH), 129.00 (ab, C), 134.71 (+ve, CH), 135.73 (ab, C), 140.72 (ab, C), 150.88 (ab, C); decoupling of 2H multiplet at δ 2.62–2.67 changes 1H triplet at δ 4.01 to singlet and multiplet at δ 5.64–5.79 into double doublet. Decoupling of dd at δ 3.53 converts double doublets at δ 3.74 and 3.95 into doublets; FAB mass (M^+−CH(C_6H_5)CH_2OH) m/z 242. Anal. Calcd for $C_{23}H_{26}N_2O_3$: C, 72.99%; H, 6.92%; N, 7.40%. Found: C, 72.80%; H, 6. 75%; N, 7.53%.

6.2.8. (1*R*,1′*R*)-3-[1-(2-Hydroxy-1-phenyl-ethylamino)-but-3-enyl]-indole-1-carboxylic acid e thyl ester (10). Yield 65%, liquid, $[\alpha]^{25}$ = −20.60 (c 0.66, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.46 (t, J = 7.2 Hz, 3H,CH_3), 2.26 (br s, 1H, NH, exchanges with D_2O), 2.62–2.67 (m, 2H, CH_2), 3.41 (br s, 1H, OH, exchangeable with D_2O), 3.54 (dd, J = 8.0 Hz, J = 10.8 Hz, 1H, CH_2OH), 3.74 (dd, J = 4.5 Hz, J = 10.8 Hz, 1H, CH_2OH), 3.96 (dd, J = 4.5 Hz, J = 8 Hz, 1H, CH), 4.01 (t, J = 6.6 Hz, 1H, NCH), 4.46 (q, J = 7.2 Hz, 2H, CH_2), 5.00–5.09 (m, 2H, $=CH_2$), 5.64–5.78 (m, 1H, =CH), 7.15–7.33 (m, 7H, ArH), 7.43 (d, J = 7.2 Hz, 2H, ArH), 8.14 (d, J = 7.8 Hz, 1H, InH-2); ^{13}C NMR (normal/DEPT-135) (75 MHz): δ 14.38 (+ve, CH_3), 38.94 (−ve, CH_2allyl), 51.74 (+ve, NCH), 61.60 (+ve, PhCH), 63.08 (−ve, OCH_2), 66.06 (−ve, CH_2OH), 115.26 (+ve, H-6_{indole}), 117.55 (−ve, $=CH_2$), 119.56 (+ve, CH), 122.56 (+ve, CH), 122.73 (+ve, CH), 123.36 (ab, C), 124.55 (+ve, CH), 127.11 (+ve, CH), 127.51 (+ve, CH), 128.50 (+ve, CH), 128.98 (ab, C), 134.65 (+ve, =CH), 135.70 (ab, C), 140.60 (ab, C), 150.85 (ab, C); decoupling of 2H multiplet at δ 2.62–2.67 changes 1H triplet at δ 4.01 to singlet and multiplet at δ 5.64–5.78 into double doublet. Decoupling of dd at δ 3.54 converts double doublets at δ 3.74 and 3.96 into doublets. In ^{1}H–^{13}C HETCOR spectrum, cross peaks are observed between: carbon at δ 14.38 and triplet at δ 1.46 (CH_3); CH_2 carbons at δ 38.94 and multiplet at δ 2.62–2.74; CH_2 at δ 117.55 and multiplet at δ 5.00–5.09; CH at δ 51.74 and triplet at δ 4.01; carbon at δ 61.60 and dd at δ 3.96; CH_2carbon at δ 63.08 and quartet at δ 4.46 (OCH_2); carbon at δ 66.06 and dds at δ 3.54 and 3.74; carbon at δ 115.26 and doublet at δ 8.14; carbon at δ 136.65 and multiplet at δ 5.64–5.78; carbons at δ 119.56, 122.56, 122.73, 124.55, 127.11, 127.51, and 128.50 with multiplet at δ 7.15–7.33 and doublet at δ 7.43 (ArH). FAB mass (M^+−CH(C_6H_5)CH_2OH) m/z 242. Anal. Calcd for $C_{23}H_{26}N_2O_3$: C, 72.99%; H, 6.92%; N, 7.40%. Found: C, 72.80%; H, 6. 75%; N, 7.53%.

