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Review

Nitrogen-containing heterocyclic compounds: A class of potential anticancer agents

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Abstract: This review discusses the nitrogen-containing heterocyclic compounds reported during 2000 to 2010 with excellent anticancer activity. These compounds have been classified according to their chemical entities and include acridine, carbolines, carbazoles, indoles, purines, pyridine, pyrimidines, sulfonamides, quinolines and quinazolines, which are further sub-classified on the basis of their structures. Along with the activity profile their mode of action has also been discussed.

Introduction

Cancer forms a group of different diseases characterized by uncontrolled growth of highly heterogeneous malignant cell population. The estimated worldwide incidence of different types of cancer is around 10 million, roughly half of which is in the developed countries. A total of 1,437,180 new cancer cases and 565,650 deaths from cancer are projected to occur in the United States in 2008 by American Cancer Society (1). In spite of impressive progress in diagnosis, surgery and therapy, occurred since the sixties, the overall cancer mortality, even somewhat declined in the nineties in some countries, is still very high, with some exceptions for some specific tumor types (2). A dramatic decrease of mortality occurred only for those

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cancers in which both early diagnosis and full organ surgery are possible, as in the case of uterus and cervix, or for which also a substantial drop of incidence occurred, as in the case of the stomach. In spite of the large number of available chemotherapeutic agents the medical need is still largely unmet. The main reasons are: the lack of selectivity of conventional drugs, leading to toxicity; the metastatic spreading, implying early tumor implantation in organs other than primary site; the heterogeneity of the disease, comprising about 100 types of cancer; the intrinsic or acquired resistance to chemotherapy developed after few therapeutic cycles, i.e. multi-drug resistance (3, 4). With the revolutionary discoveries in molecular biology however it became obvious, that specific targets can also be identified in tumor cells, the function of which are necessary prerequisites for their replication. These "targets" might be specifically blocked by molecules designed and synthesized for this purpose ("specifically targeted anticancer therapy"). Thus, a massive search of new anticancer agents has primarily been fueled by unveiling new molecular targets on which to intervene, followed by the discovery of novel classes of compounds that interact with such targets (5, 6). A significant fraction of current research in this area has now moved towards the heterocyclic compounds containing nitrogen because a large number of compounds both synthetic and natural, bearing nitrogen-containing simple (pyrrole, pyrimidine, indole, quinoline and purine rings) and fused heterocyclic skeletons (4-anilinoquinazolines, pyrazolopyrimidines, triazolopyrimidines, pyrrolopyrimidines, pyrazolopyridazinesand imidazopyrazines), have been discovered with excellent anticancer activity and many of them are presently in clinical trials (7-11). In this review it is our intention to list those synthetic nitrogen containing heterocycles which have shown promising preclinical results in the last few years. Here focus is being directed mainly to three aspects: chemical structure, activity profile and mode of action.

1. Acridines as anticancer agents

Acridine derivatives play an important role in the class of DNA-intercalating anticancer drugs, which are structurally characterized by the presence of a planar or semiplanar chromophore portion possibly capable of intercalation into DNA. The linear tricyclic ring system of acridine is a versatile moiety in the synthesis of this family of antitumor agents and may constitute either the whole or part of the chromospheres. We have studied a number of acridine derivatives with interesting antitumor properties, and the derivatives which came out in the recent years with potent antitumor activity are focused here.

(i) Acridone derivatives-

It is known that F substituent leads to a slight enhancement of the binding affinity in protein-ligand complexes due to an increase lipophilicity of the molecule. Keeping this in mind a series of simple fluorinated acridones were synthesized from 5-triflouromethyl-1, 3-cyclohexanedione and among all, compound **1** was found to be most active with GI_{50}= 0.13 µM in breast cancer cell line (12). Compounds having pyrrolobenzodiazepine (PBDs) hybrids linked to acridone ring system at C-8 position have been synthesized by Ahmed Kamal group (13). Among all, one of the representative compound **2** with enhanced DNA-binding affinity (ΔT_m= 12.5°C) showed potent in vitro anticancer activity with LC_{50} of 0.07µM against non-small cell lung cancer cell line (H23), <0.01 µM against melanoma cell lines (M14, UACC-62) and 0.05 µM against renal cancer cell

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line (A498) .This reveals the significance of combining a non-covalent DNA-binding agent (acridone) to the covalent binding component (PBD). The detailed mechanistic and molecular modeling studies for these PBD hybrids are in progress.

(ii) Anilino acridines-

A series of 9-anilino acridine derivatives bearing an alkylating N-mustard at C-4 of acridine chromospheres was synthesized by Tsann-Long Su group (14). Two compounds **3a** and **3b** found to be very potent cytotoxic against human lymphoblastic leukemic cell lines (CCRF-CEM) with IC_{50} in the range of 0.0037-0.0512 µM and are 100-fold more potent than parent compound AHMA and also comparable to taxol (IC_{50}=0.0011 µM). Though they are slightly less potent than taxol in vitro, but their optimal therapeutic doses of 10mg/kg for **3a** and 2mg/kg for **3b** were found to be lower than that of taxol (20 mg/kg) against the human breast carcinoma MX-1 xenograft. The intravenous injection of these two with their respective doses resulted 96% tumor suppression (day 15) for **3a** and 77% (day 14) in case of **3b**. They are found as DNA cross linking agents rather than TopoII inhibitors. On the other hand, Bacherikov and his colleagues synthesized a series of 5-(9-acridinylamino)-O/M/P-anisidine derivatives using the complicated QSAR studies of 9-anilinoacridines which demonstrated that the electronic effect of substituent(s) is associated with the drug's binding site, while hydrophobicity is associated with drugs entrance to the active site and steric effect of the substituent is associated with drug's binding to an active site on a macromolecule (15). It was found that compounds **4**, **5, and 6** bearing $CONHCH_2CH_2NMe_2$ and Me substituent's at C-4 and C-5 positions of acridine chromophore exhibited significant in vitro cytotoxicity against human tumor cell growth with IC_{50} of 0.01 µM against MCF-7 cell line, IC_{50} of 0.03 and 0.02 µM against H460 cell line for compounds **4**, **5**, and **6** respectively. The most potent compound **4** on intravenous injection in nude mice bearing human breast carcinoma MX-1 xenograft resulted in 60% (day 26) suppression of tumor volume at a dose of 20mg/kg. Their structure–activity relationship studies revealed the following degree of potency: AOAs > AMAs > APAs.

(iii) Polycyclic acridines-

(a)Tetracyclic acridine derivative-

A series of potential non-covalent DNA-binding antitumor agents, 3-[ω-(alkylamino)alkyl]-6-nitro-[1,2,6]thiadiazino[3,4,5-kl]acridines have been synthesized by Ippolito Antonini group (16). Among all , dimethyl amino derivative **7** has been identified as a new lead in the development of anticancer tetracyclic acridine derivatives with IC_{50} of 0.027 µM against HT29 cell line, similar to that of doxorubicin (IC_{50}=0.026 µM) and significant antitumor activity with %T/C of 70 at a dose of 25mg/kg against marine leukemia (P388).

(b) Pentacyclic acridine derivatives-

A series of 2, 6-di(ω-aminoalkyl)-2,5,6,7-tetrahydro pyrazolo[3,4,5-mn]pyrimido[5,6,1-de] acridine-5,7-diones have been synthesized as DNA-intercalating agents (17). Compound **8** showed excellent cytotoxicity with IC_{50} of 0.040nM against HT29 cell line. The nitro derivative **9** with IC_{50} of 0.98nm against same cell line, found to be potent cytotoxic against both LoVo sensitive cell lines and LoVo/Dx-resistant cell line with IC_{50} of 0.016 and 0.013 µM respectively with no cross resisitance with Dx.