6.2.9. (1*S*,1′*S*)-3-[1-(1-Hydroxymethyl-2-methyl-propyl-amino)-but-3-enyl]-indole-1-carboxylic acid ethyl ester (11). Yield 64%, liquid, $[\alpha]^{25}$ = −15.99 (c 0.58, $CHCl_3$)^{1}H NMR (300 MHz): δ 0.77–0.92 (m, 6H, 2× CH_3), 1.47 (t, J = 6.9 Hz, 3H,CH_3), 1.50 (br s, 1H, NH, exchanges with D_2O), 1.73–1.77 (m, 1H, $CH(CH_3)_2$), 2.41–2.44 (m, 1H,CH–CH_2OH), 2.58–2.63 (m, 2H, CH_2), 3.39 (dd, J = 4.2 Hz, J = 10.8 Hz, 1H, CH_2OH), 3.42 (br s, 1H, OH, exchanges with D_2O), 3.64 (dd, J = 5.4 Hz, J = 10.8 Hz, 1H, CH_2OH), 4.04 (t, J = 6.6 Hz, 1H, NCH), 4.49 (q, J = 7.2 Hz, 2H, OCH_2), 5.01–5.10 (m, 2H, $=CH_2$), 5.73–5.75 (m, 1H, =CH), 7.22–7.34 (m, 2H, ArH), 7.51 (s, 1H, InH-2), 7.66 (d, J = 7.8 Hz, 1H, InH), 8.18 (d, J = 7.5 Hz, 1H, InH-2); ^{13}C NMR (normal/DEPT-135, DEPT-90) (75 MHz): δ 14.36 (+ve, CH_3), 18.74 (+ve, CH_3), 19.51 (+ve, CH_3), 29.3 (+ve, CH), 55.2 (+ve, CH), 40.79 (−ve, CH_2), 60.13 (−ve, CH_2), 61.37 (+ve, CH), 63.11 (−ve, CH_2), 117.38 (−ve, CH_2), 117.43 (+ve, CH), 119.73 (+ve,

CH), 122.59 (+ve, CH), 122.62 (ab, C), 122.61 (+ve, CH), 124.59 (+ve, CH), 128.98 (ab, C) 135.12 (+ve, CH), 135.38 (ab, C), 150.93 (ab, C); decoupling of multiplet at δ 0.77–0.92 converts multiplet at δ 1.73–1.77 into doublet. Decoupling of triplet at δ 4.04 converts multiplet at δ 2.58–2.63 into doublet. Decoupling of multiplet at δ 5.73–5.75 converts the multiplet at δ 2.58–2.63 into doublet, FAB mass (M^++1) *m/z* 345, 303 (M+-allyl). Anal. Calcd for $C_{20}H_{28}N_2O_3$: C, 69.74%; H, 8.19%; N, 8.13%. Found: C, 69. 82%; H, 8.02%; N, 8.25%.