(iv) Acridine carboxamides-

Ippolito Antonini group synthesized a series of DNA-binding potential antitumor agents bearing a cationic carboxamide side chain

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attached in position peri to an electron withdrawing atom (18). Two highly DNA-affinic compounds **10** and **11** with $K_{app}\times 10^{-7}M^{-1}$ value of 142 and 96.9 found to be the most cytotoxic compounds with IC_{50} of 0.0039 and 0.031 µM against human colon adenocarcinoma cell line (HT29). A series of compounds, pyrazolo[3,4,5-kl]acridine-carboxamides with combined structural features of both pyrazolo[3,4,5-kl]acridines and acridine-4-carboxamide have been synthesized by Xianyong group (19). Among all, compound **12** was appreciably cytotoxic in a panel of cell lines with IC_{50} of 26 nM and 48 nM against murine lewis lung carcinoma (LLTC) and human Jurkat leukemia (JL_C) cell lines. These values are more than that of DACA, a compound in clinical trials which have IC_{50} of 189 and 580nM against same mentioned cell lines.

(v) Bisacridines-

In comparison with monomer, the two planar structures connecting appropriate linker length are considered to be the two major factors for increasing cancer cell cytotoxicity. Therefore in order to enhance the DNA binding affinity and cell killing effects of monomers, a series of N-substituted triamine-linked acridine dimers having the bridge length of 6-7 C on triamine linker have been synthesized (20). Most of the compounds have shown IC_{50} <0.02 µM against peripheral blood lines (MOLT-4) and found to be more potent than adriamycin (IC_{50} =0.02 µM).Compound **13** with MTD of 15mg/kg introduced into nude mice, carrying COLO 205 solid tumor by iv administration, produced 80% tumor inhibition in comparison to other testing compounds which produced only 2%-30% tumor inhibition.

In 2004, Ippolito Antonini group synthesized a series of bis (pyrimido [5, 6, 1-de]acridines) and bis (pyrazolo [3, 4, 5-kl] accridine-5- carboxamides) .Among all compounds, **14a-14d** and **15** exhibit enhanced cytotoxic activity with IC_{50}<0.1nM and 3.0nM against human colon adenocarcinoma cell line (HT29) and higher DNA-affinity than corresponding monomers having $K_{app}\times 10^{-7}M$ of values 7.1, 2.1, 8.5, 14, and 6.3 with CT-DNA. Compound **15** undergo preliminary in vivo testing and it largely exceeds the limit of combined ip + sc score $\geq$ 20 and of the sc score $\geq$ 8, indicating **15** as a good candidate for preclinical studies (21).

In continuation of these findings Peng Yang and his colleagues synthesized a series of compounds in which acridine unit was effectively fused with electron deficient group and several polyamine chains ranging from 7.3Å – 12.3Å, were used as linkers to bridge two heterocyclic fused acridine chromophores at 8-site of the compound (22). Among all, compound **16** and **17** proved to be most potent with IC_{50} of 0.025µM against A549 and 0.0246µM against P388 cell lines respectively. The DNA-unwinding angles of these compounds found to be 1.9-2.2 fold more than that of monomer, which indicate their bis-intercalation with pBR322 DNA and also the key role of linkers on unwinding supercoiling of DNA

In 2003, Ippolito Antonini with his group designed and synthesized two classes of bis-acridine-4-carboxamides, one with a linker between the 4, 4'and the other with a linker between 1,1´ positions (23). Compounds **18a**, **18b** with IC_{50} of 0.057 µM, 0.0020 µM and **19a**, **19b** with IC_{50} of 0.00043 µM, <0.0001 µM against HT29 cell line, represent new leads in the field of anticancer acridines, being endowed with excellent DNA affinity ($K_{app}\times 10^{-7}M^{-1}$ values of these compounds with CT-DNA found in the range of 6.3-14), a broad spectrum of activity and remarkable cytotoxic potency.

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2. Carbolines as anticancer agents

β-carboline nucleus is a recurring motif in a wide variety of cytotoxic compounds, both natural and synthetic. In addition to simple, substituted harman and norharman derivatives, more complex structures such as the manzamines, eudistomine K, azatoxin, fascaplysine, picrasidine L and javacarboline display cytotoxic activities in various cancer cell lines. These compounds have been shown to intercalate into DNA, to inhibit CDK, Topisomerase, and monoamine oxidase, and to interact with benzodiazepine receptors and 5-hydroxy serotonin receptors. In the past eight years many β-carboline derivatives have been synthesized and that have shown potent antitumor activities are listed below.

(i) Tetrahydro/dihydro-β-carbolines-

Fascaplysin, a natural pigment is a potent inhibitor of CDK4 has limited potential as anticancer drug due to its toxic side effects, which are thought to arise largely from the ability of its planar structure to intercalate into the structure of DNA. Therefore to devise a potent, non-toxic (non-planar) CDK4 inhibitor based on fascaplysin, Jenkins group designed and synthesized a series of related tetrahydro-β-carbolines (24). Compound **20** with IC_{50} of 9.0 µM found to be most potent which had *para*-substituted biphenyls with methyl in *para*-position at 2-nd position of carboline moiety. This suggests that a strong lipophylic component in the binding mode of compound, as well as the proposed π-stacking interaction of the inhibitors within the 'Phe 93 pocket' could be responsible for the observed CDK4/cyclin D1 inhibition. Similarly, Marcos and his colleagues designed and synthesized a series of non-planar dihydro/dehydro- β -carboline based derivatives of toxic fascaplysin (25). For this series the best hits correspond to the *ortho*-brominated compounds **21** and **22** which showed selective inhibition of CDK4 over CDK2 with IC_{50} of 11 and 14 µM. On crystallographic analysis, it was found that they exist in a rigid conformation, differing from fascaplysin only in the relative position of outer phenyl group, so a similar mode in the ATP site of enzyme was expected.

To improve the specificity and selectivity of Fumitremorgin C, a selective inhibitor of the breast cancer resistance protein (BCRP/ABCG2), Jiawang Liu group designed and synthesized a series of novel 2-substituted tetracyclic derivatives of tetrahydrocarboline based on the structural analysis of fumitremorgin C (FTC), imidazoline and β -carboline amino acid benzylester (26). The exposure of doxorubicin resistant MES-SA/Dx5 cells to some of these compounds resulted in significant reduction of resistance of the cells against doxorubicin, which was accompanied by lowering of IC_{50} value to doxorubicin from 1.55 ± 0.26 µmol/L to 0.33 ± 0.05 µmol/L for 2-(2-butyl)-derivative **23a**, to 0.46± 0.04 µmol/L for 2-benzyl-derivative **23b**, to 0.36 ±0.03 µmol/L for 2-benzyloxycarbonylmethyl-derivative **23c**, to 0.77 ±0.08 µmol/L for2-benzyloxycarbonylethyl-derivative **23d**. These compounds were able to inhibit the proliferation of MES-SA/Dx5 cells with % inhibition of 38.9, 31.2, 31.2, and 13.4 respectively. Recently a series of 1-substituted 1,2,3,4-tetrahydro-and 3,4- β -carbolines have been synthesized by Shen group (27). Among all, compound **24** found to be more active that manzamine A with IC_{50} <0.001µg/ml against murine P-388 and KB-16, A-549, HT-29 human tumor cell lines. The cytotoxic mechanism of this compound has been reported and was found that it induced cell death resulting from chromosome missegregation.