6.2.10. (1*R*,1′*R*)-3-[1-(2-Hydroxy-1-phenyl-ethylamino)-but-3-enyl]-indole-1-*p*-toluenesulfonyl (12). Yield 67%, liquid, $[\alpha]^{25} = -14.15$ (*c* 0.42, $CHCl_3$); ^{1}H NMR (300 MHz): δ 2.58 (s, 3H, CH_3), 2.56–2.60 (m, 2H, CH_2), 3.53 (dd, J = 7.8 Hz, J = 10.5 Hz, 1H, CH_2OH), 3.71 (dd, J = 4.5 Hz, J = 10.5 Hz, 1H, CH_2OH), 3.89 (dd, J = 4.5 Hz, J = 7.8 Hz, 1H, CH), 3.97 (t, J = 6.3 Hz, 1H, NCH), 4.82–5.00 (m, 2H, =CH_2), 5.54–5.68 (m, 1H, =CH), 7.12–7.39 (m, 9H, ArH), 7.69 (d, J = 8.1 Hz, 2H, ArH), 7.78 (d, J = 8.7 Hz, 1H, InH-2); ^{13}C NMR (normal/DEPT-135) (75 MHz): δ 21.52 (+ve, CH_3), 38.84 (−ve, CH_2), 51.85 (+ve, CH), 61.67 (+ ve, CH), 66.12 (−ve, CH_2), 113.79 (+ve, CH), 117.78 (−ve, CH_2), 120.02 (+ve, CH),122.98 (ab, C), 123.01 (+ve, CH), 123.63 (+ve, CH), 124.678 (+ve, CH), 126.76 (+ve, CH), 127.12 (+ve, CH), 127.64 (+ve, CH), 128.58 (+ve, CH), 129.36 (ab, CH), 129.74 (+ve, CH), 134.37 (+ve, CH), 135.14 (ab, C), 135.44 (ab, C), 140.44 (ab, C), 144.82 (ab, C); decoupling of dd at δ 3.53 converts dd at δ 3.71 and double doublet at δ 3.89 into doublets. Decoupling of multiplet at δ 2.56–2.60 converts triplet at δ 3.97 into singlet; FAB mass (M^+−CH(C_6H_5)CH_2OH) *m/z* 329. Anal. Calcd for $C_{27}H_{28}N_2O_3S$: C, 70.41%; H, 6.13%; N, 6.08%. Found: C, 70.55%; H, 6.21%; N, 6.13%.

6.3. General procedure for the synthesis of compounds 14–19

Same reaction procedure has been followed as given in Section 6.2 except the use of pyrimidin-5-carbaldehyde, pyridine-2-carbaldehyde, and quinolin-2-carbaldehyde instead of indol-2-carbaldehyde.

6.3.1. (1*R*,1′*R*)-1,3-Bis-(2-chlorobenzyl)-5-[1-(2-hydroxy-1-phenyl-ethylamino)-but-3-enyl]-1H-pyrimidin-2,4-dione (14). Yield 80%, liquid, $[\alpha]^{25} = +38.0$ (*c*, 0.40, $CHCl_3$), ^{1}H NMR (300 MHz): δ 2.46 (t, J = 7.2 Hz, 2H, CH_2), 3.38–3.45 (m, 1H, CHPh), 3.34–3.45 (m, 1H, CHNH), 3.58–3.61 (m, 2H, CH_2OH), 4.78 (s, 2H, CH_2Ph), 4.89 (s, 2H, CH_2Ph), 4.94–5.20 (m, 2H, =CH_2), 5.67–5.80 (m, 1H, =CH), 7.07–7.37 (m, 8H, ArH), 7.48 (s, 1H, Uracil H-6); ^{13}C NMR (normal/DEPT-135) (75 MHz): δ 38.95 (−ve, CH_2), 42.52 (−ve, CH_2Ph), 49.64 (−ve, CH_2Ph), 62.81 (+ve, NCH), 64.10 (+ve, CHPh), 66.08 (−ve, CH_2OH), 117.76 (−ve, CH_2), 126.46 (+ve, ArCH), 126.78 (+ve, CH), 128.74 (+ve, ArCH), 127.18 (+ve, ArCH), 127.96 (+ve, ArCH), 128.12 (+ve, ArCH), 128.23 (ab, CH), 129.41 (+ve, ArCH), 129.59 (+ve, ArCH), 129.76 (+ve, ArCH), 130.54 (+ve, ArCH), 133.14 (ab, C), 133.85 (ab, C), 133.57 (ab, C), 133.61 (ab, C), 134.79 (+ve, ArCH), 140.02 (+ve, ArCH), 142.10 (+ve, CH), 150.74 (ab, C), 161.95 (ab, C); FAB mass (M^++1) *m/z* 551. Anal. Calcd for $C_{30}H_{29}Cl_2N_3O_3$: C, 65.46%; H, 5.31%; N, 7.63%. Found: C, 65.12%; H, 5.62%; N, 7.51%.