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(ii) Carboline carboxamides-

Xiao and his colleagues synthesized a series of β-carboline derivatives with carboxamide side chain at position-3 to study the effects of flexible side chain on the intercalating ability and antitumor activity (28). Compound **25** having – $CONH(CH_2)_4NH_2$- as a side chain exhibited the strongest stabilization of CT-DNA (ΔT_m= 5.7ºC) with greatest binding affinity ($K=4.503\times10^4M^{-1}$), the lowest docking binding energy (-167.28kJ/mol) and high inhibition rate with IC_{50} of 1.9×10^{-6}M and 8.6×10^{-6}M against HL-60 and BGC cell lines respectively. Results from several different techniques indicated that this chain was favorable for the terminal amine group to form hydrogen bonds with the N_7 of guanine along the groove of the DNA helix. The further in vivo study of this compound is in progress. On the other hand, Huaji Guan and his colleagues synthesized a series of 41 compounds and proved that substituent in position-9 of the β-carboline
ring could reinforce the DNA intercalating ability and consequently cytotoxicity to tumor cell lines, and the amidation of amino group at the end of the DNA targeting side chain in position-3 could cripple the DNA intercalating activity of the compounds, which resultingly initiated the cytotoxic selectivity to tumor cell lines rather than to normal ones (29). Furthermore, the S and G2-M arrest induced by these compounds confirmed that they could target DNA and lead to DNA destructions in Hela cells. Among all the 41 synthesized compounds, two compounds **26a** and **26b** found to be most potent with IC_{50} of 0.0068 and 0.0117µmol/ml respectively against Hela tumor cell line and IC_{50} of 0.047 and 0.038µmol/ml respectively against HFL-1 normal cell lines. The values were found to be comparable with harmine, which have IC_{50} of 0.0640µmol/ml and 0.06230117µmol/ml against above mentioned cell lines.

(iii) 1-amino-β-carbolines-

A series of 1-amino-substituted--β-carbolines have been prepared by Yohan and Iain as a simple mimic of manzamine A (30). Among all, compound **27** showed the best activity with GI_{50} of 0.38µM against non small cell lung cancer (HOP-92), which is comparable to that of natural product manzamine A (GI_{50} = 0.25µM). Viscosity studies of these compounds with the standard agents like norharman and harmol, suggested that they binds to CT-DNA by intercalation.

(iv) Annulated carbolines-

A series of cis- and trans-tetrahydro-β-carbolines annulated to a diketo piperazine was prepared by Wang and his colleagues as analogues of natural product dimethoxyfumitremorgin C (31). The most active compound **28** was trans isomer with IC_{50} of 5.9µM and found to more active than tryprostatin B, as it induced cell cycle arrest at the M phase and disruption of the microtube network at 250 µM. This compound is relatively nontoxic with MTD of 40mg/kg in mice and currently undergoing evaluation in NCI's hollow fiber in vivo tumor model. In 2001, Martial Bertrand group prepared novel hexahydroindolizino[8,7-b]indole
derivatives (32). Among all, the two most active derivatives, the 1-cyano **29** and 2-cyano **30** with IC_{50} of 8.0 µM and 8.2 µM respectively against doxorubicin sensitive (K562S) tumor cell line and with IC_{50} of 9.0 µM and 8.2 µM against doxorubicin resistant (K562R) cancer cells, were found to induce significant accumulation of the L1210 cells in the G_2M (45%) and 8N (>G_2M) (17-33%) phases of the cell cycle at the concentration of 25 µM. Also the growth

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inhibitory potency of these compounds showed no loss of cytotoxicity in K562R cancer cells resistant to doxorubicin.

On the other hand Alberto Fontana group synthesized pyridazino[1', 6': 1,2]pyrido[3,4-b]indol-5-inium derivatives from commercially available β-carboline derivative harmine (33). The two most active compounds **31a** and **31b** with IC_{50} of 0.048 and 0.065 µM respectively against L1210 cancer cells, which is more than that of drugs like adriamycin (0.025 µM) and camptothecin (0.03µM) found to exert their effect in the G_1 phase of the cell cycle. Similarly, Bipul Baruah and his colleagues synthesized a series of 3, 10-substituted quinazolino-β-carbolines (34). Three compounds **32a**, **32b** and **32c** showed promising in vitro cytotoxic activity with GI_{50} values of 2 µM against SKOV3 and DU145 cell lines, 1 µM against MCF7 and ACHN cell lines and 2 µM against SW620 and UACC62 cell lines respectively. But because of their poor bioavailability their good in vitro activity did not translate in the xenograft model, therefore further work to impart the desired in vivo activity is in progress.

(v) Carboline homodimers-

Recently, Deveau and his colleagues synthesized a series of diketopiperazine-base carboline homodimers similar in structure to azatoxin and fomitremorgin class of natural products (35). Phenol **33a** with GI_{50} of 21.50µM against H520 cell line and 21.90 µM against PC-3 cell line, inhibited cancer cell growth approximately three times better than its enantiomer **33b** (GI_{50}=61.50 and 55.30 µM), which is also comparable to the clinically used etopside having GI_{50} of 13.50 and 12.50 µM respectively against above mentioned cell lines. Because of **33a'**s structural similarity to etoposide and axatoxin, further biological testing is intended to determine whether **33a** may target topoisomerase II, tubulin, or interact with DNA.

3. Carbazoles as anticancer agents

Natural and synthetic carbazoles, either in a pure substituted or in an annulated substituted form, represent an important and heterogeneous class of anticancer agents, which has grown considerably over the last two decades. Many carbazole derivatives have been tested for cyctotoxic activity, some of them have entered into clinical trials, but only very few have been approved for the treatment of cancer so far, since the clinical application of many carbazoles has encountered with severe side effects or multidrug resistance. Due to their polycyclic, planar and aromatic structure carbazoles DNA remains one of the main targets for cytotoxic carbazoles apart from the targets include enzyme inhibition such as topoisomerase I/II and telomerase, cyclin-dependent kinase. In order to overcome these problem many carbazoles derivatives have been synthesizing today also and the derivatives which have gained our attention because of their potent antitumor activities in the last few years are as follows.

(i) Indolocarbazoles-

Recently, Myriam Lefoix group synthesized a series of 5-azaindolocarbazoles as Chk1 inhibitors as Chk1 plays a very important role in the cell cycle regulation via the DNA damage check point (36). Among all, three compounds **34a, 34b** and **34c** found as promising novel Chk1 inhibitors with IC_{50} of 72, 27 and 14nM respectively. Whereas, the two compounds **35** and **36** found to be most potent cytotoxic agents against L1210 cell line with IC_{50} of 0.495 and 0.195 µM respectively.

(ii) Phenylcarbazoles-

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In 2006, Sylvain Routier and his colleagues synthesized a series of phenylcarbazole derivatives and compound **37** found to be most cytotoxic with IC_{50} of 0.0122 and 0.0187 µM against CEM and camptothecin resistant (CEM/C2) human leukemia cell lines (37). Although binding of these agents to DNA likely to contributes to the cytotoxic action, the exact molecular target still remain undiscovered and thus warrants further investigations.

(iii) Pyrrolocarbazoles-

Joseph and his group synthesized a set of three tetrahydropyrrolo[3,4-a]carbazole-1,3-diones. Among these three compounds, one compound **38** exhibited high toxicity to P388 murine leukemia cells with IC_{50} of 3.90 µM and also provoke a marked accumulation in the G_2/M phase of the cell cycle (38). Laronze and his colleagues synthesized a series of 'bended' 1, 3 or 'linear' 2 pyrrolidino-fused (aza) carbazoles and proved that members of linear family are more toxic than bended ones (39). Among all, compound **39** found to be the most cytotoxic with IC_{50} of 0.34µM against L1210 cell line. Compound **39**, a potent DNA binder (ΔT_m=22°C) induced strong accumulation (80%) of the cells in the G_2M phase at 2µM.

4. Indoles as anticancer agents

Interest in the synthesis of novel indole-based heterocycles has increased in recent years due to the prevalence of indoles in biologically-active natural products such as the fumitremorgin class and the significance of the indole moiety in clinical chemotherapeutics like ellipticine. Many MDR cell lines which are found to be resistant to many present pharmacological agents, proved as non-resistant to many of the synthetic indole derivatives. Therefore indole derivatives have gained much attention in the field of discovering potent and effective anticancer agents. Recently discovered indole derivatives with potent cytotoxic profile are discussed here.