6.3.2. (1*S*,1′*S*)-1,3-Bis-(2-chlorobenzyl)-5-[1-(2-hydroxy-1-phenyl-ethylamino)-but-3-enyl]-1H-pyrimidin-2,4-dione (15). Yield 70%, $[\alpha]^{25} = -39.4$ (*c*, 0.40, $CHCl_3$), liquid, ^{1}H NMR (300 MHz): δ 2.44 (t, J = 7.2 Hz, 2H, CH_2), 3.44–3.47 (m, 1H, CHPh), 3.62–3.68 (m, 1H, CHNH), 3.74–3.78 (m, 2H, CH_2OH), 4.82 (s, 2H, CH_2Ph), 4.91 (s, 2H, CH_2Ph), 4.99–5.10 (m, 2H, =CH_2), 5.71–5.78 (m, 1H, =CH), 7.17–7.39 (m, 8H, ArH), 7.51 (s, 1H, Uracil H-6); ^{13}C NMR (normal/DEPT-135) (75 MHz): δ 38.99 (−ve, CH_2), 42.60 (−ve, CH_2Ph), 49.72 (−ve, CH_2Ph), 62.87 (+ve, NCH), 65.12 (+ve, CHPh), 66.78 (−ve, CH_2OH), 116.89 (−ve, CH_2), 126.44 (+ve, ArCH), 126.68 (+ve, CH), 126.74 (+ve, ArCH), 127.18 (+ve, ArCH), 127.96 (+ve, ArCH), 128.19 (+ve, ArCH), 129.23 (ab, C), 129.41 (+ve, ArCH), 130.59 (+ve, ArCH), 130.76 (+ve, ArCH), 131.54 (+ve, ArCH), 133.14 (ab, C), 133.88 (ab, C), 133.99 (ab, C), 134.61 (ab, C), 134.79 (+ve, ArCH), 140.02 (+ve, ArCH), 142.10 (+ve, CH), 150.74 (ab, C), 161.95 (ab, C); FAB mass (M^++1) *m/z* 551. Anal. Calcd for $C_{30}H_{29}Cl_2N_3O_3$: C, 65.46%; H, 5.31%; N, 7.63%. Found: C, 65.52%; H, 5.68%; N, 7.48%.

6.3.3. (1′*R*,2*R*)-2-Phenyl-2-(1′-pyridin-2-yl-but-3′-enyl-amino)ethanol (16). Yield 80%, liquid, $[\alpha]^{25} = +24.4$ (*c* 0.60, $CHCl_3$), ^{1}H NMR (300 MHz): δ 2.78 (m, 2H, CH_2), 3.90 (br s, 2H, 1H of OH, 1H of NH), 3.44–3.53 (m, 1H, CHPh), 3.58–3.74 (m, 1H, CHNH), 3.74–3.77 (m, 2H, CH_2OH), 4.96–5.10 (m, 2H, =CH_2), 5.57–5.70 (m, 1H, =CH), 6.96–7.12 (m, 7H, ArH), 7.39–7.46 (m, 1H, ArH), 8.34 (d, 1H, ArH); ^{13}C NMR (normal/DEPT-135) (75 MHz): δ 38.53 (−ve, CH_2), 62.14 (+ve, CH), 64.22 (+ve, CH), 64.31 (−ve, CH_2), 119.79 (−ve, CH_2), 123.18 (+ve, CH), 127.92 (+ve, CH), 128.74 (+ve, CH), 128.88 (+ve, CH), 131.91 (ab, C), 131.91 (ab, C), 136.86 (+ve, CH), 149.04 (+ve, CH), 156.36 (ab, C). FAB mass (M^++1) *m/z* 269. Anal. Calcd for $C_{17}H_{20}N_2O$: C, 76.09%; H, 7.51%; N, 10.44%. Found: C, 76.31%; H, 7.62%; N, 10.46%.