(i) Indole analogues

Indole analogues of **39a** were evaluated for their cytotoxic activity against human breast tumor cell lines (39a). A thiazolyl indolequinone, BE 10988 **39b** , isolated from culture broths of Streptomyces strain, is known to increase DNA-topoisomerase complex formation and displayed significant anticancer activities(39b).

Kumar et al (39c-39e). reported synthesis of diverse 4-(3-indolyl)oxazoles **39c,** 5-(3-indolyl)-1,3,4-oxadiazoles, 5-(3-indolyl)-1,3,4-thiadiazoles and 5-(3-indolyl)-1,2,4-triazoles **39d** as potential anticancer agents against many types of human cancer cell lines. The cytotoxicity results of various 5-(3-indolyl) azoles indicates that the five-membered heterocyclic ring and substituents at C-2 and C-5 positions play a vital role in the activity and selectivity of indolyl azoles towards cancer cells. The most potent compounds in various indolyl azoles bearing a common C-5 indole moiety have different substituents at C-2 position of five-membered heterocyclic ring. The anticancer activity of 5-(3-indolyl)-2-substituted 1,3,4-thiadiazoles was found to be relatively better than that of 4-(3-indolyl)oxazoles, whereas, comparable to 5-(3-indolyl)-1,3,4-oxadiazoles and 5-(3-indolyl)-1,2,4-triazoles.

There are many diarylazoles reported as analogs of chalcones in which enone moiety has been successfully replaced with a five-membered heterocyclic unit. Replacement of an enone moiety with a five-membered heterocyclic ring or vice versa has been proved to be beneficial for the biological activity. Kumar et al (39e) prepared an interesting series of indolyl chalcones **39f** and **39g** as analogues of indolylazoles **39e**

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and evaluated *in vitro* for their anticancer activity against three human cancer cell lines. Some of the indolyl chalcones were identified as potent and selective anticancer agents with IC_{50} values 0.03 and 0.09 μM, against PaCa-2 cell line. The preliminary anticancer activity study of indolyl chalcones revealed that 3,4,5-trimethoxy-phenyl, 4-pyridyl and *N,N*-dimethylphenyl moieties are critical for anticancer activity and selectivity.

(ii) Naphthoindoles-

The presence of indole moiety in anthracyclines can decrease the formation of semiquinones and free radicals, which frequently determine the cumulative cardiotoxicity of anthracyclines. Therefore, a series of compounds that combine indole and anthraquinone moieties in their structures was synthesized as 1-(ω-aminoalkyl) naphthoindolediones (40). Among all compounds, N-(4-amino butyl) derivatives **40a**, **40b**, **40c** showed higher potency than adriamycin or mitoxantrone against MDR breast cancer cell line (NCI/ADR) with GI_{50} of 4.50, 2.30 and 2.70 μM respectively.

Andrey with his colleagues, synthesized mannich derivatives of 4,11-dihydroxynaphtho[2,3-f]indole-5,10-dione with an additional amino function in their side chain (41). The 3-(1-piperazinyl) methyl derivative **41a** and 3-(quinuclidin-3-yl) amino methyl derivative **41b** with GI_{50} of 1.30 and 1.20mKM respectively killed HCT116 colon carcinoma cells (carrying wild type p53) and their p53-null variant within the similar range of concentrations. Both compounds also showed high potency for NCI/ADR multi drug resistant cells with same GI_{50} of 1.5 mKM and conferred an important feature to the resulting compounds, namely, the potency for tumor cells otherwise resistant to a variety of anticancer drugs. Recently, they also synthesized a series of 4,11-diaminonaphtho[2,3-f]indole-5,10-diones and found that their cytotoxicity for MDR, P-glycoprotein-expressing tumor cells was highly dependent on the N-substitution at the terminal diamino group of the ehtylenediamine moiety (42). Naphthoindoles carrying N-Me group **42a** and N-N-dimethylamino group **42b** showed remarkable activity against Pgp-positive MDR cells with GI_{50} of 1.30 and 1.0 μM respectively and with IC_{50} of 0.8 and 1.0 μM respectively against K562 cells. It was also found that methylation of hetero N in **43a, 43b** and **43c** with IC_{50} of 1.50, 2.40 and 1.30 μM respectively against HCT116 cells resulted in a 10-20 fold increase of activity compared with their unsubstituted congeners.

(iii) Indole craboxylate/carboxamide derivatives-

Novel 6,11-dioxo-6,11-dihydro-benzo[f]pyrido[1,2-a]indole-12carboxamide derivatives were designed in accordance with Moores and Pindur's theory and synthesized based on structural similarity with known antitumor agents like ellipticine, mitoxantrone (43). Among all, the cytotoxicity (GI_{50}=0.638 μM) of compound **44** against the adriamycine-resistant breast tumor cell line (ADR-RES) at a concentration< 1 μM turned out to be higher than those of clinically used anticancer agents like daunorubicin (GI_{50}=1.25 μM) and mitoxantrone (GI_{50}=3.98 μM). It also showed good selectivity towards leukemia (HL60), colon (COLO205) and renal cancer (ACHN) cell lines withGI_{50} of <0.01, 0.31 and 0.169 μM respectively. DC-81, **45** an antitumor antibiotic produced by the *Streptomyces* species, belongs to pyrrolo[2,1-*c*] [1,4]-benzodiazepine (PBD), which are potent inhibitors of nucleic acid synthesis. Hu and his colleagues previously

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reported the synthesis of PBD hybrids linked with indole carboxylates and recently they demonstrated the mechanism of the anticancer effect of PBD hybrid (IN6CPBD) agent **46** on human melanoma A375 cells (44). Their studies indicate that IN6CPBD-treated cells exhibited higher cytotoxicity than DC-81 and it induces apoptosis in A375 cells through a mitochondrial dysfunction pathway, leading tocaspase-3 substrate PARP cleavage and subsequent apoptotic cell death. Similarly, Wang and his group synthesized a series of PBD hybrids linked indole carboxylates by linking C-8 of (DC-81) with an indole 2-carbonyl moiety through carbon chain linkers (45). The two most active compounds **47** and **48** with mean GI_{50} values of 0.38 and 0.182µM over 60 cell lines tested were examined in an in vivo hollow fiber assay and it was found that they had total scores of 22 and 30 and thus considered to be active and to have potential as an antitumor/anticancer drug candidate. Their studies also proved these hybrids as potent inducers of cell apoptosis in A2058 cells as compare to DC-81.

(iv) Synthetic indole alkaloids-

(a) Tryprostatin A analogues-

Recently, a series of tryprostatin A, an inhibitor of breast cancer resistance protein (BCRP) analogues have been synthesized by Hiteshkumar and his colleagues (46). Among all, two analogues **49a** and **49b** with IC_{50} of 10 and 19 µM found to be several folds more potent than tryrostatin in the inhibition of the growth of tsFT210 cells. It was also proved that the diastereomer-2 of tryprostatin B **50** was a potent inhibitor of the growth of three human carcinoma cell lines: H520 (IC_{50} = 11.9 µM), MCF-7 (IC_{50} = 17.0 µM) and PC-3 (IC_{50} = 11.1 µM) and was equipotent with etoposide, a clinically used anticancer agent.

(b) Acryiaflavins analogues-

A series of new oxophenyl acryriaflavins was designed and synthesized by Bourderioux group and the compound **51** bearing cationic chain on the top of the maleimide ring showed the most cytotoxic activity in the series with IC_{50} of 0.31µM against HL60, close to that of rebeccamycin (IC_{50}= 0.16 µM) and also marked DNA interaction with ΔT_m of 7ºC (47).

(v) Miscellaneous indole derivatives-

Two tetrahydropyrido[3,2-b]pyrrolo[3,4-g]indole-1,3-diones **52a** and **52b** have been synthesized (48). These two compounds having high toxicity with IC_{50} of 1.9 and 1.0µM respectively against P388 cells, found to provoke a marked accumulation of 50% and 61% respectively in the G_2/M phase of the cell cycle, when P388 cells treated for 8 h with 10µM of these compounds.