6.3.4. (1′*S*,2*S*)-2-Phenyl-2-(1′-pyridin-2-yl-but-3′-enyl-amino)ethanol (17). Yield 85%, liquid, $[\alpha]^{25} = -23.4$ (*c* 0.40, $CHCl_3$), ^{1}H NMR (300 MHz): δ 2.53–2.58 (m, 2H, CH_2), 2.58 (br s, 2H, 1H of OH, 1H of NH), 3.56–3.60 (m, 1H, CHPh), 3.70–3.71 (m, 1H,CHNH), 3.71–3.83 (m, 2H, CH_2OH), 4.99–5.06 (m, 2H, =CH_2), 5.56 (m, 1H, =CH), 7.05–7.07 (m, 2H, ArH), 7.14–7.27 (m, 6H, ArH), 7.49 (m, 1H, ArH), 8.46 (d, J = 7.5 Hz, 1H, ArH); ^{13}C NMR (normal/DEPT-135) (75 MHz): δ 40.62 (−ve, CH_2), 61.19 (+ve, CH), 62.56 (+ve, CH), 65.88 (−ve, CH_2), 117.48 (−ve, CH_2), 121.82 (+ve, CH), 122.12 (+ve, CH), 127.19 (+ve, CH), 128.24 (+ve, CH), 134.81 (+ve, CH), 134.97 (ab, C), 136.02 (+ve, CH), 141.00 (ab, C), 149.02 (+ve, CH), 162.36 (ab, C); FAB mass (M^++1) *m/z* 269. Anal. Calcd for $C_{17}H_{20}N_2O$: C,

76.09%; H, 7.51%; N, 10.44%. Found: C, 76.31%; H, 7.62%; N, 10.46%.

6.3.5. (1′*R*,2*R*)-2-Phenyl-2-(1′-quinolin-2-yl-but-3′-enylamino)ethanol (18). Yield 80%, liquid, $[\alpha]^{25} = +47.5$ (*c*, 0.40, $CHCl_3$), ^1H NMR (300 MHz): δ 2.62 (br s, 1H, NH, exchanges with D_2O), 2.66 (m, 2H, CH_2), 3.64 (dd, $J = 7.5$ Hz, $J = 10.8$ Hz, 1H, 1H of CH_2OH), 3.78 (dd, $J = 4.5$ Hz, $J = 10.8$ Hz, 1H, 1H of CH_2OH), 3.90 (dd, $J = 4.5$ Hz, $J = 7.5$ Hz, 1H, CHPh), 4.08 (t, $J = 6.3$, 1H, CHNH), 5.01–5.12 (m, 2H, $=CH_2$), 5.73–5.82 (m, 1H, =CH), 7.10–7.28 (m, 6H, ArH), 7.47–7.52 (m, 1H, ArH), 7.65–7.76 (m, 2H, ArH), 7.97–8.04 (m, 2H, ArH); ^{13}C NMR (normal/DEPT-135) (75 MHz): δ 40.73 (−ve, CH_2), 61.42 (+ve, NCH), 62.68 (+ve, CHPh), 65.77 (−ve, CH_2OH), 117.89 (−ve, CH_2), 119.98 (+ve, CH), 126.1 (+ve, CH), 127.20 (ab, C), 127.26 (+ve, CH), 127.45 (+ve, CH), 128.27 (+ve, CH), 128.97 (+ve, CH), 134.65 (+ve, CH), 136.18 (+ve, CH), 140.83 (ab, C), 147.33 (ab, C), 162.61 (ab, C); decoupling of 2H multiplet at δ 2.66 converts the 1H triplet at δ 4.08 to singlet and 1H multiplet at δ 5.73–5.82 into double doublet and assigns these signals to HN–$CHCH_2$–CH = moiety. The decoupling of 1H dd at δ 3.90 converts two 1H dds at δ 3.64 and 3.78 into doublets and assigns these signals to $CHCH_2OH$ moiety. In ^1H–^{13}C HETCOR experiment, the correlation of CH_2 (−ve signal in DEPT-135) at δ 65.77 with two 1H signals at δ 3.64 and 3.78 assigns these protons to CH_2OH group; FAB mass (M^++1) *m*/*z* 318. Anal. Calcd for $C_{21}H_{22}N_2O$: C, 79.21%; H, 6.96%; N, 8.80%. Found: C, 79.34%; H, 7.05%; N, 8.93%.