A series of indole containing oxazolines has been discovered as a result of structural modifications of the lead compound **53** (A-105972). These compounds exert their anticancer activity through inhibition of tubulin polymerization by binding at the colchicines site. Among all, the most active compound **54** (A-289099), the S-isomer with IC_{50} of 8.60 and 6.20nM respectively against HCT-15 and NCI-H460 and with IC_{50} of 6.3nM against human lung cancer with mutated β-tubilin, found to be 74 fold more potent than R-isomer and comparable to combretastatin A4 (49). A-289099 with MTD of 100mg/kg/day achieved 206% increase in life span and an impressive 28 day delay to 1 g tumor volume in mice with M5076 murine ovarian sarcoma. BPR0L075 is a novel synthetic 3-aroylindole compound, **55** that exerts a broad spectrum of activity against human leukemia, glioblastoma, oral, nasopharyngeal, breast, gastric, colorectal, and liver cancer cells *in vitro* and strongly inhibits tubulin

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polymerization through binding of tubulin's colchicine-binding site (50). The potential antitumor effect of BPR0L075 in vivo was assessed in human tumor KB-xenografts in mice and 82% decrease in tumor volume (day 30) at a dose of 50mg/kg/day was observed. It was also proved that the several KB-derived multidrug-resistant cell lines over expressing P-gp170/MDR and MRP, which are resistant to vincristine with IC_{50}= 0.6nM, 90.10nM and 1.2nM, paclitaxel with IC_{50}=4.1nM, 16,500nM and 7.9nM, and colchicines with IC_{50}=10.5nM, 11.5 and 55.2nM found to be non-resistant to BPR0L075 with IC_{50}=3.60nM, 2.9nM and 4.2nM against KB and KB-derived MDR-positive cell lines P-gp170 and MRP respectively.

(vi) Bisindoles-

Number of bisindole derivatives have been synthesized as analogues of cytotoxic bis(indole) alkaloids, which possessed strong inhibitory activity against a wide range of human tumor cell lines. A series of 3,5-bis(2-indolyl)pyridine was designed by Jacquemard group as potential CDK inhibitors (51). Among all, the most active compound **56** showed CDK1 inhibition with IC_{50} of 0.54µM with a good selectivity over GSK-3 (IC_{50}=30 µM). Few years back a series of bis(indolyl)-4-trifluoromethyl pyridine was synthesized by Xiong and his colleagues compound **57** the most potent compound of the series found to exhibit strong inhibitory activities against P388 cell lines with IC_{50} values of 4.3 mM and A-549 cell lines with IC_{50} values of 1.7 mM (52). Recently, Aldo Andreani group reports the synthesis of compounds formed by two indole systems separated by a heterocycle (pyridine or piperazine) and it was found that the pyridine derivatives were far more active than the piperazine derivatives and also are much more active than the numerous, so far prepared and tested 3-indolylmethylene-2-indolinones (53). Two compounds **58a** and **58b** proved to be the most active compounds with mean pGI_{50} of 6.34 and 5.92 respectively when evaluated in the full panel of 60 human tumor cell lines. Compound **58b,** bearing the 5-methoxy-2-indolinone moiety was subjected to the first in vivo experiment (hollow fiber assay) and was active, therefore it was selected for the second in vivo experiment (human tumor xenograft in mice) but did not show significant activity in the tumor employed (HL-60-TB leukemia).

A series of 3,6-bis[30-(N-methyl-indolyl)]pyrazine have been synthesized by Jiang and Xiao-Hui Gu and compound **59a** showed low cytotoxicity, but its N-Me derivative, **59b** possessed very strong inhibitory activity against all cell lines with GI_{50} values 0.72, 0.248, 0.058, 0.287, and 0.29 µM against NCI-H322M lung, HCT-15 and KM12 colon, SK-MEL-5 melanoma, and MCF 7 breast cancer cell line respectively (54). A series of bis(benzo[g]indoles) bridged by CX-$(CH_2)_n$N(Me)$(CH_2)_n$-CX (X = O, S, H; n= 2,3) was synthesized as bifunctional antitumor agents (55). Compounds **60a** exhibited a good level of activity with IC_{50} of 0.36µM, 0.297 µM, against K-562 and HCC-2998 cell lines and one of its derivate **60b** demonstrated significant inhibitory effects with IC_{50} of 1.82µM and 1.41 µM respectively against the above mentioned cell lines. Compound **60a** was then tested in the hollow fiber cell assay to evaluate its in vivo antineoplastic activity and found that compound **60a** with IP: 4, SC: 2, total score: 6, produced a moderate reduction in the viable cell mass below the level present at the start of implantation. These compounds were also found to behave as typical DNA intercalating agent, as judged from viscosity measurements with Poly (dA-dT)...poly (dA-dT).

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5. Pyridine derivatives as anticancer agents

Since its discovery in 1932, the 2,2';6',2"-terpyridine molecule has attracted medicinal chemists and biologists due to its ability to form metal complexes and binding ability to DNA .It has been shown that terpyridine derivatives as well as the bioisosteres of terpyridine possessed strong cytotoxicity against several human cell lines. Such previous studies prompted researchers to do the systematic study on the effects of substituted pyridines and of the substituent's on the pyridine nucleus, which gave large number of pyridine derivatives and those have shown potent antitumor activities in the last few years are listed below.

A series of fused pyridine, pyrane, and pyrimidine derivatives were synthesized by Abdel and his colleagues (56). Among all synthesized pyridine derivatives compound **61** and **62** exhibited better in vitro antitumor activities at low concentration compared with 5-fluorodeoxyuridine, $\log_{10}$ GI_{50} = -4.7 used as reference control and were highly selective to inhibit leukemia cell lines with $\log_{10}$ GI_{50} of -5.3.

Qun Li and his group designed and synthesized a series of 3,4'-bispyridinylethylene series, which led to the discovery of 3-isoquinolinylpyridine **63** as a potent PKB/Akt inhibitor with an IC_{50} of 1.3 nM against Akt1 (57). Compound **63** showed excellent selectivity against distinct families of kinases such as tyrosine kinases and CAMK, and displays poor to marginal selectivity against closely related kinases in the AGC and CMGC families. Moreover, **63** demonstrate potent cellular activity comparable to staurosporine, with IC_{50} values of 0.42 and 0.59µM against MiaPaCa-2 and the Akt1 overexpressing FL5.12-Akt1, respectively. Inhibition of phosphorylation of the Akt downstream target GSK3 was also observed in FL5.12-Akt1 cells with an EC_{50} of 1.5 µM. Further the structure–activity relationships of a series of isoquinoline–pyridine-based protein kinase B/Akt antagonists have been investigated in an effort to improve the major short-comings of this lead compound **63,** including poor pharmacokinetic profiles in several species e.g., mouse (iv $t_{1/2}$ = 0.3 h, po F = 0%). Chlorination at C-1 position of the isoquinoline **63a** improved its pharmacokinetic property in mice (iv $t_{1/2}$ = 5.0 h, po F = 51%) but resulted in >500-fold drop in potency (58). Also the 3-amino analog **63b** was statistically more active in both FL5.12-Akt and MiaPaCa-2 cells with IC_{50} of 0.20 and 0.1 µM as compare to compound **63** and it was also found to slowed the tumor growth significantly, in a mouse MiaPaCa-2 xenograft model. Gui-Dong group also describe a series of potent and selective oxindole–pyridine-based protein kinase B/Akt inhibitors (59). The most potent compound **64** in this series demonstrated an IC_{50} of 0.17 nM against Akt1 and more than 100-fold selectivity over other Akt isozymes. Compound **64** also inhibited tumor growth MiaPaCa-2 mouse xenograft model at a dose of 15mg/kg/day with %T/C of 69 at d24.

Jew and his colleagues synthesized a series twenty-one pyridine-2-carboxylate derivatives (60). Among them, the 3,4-dichlorothiophenolester **65** with potent in vitro telomerase inhibitory activity (IC_{50} =68µM) showed quite significant in vivo tumor suppression. Its in vivo antitumor activity assay was performed in CX-1 human clone-bearing athymic nude mice and a clear tumor-suppressing effect, by 30% in tumor volume at the dose of 20 mg/kg/day, was observed after 37 days which was associated with its telomerase inhibitory activity, not with cytotoxicity.

For the first time, the topoisomerase I inhibitory activity of 2,4,6-trisubstituted pyridines was reported by Zhao group (61).

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Compounds **66a, 66b** and **66c** exhibited strong topoisomerase I inhibitory activities with IC_{50} of 400µM, <10µM and 50µM respectively, while **67** exhibited moderate inhibition of 500µM, compared to that of camptothecin, which revealed that the 2-thienyl-4-furylpyridine skeleton is important for topoisomerase I inhibitory activity.

A series of N-(2-(trifluoromethyl)pyridin-4-yl)anthranilic acid ester and amide derivatives were synthesized by Cocco and his colleagues (62). Among all ester derivatives, compound **68** exhibit potent antiproliferative activity against all tested cell lines with GI_{50} values in the range of 0.026-8.6µM and showed particular selectivity against melanoma (LUX-IMVI) with GI_{50} of 0.026 µM and against leukemic MOLT-4, CCRF-CEM, and K-562 with GI_{50} of 0.028, 0.032 and 0.051 µM, respectively, while **69** exhibited potent cytotoxicity with GI_{50} in the rage of 0.010-0.72µM against all cancer cell lines. Among all amide derivatives, N-anthraniloylglycinate **70** shown moderate inhibitory activity in the full panel cancer cell line screening, with selective inhibitory activity against non-small cell lung cancer (HOP-92) with GI_{50} of 0.057µM.

Recently, Anchoori and his colleagues synthesized a 30-compound library of phenoxy pyridine and phenyl sulfanyl pyridine derivatives as microtubule inhibitors (63). Of all 30 compounds tested, compounds **71** and **72** showed the largest decrease in proliferation against Panc1 and HS766T human pancreatic cancer cells with IC_{50} of 0.8, 0.15 µM and 0.7, 0.5µM respectively. Cell cycle analysis on breast cancer MCF7 cells treated with **71** or **72** revealed that both agents caused mitotic arrest and these compounds are currently being evaluated for their in vivo efficacy in animal models. It was also found that these analogues inhibited cell survival in both the paclitaxel-sensitive and paclitaxel-resistant ovarian cancer cells (SKOV3) with equivalent activity.

6. Pyrimidine derivatives as anticancer agents

Pyrimidine derivatives have been very well known in medicinal chemistry for their therapeutic applications. One possible reason for their activity is presence of a pyrimidine base in thymine, cytosine and uracil, which are essential building blocks of nucleic acids, DNA and RNA. Recently, [1,2,4]triazolo[1,5-*a*]pyrimidines have aroused increasing attentions from chemical and biological viewpoints since they were proved to be the promising anticancer agents with a unique mechanism of promoting tubulin polymerization as well as the mechanism of cyclin-dependentkinases-2 inhibition. Therefore, in the course of research devoted to the development of new classes of pyrimidine and condensed pyrimidine moieties, a large number of compounds bearing nitrogen-containing fused heterocyclic skeletons, such as 4-anilinoquinazolines, pyrazolopyrimidines, pyrrolopyrimidines, pyrazolopyridazines and imidazopyrazines, have been discovered particularly and many of them exhibited excellent anticancer activity. Those recent derivatives with potent anticancer activities are reported here.

(i) Thiazolo pyrimidines-

Fahmy and his group described several fluorophenyl substituted thiazolo[4,5-d]pyrimidines (64). Compound **73** displayed good antitumor activity against all of the cell lines used with good selectivity against ovarian cancer (GI_{50} = 0.004 µM/mL) and prostate cancer (GI_{50} = 0.003 µM/mL).Compounds **74** and **75** being non-selective showed GI_{50} values in the range of 0.054-0.144 µM/mL and 0.021–0.038 µM/mL respectively against the nine tumor sub-panels tested.

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(ii) Amino pyrimidines-

Cocco and his colleagues designed and synthesized a novel series of highly functionalized alkyl-and arylidenhydrazinopyrimidines (65). 2,4-dichlorosubstituted compound **76**, the most active in the series showed high cytotoxic activity on leukemia (SR), colon cancer (HCT-15), ovarian cancer (IGROV1) and (OVCAR-3), melanoma (SK-MEL-5), renal cancer (A498), and breast cancer (MDA-MB-435) cell lines with GI_{50} values in the range of 3.15×10^{-7} to 8.78×10^{-7} M. COMPARE analysis results suggested that this compound may exert its antitumor activity partly through affecting mitosis. A series of 4-chloro-2-cyanoamino-6-fluoroalkylamino-5-phenylpyrimidines was prepared by Zhang group, as a result of modifications made in a series of [1,2,4]triazolo[1,5-a]pyrimidines that proved to be potent anticancer agents with a unique mechanism of tubulin inhibition (66). The most active compound **77** this promotes polymerization of either MAP-rich tubulin or pure tubulin in vitro, showed inhibition of COLO 205cells with IC_{50} of 36 nM. Its good water solubility (>100 µg/mL at pH 7.4) and high microsomal stability (92% remaining after incubation in nude mouse microsomes for 30 min) make it suitable to be use as pharmaceutical agent. Compared with TTI-237(in phase I clinical trials), compound **77** retains in vitro activity and the capability to overcome multidrug resistance due to P-gp in the sensitive KB line and in the clinically more relevant KB 8.5 line with IC_{50} of 24 and 59nM respectively.

(iii) Pyrrolo and pyrazolo pyrimidines-

Dalal and his group designed a series of pyrrolo[2,3-d]pyrimidine derivatives based upon the molecular modeling simulation of the fitting values and conformational energy values of the best-fitted conformers to VEGFRTK inhibitor hypothesis (67). Compound **78**, possesses thioureido moiety which is known to have antitumor activity, found to be the most active compound with IC_{50} of 26.5µmol/ml, much more than that of doxorubicin (IC_{50} = 81.5µmol/ml). Docking studies revealed that compound **78** showed VEGFRTK inhibitory effects similar to vatalanib (VEGFRTK inhibitory lead compound). Daniela Moravcova with his colleagues, identified substituted pyrazolo[4,3-d]pyrimidines as novel inhibitors of CDK1/cyclin B and also proved that these derivatives strongly inhibited CDK1 kinase at concentrations approximately 2–10 times lower than the respective 6,9-disubstituted purines (68). The most active compound **79**,
bearing a 2-hydroxybenzylamino moiety at C7 showed CDK inhibiton with IC_{50} of 0.44µmol/dm^3, 10 times more than that of its corresponding purine analogue.

Gangjee and his colleagues designed and synthesized a series of thirteen N4-phenylsubstituted-6-(2-phenylethylsubstituted)-7H-pyrrolo [2,3-d]pyrimidine-2,4-diamines as multiple receptor tyrosine kinase (RTKs) inhibitors (69). Two compounds **80** and **81** proved as multi-RTK inhibitors with IC_{50} of 0.3, 45.1, 11.8µM and 4.2, 11.2, 11.1µM against EGFR, VEGFR-1 and PDGFR-β respectively, while two compounds **82a** and **82b** as potent inhibitors of angiogenesis with IC_{50} of 0.03 and 0.12 µM respectively.