6.3.6. (1′*S*,2*S*)-2-Phenyl-2-(1′-quinolin-2-yl-but-3′-enylamino)ethanol (19). Yield 85%, liquid, $[\alpha]^{25} = -47.5$ (*c*, 0.40 $CHCl_3$), ^1H NMR (300 MHz): δ 2.50 (br s, 1H, NH, exchanges with D_2O), 2.63 (m, 2H, CH_2), 3.63 (dd, $J = 7.5$ Hz, $J = 10.8$ Hz, 1H, 1H of CH_2OH), 3.80 (dd, $J = 4.5$ Hz, $J = 10.8$ Hz, 1H, 1H of CH_2OH), 3.89 (dd, $J = 4.5$ Hz, $J = 7.5$ Hz, 1H, CHPh), 4.05 (t, $J = 6.3$ Hz, 1H, CHNH), 5.01–5.11 (m, 2H, $=CH_2$), 5.73–5.82 (m, 1H, =CH) 7.09–7.26 (m, 6H, ArH), 7.46–7.52 (m, 1H, ArH), 7.65–7.76 (m, 2H, ArH), 7.96–8.04 (m, 2H, ArH); ^{13}C NMR (normal/DEPT-135) (75 MHz): δ 40.80 (−ve, CH_2), 61.39 (+ve, CH), 62.61 (+ve, CH), 65.86 (−ve, CH_2), 117.76 (−ve, CH_2), 119.99 (+ve, CH), 126.06 (+ve, CH), 127.18 (+ve, CH), 127.24 (+ve, CH), 127.44 (+ve, CH), 128.25 (+ve, CH), 128.97 (+ve, CH), 129.36 (+ve, CH), 134.78 (+ve, CH), 136.13 (+ve, CH), 141.03 (ab, C), 147.3 (ab, C), 162.8 (ab, C); decoupling of 2H multiplet at δ 2.63 converts the 1H triplet at δ 4.05 to singlet and 1H multiplet at δ 5.73–5.82 into double doublet and assigns these signals to HN–$CHCH_2$–CH = moiety. The decoupling of 1H dd at δ 3.89 converts two 1H dds at δ 3.63 and δ 3.80 into doublets and assigns these signals to $CHCH_2OH$ moiety. In ^1H–^{13}C HETCOR experiment, the correlation of CH_2 (−ve signal in DEPT-135 spectrum) at δ 65.86 with 1H signals at δ 3.63 and 3.80 assigns these protons to CH_2OH group; FAB mass (M^+) *m*/*z* 318. Anal. Calcd for $C_{21}H_{22}N_2O$: C, 79.21%; H, 6.96%; N, 8.80%. Found: C, 79.34%; H, 7.05%; N, 8.93%.

6.4. In vitro anti-caner activities

The pre-screening of compounds at three cell lines followed by the detailed evaluation for anti-cancer activities at 59 human tumor cell lines was carried out by screening unit of NCI at NIH Bethesda, USA, following their standard procedure (www.dtp.nci.nih.gov/). For pre-screening, the compounds were evaluated only at 10^{-4} M concentration. Evaluations at the complete cell line panel were carried out at five concentrations viz. 10^{-4}, 10^{-5}, 10^{-6}, 10^{-7}, and 10^{-8} M. The percentage growth of tumor cells was calculated at each cell line for each concentration of the compound. The results are expressed as growth inhibition of 50% (GI_{50}) which is the concentration of the compound causing 50% reduction in the net protein increase (as measured by SRB staining) in control cells during drug incubation. However, in these studies the particular cellular target of the compounds has not been identified.

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