(iv) Pyrido pyrimidines-

Recently, Cordeu and his group synthesized a series of twenty 2,4-pyrido[2,3-d]pyrimidine derivatives as apoptotic agents (70). The most active compound **83 (**HC-6) showed IC_{50} of 8.9, 5.0 and 1.5µM against HT-29, T-24 and HTB-26 tumor cell lines respectively. It was found that HC-6 showed dose-dependent cytostatic and proapoptotic effects through activation of two different signaling pathways namely a pathway

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leading to cell cycle arrest and a transcription-independent route leading to rapid apoptosis and thus makes HC-6, a promising candidate as a novel therapeutic agent.

(v) Triazolo pyrimidines-

Nan Zhang and his colleagues synthesized a series of [1,2,4]triazolo[1,5-*a*]pyrimidines and is the only series of small, synthetic molecules to promote tubulin polymerization (71). It was also found that a (1*S*)-2,2,2-trifluoro-1-methylethylamino group or an achiral 2,2,2-trifluoroethylamino group at the 5-position and also on the phenyl ring, both fluoro atoms, at the positions ortho to the triazolopyrimidine core, are needed for optimal activity. Compound **84,** the most potent compound of this series with IC_{50} of 31nM against COLO205 and of 23 and 67nM against KB and KB 8.5 cell lines, respectively was found to possessed excellent pharmaceutical properties like high metabolic stability in female nude mouse, rat and human liver microsomes ($t_{1/2}$ = 433, 88, and 133 min, respectively) and high solubility in water (0.89 mg/mL at pH 6.74). On both intravenous and oral administration it showed significant inhibition of tumor growth *in vivo* in A549 non-small cell lung carcinoma. This compound **84** (TTI-237) is currently in phase I clinical trials. Recently Zhai group synthesized a series of [1,2,4]triazolo[1,5-*a*]pyrimidine-7-amines and it was found that their cytotoxicity depends strongly on substitution pattern of the side chains at C-2 position (72). Compound **85** with 3-((5-(pyrrolidin-1-ylmethyl)furan-2-yl) methylthio as a side chain found to the most potent among all with IC_{50} of 15.0mM and 7.8mM against Bel-7402 and HT-1080 cell lines, respectively), and thus can considered as promising lead for further structural modifications.

(vi) Fused pyrimidines-

As mentioned above Abdel and his colleagues synthesized a series of fused pyrimidine derivatives (56) and it was found that compound **86** showed better in vitro antitumor activities at low concentration compared with 5-fluorodeoxyuridine, $\log_{10}$ GI_{50} = -4.7 used as reference control and were highly selective to inhibit leukemia cell lines with $\log_{10}$ GI_{50} of -5.3, while compound **87** showed good anticancer activity against all the tested cell lines with $\log_{10}$ GI_{50} = -4.0.

7.Purines-

Modified purines possess diverse biological activities, and lead to a better understanding of some biological effects of DNA-damaging agents as well as enzymes-substrate interactions. This lead has been used in the development of many potent anticancer agents. A series of 8-substituted methylxanthine derivatives was prepared by Rida and his group (73). Among all derivatives compound **88** exhibited a super sensitivity profile towards leukemia K-562 with a GI_{50} value of <0.01 µM, whereas compound **89a** showed significant activity against colon cancer HCT-15 and renal cancer CAKI-1 with GI_{50} of 0.47 and 0.78 µM, respectively and compound **89b** displayed high activity against colon cancer HCT-15 with GI_{50} = 0.8 µM.

A series of (RS)-6- substituted-7- or 9-(1,2,3,5-tetrahydro-4,1-benzoxazepine-3-yl)-7H- or 9H-purines have been prepared by Gavilan and his colleagues (74). Benzoxazepine O,N-acetals containing purine ring with chlorine substituent at 6-position **90** found to be the most active compound with IC_{50} of 0.67 µM against MCF-7 cell lines. The main molecular targets of this compound were pro-apoptotic genes with protein kinase activity such as GP132, ERN1 or RAC1, which prevent the metastatic progression. With the aim of

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diminishing the toxicity and obtaining biologically active derivatives of 5-FU suitable for oral administration, the pyrimidine base was substituted by the purine moiety with the objective of increasing both the lipophilicity and the structural diversity of the target molecules (75). The 6'-halogen substituent of the (RS)-9- or 7-(2,3-dihydro-5H-1,4-benzodioxepin-3-yl)-7H-purines **91a, 91b,** and **91c** showed significant antiprolifertaive activity against MCF-7 cell line with IC_{50} of 2.74, 4.01 and 1.28 µM respectively.

8. Sulfonamides as anticancer agents

Sulfonamides constitute a useful class of drugs, displaying a variety of activities including antibacterial, anticarbonic anhydrase, diuretic, hypoglycemic, and antithyroid effectiveness. Since the discovery of **92** (E-7010) in 1992, which is presently in phase II clinical trials, a large number of structurally novel sulfonamide derivatives have ultimately been reported to show substantial antitumor activity *in vitro* and *in vivo*. Although they have a common chemical motif of aromatic/heterocyclic or amino acid sulfonamide, there are a variety of mechanisms of their antitumor action, such as carbonic anhydrase inhibition, cell cycle perturbation in the G1 phase, disruption of microtubule assembly, functional suppression of the transcriptional activator NF-Y, and angiogenesis (matrix metalloproteinase, MMP) inhibition among others. Among those, most potent recently discovered sulfonamides are listed below.

(i) Indoline-sulfonamides-

Chang and his colleagues, identified 7-aroylaminoindoline-1-benzenesulfonamides as a novel class of highly potent antitubulin agents, acting through the binding with the colchicine binding site on the tubulin (76). Lead compounds **93** (J-30) and **94** showed excellent tubilin inhibition with IC_{50} of 1.1 and 1.2µM respectively. Compound **93** also inhibited the human cancer cell growth of KB, MKN45, H460, HT29, and TSGH, as well as one human-resistant cancer line of KB-vin 10, with an IC_{50} of 9.6, 8.8, 9.4, 8.6, 10.8, and 8.9 nM, respectively. Recently, the oral administration of J-30 against human tumors implanted in NOCD/*scid* mice was determined and found to be active (77). For KB, at the dose of 15 and 20 mg/kg (5 days/week) for 2 weeks it caused tumor suppression of 31% and 49% respectively (compared with controls) on day 26 and for MKN45-bearing mice, where the tumor growth inhibitions were 27% at 15 mg/kg and 48% at 20 mg/kg on day 28. It was also found that oral J-30 exhibited significant antitumor activity against vincristine-resistant cells as well (41%).

(ii) Carbazole-sulfonamides-

A series of carbazole sulfonamides related to Combretastatin A4 were synthesized by Laixing and his group (78). 9-Ethyl-*N*-(3,4,5-trimethoxyphenyl)-carbazole-3-sulfonamide **95a** showed strong cytotoxic activity against CEM and MOLT-3 with IC_{50} of 56 and 20nM respectively. 9-Me substitution compound **95b** also showed similar cytotoxity with IC_{50} of 46 and 19nM against CEM and MOLT-3 cell lines. Evaluation of in vivo anticancer efficacy for this compound **95a** in human tumor xenograft models for MCF-7 breast cancer showed reduction in tumor volume by 75% after 35 days at a dose of 100 mg/kg (ip), and was somewhat more effective than adriamycin which showed a 67% reduction in tumor volume. Preliminary mode of action studies demonstrated that this compound arrests tumor cell cycle at M-phase and induces apoptotic cell death by increasing expression of p53 and promoting bcl-2 phosphorylation

(iii) Benzene sulfonamides incorporating different heterocyclic systems--

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Amarnath Natarajan and his colleagues synthesized a series of novel arylsulfoanilide-oxindole hybrid as an anticancer agent that inhibits cancer cell growth by partial depletion of intracellular Ca^{+2} stores and phosphorylation of eIF2R (79). The most potent arylsulfoanilide-oxindole hybrid **96** showed growth inhibition of lung cancer cells (A549) with GI_{50} of 0.8µM.To evaluate the efficacy of **96** in animal models of experimental cancer its preclinical studies is going on. A novel class of sulfenamide compounds incorporating three pharmacophoric groups: the 1,2,4-thiadiazole ring, arylsulfonamide and dithiocarbamate moieties have been designed and synthesized by czewski and his group (80). The most active compound **97** (-log GI_{50} = 8.00, -log TGI = 7.66) was also found to exhibit high selectivity toward leukemia CCRF-CEM cell line (Δ^f = 3.08 and 3.31, respectively). The mechanism of anti-proliferative action of the compounds has not been investigated in detail but it is estimated that the reactive oxygen species which play important role in apoptosis may be responsible for anti-proliferative action of the compounds.

A series of sulfonamides, obtained by applying the tail approach to the sulfanilamide and 5-amino-1,3,4-thiadiazole-2-sulfonamide scaffolds as carbonic anhydrase (CAIs) inhibitors have been designed and synthesized (81). All the acetazolamide-like derivatives **98a-98e**, act as very potent inhibitors of hCAI with inhibition constants in the range of 7.1–14.0nM and of hCAII with inhibition constants in the range of 0.9–3.8nM, being much more effective than clinically used derivatives. Similarly, a series of sulfonamides incorporating 4-thioureido-benzolamide moieties have been prepared and investigated as inhibitors of cytosolic isozymes hCA I and II, as well as the tumor-associated isozyme hCA IX (all of human origin). Five compounds **99a-99e** showed excellent inhibitory properties against all three isozymes with inhibition constants in the range of 0.6-0.7nM against hCA I and 0.5-0.9nM against hCA II, while two compounds **99d** and **99b** showed K_I of 3.0 and 3.2nM respectively against hCA IX isozymes Therefore these derivatives can be useful for the development of novel therapies targeting hypoxic tumors (82).

Garaj and his group syntehsized a series of aromatic benzenesulfonamides incorporating 1,2,4-triazine moieties in their molecules as inhibitors of the cytosolic and tumour-associated carbonic anhydrase isozymes I, II and IX. The first hCA IX-selective inhibitors were detected, as the chlorotriazinyl-sulfanilamide **100** and the bis-ethoxytriazinyl derivatives **101a** and **101b** of sulfanilamide/homosulfanilamide with selectivity ratios for CA IX over CA II inhibition in the range of 166–706 (83). Compound **100, 101a** and **101b** with K_i of 0.15nM, 0.12 and 0.34nM respectively for hCA IX can be proved as interesting candidates for the development of novel therapies targeting hypoxic tumors such as RCC, which is both characterized by very high CAs IX/XII expression and chemotherapy unresponsiveness, with an exceptionally elevated mortality rate (40%).

In 2005, they again synthesized a similar series and it was found that compounds incorporating compact moieties at the triazine ring like amino **102a-102g** (K_I in the range of 1.0-1.2 nM), dimethylamino **103a-103c** (K_I in the range of 1.3-1.5 nM) and amino acyl **104a-104d** 13-16 (K_I in the range of 1.0-1.7nM) against hCA IX, are more active than the derivatives incorporating bulky moieties (84). Compound **104b-104d** showed good selectivity for the inhibition of hCA IX over hCAII with selectivity ratio of 23.33, 23.57 and 32.0 respectively.

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9. Quinolines as anticancer agents

Since the discovery of camptothecin (CPT), a indoloquinoline derivative in 1966 as a potent topo I inhibitor, many of its synthetic analogues have been made and many of them are currently under clinical development at various stages and two of its analogue are being used in clinic for the treatment of cancers. Also in the search of compounds to reverse MDR, as the emergence of multidrug resistance (MDR) is a major problem in cancer chemotherapy, MS-209, a novel quinoline derivative has been proved to be the one of the most potent MDR-reversing agent. All these results promote the synthesis of quinoline derivatives in large number and among those derivatives; many quinoline derivatives condensed with another heterocyclic ring have shown promising results against different cancer cell lines. Some potent amino quinoline derivatives along with these condensed molecules with significant activities are mentioned here.

(i) Indoloquinolines-

Yeh-Long Chen and his colleagues described the synthesis and anticancer evaluation of certain 11-substituted 6H-indolo[2,3-b]quinolines and their methylated derivatives (85). Among all, **105** was the most cytotoxic with a mean GI_{50} value of 0.78µM and also exhibited selective cytotoxicities for HL-60 (TB), K-562, MOLT-4, RPMI-8226, and SR with GI_{50} values of 0.11, 0.42, 0.09, 0.14, and 0.19µM, respectively. It was also found that this 5-methylated compound was more cytotoxic than its respective 6-methylated counterparts **106** (GI_{50} = 22.91 µM) and it was expected that these 4-anilino substituent's formed hydrogen bonding with DNA molecule during the intercalation process of tetracyclic indolo[2,3-b]quinoline ring.

(ii) Pyrroloquinolines-

Ferlin and his colleagues, synthesized a new class of water soluble 3H-pyrrolo[3,2-f]quinoline derivatives (86). Compound **107** having two (2-diethylamino-ethyl) side chains linked through positions 3N and 9O, with suitable water solubility profile showed excellent cell growth inhibitory properties with IC_{50} values ranging from 4.78 to 28.28 µM, specially against leukemia (HL60) cells, with IC_{50} of 4.78µM more than that of drug amsacrine (IC_{50}=8.09 µM) and with IC_{50} of 6.23µM against melanoma (A375) cell line.

(iii) Naphthoquinolines-

A series of 7-oxo-7H-naphtho[1,2,3-de]quinoline derivatives, bearing one or two basic side chains and various substituents at the pyridone ring, have been synthesized by Maria Dzieduszycka group as tetracyclic anthraquinone analogs with a fused pyridone ring exhibit cytotoxic activity toward multidrug resistant tumor cells (87). The highest cytotoxicity was exhibited by compounds **108a, 108b,** and **108c** with IC_{50} of 146, 2798 and 7424 nM, 311, 1012 and 667 nM, 327, 415 and 2178 nM against human promyelocytic leukemia (HL-60), vincristine resistant (MDR1 type) subline HL-60/VINC, and doxorubicin resistant (MRP1 type) subline HL-60/DX.

(iv) Imidazoquinolines-

Berger and his colleagues synthesized a series of 8-anilinoimidazo[4,5-g]quinoline-7-carbonitriles as Src kinase inhibitors (88). The N-3 substituted compound **109** showed the best overall enzyme and cell activity of this series with IC_{50} of 9.0nM and 0.67 nM respectively and can be considered as potential useful agent for therapeutic intervention in cancer.

(v) Furoquinolines-

A series of certain linear 4-anilinofuro[2,3-*b*]quinoline and angular 4-anilinofuro[3,2-

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c]quinoline derivatives which can be structurally related to 9-anilinoacridines by isosteric substitution of a benzene moiety for a furan ring have been synthesized by Chen group (89). Among all linear derivatives, compound **110** was the most cytotoxic with a mean GI_{50} value of 0.025 μM and among angular ones, **111a** exhibited potent inhibitory activities on UO-31, UACC-257, and UACC-62, with GI_{50} values of 0.03, < 0.01, and < 0.01 μM respectively. The same cytotoxicity profile was observed for its methyl counterpart, **111b**, in which the GI_{50} values against UO-31, UACC-257, and UACC-62 was < 0.01, 0.04 and < 0.01 μM respectively.

(vi) Benzimidazo quinolines-

Recently, Hranjec and his colleagues, synthesized a series of novel cyano- and amidino-substituted benzimidazo[1,2-*a*]quinolines (90). Among all, imidazolyl-substituted compound **112** was found to be the most cytotoxic compound with pronounced selectivity toward colon carcinoma cells (IC_{50} = 0.4μM) and also the potent topoisomerase II inhibitor which induced strong G_2/M cell cycle arrest, pointing to the impairment in mitotic progression.

(vii) Amino quinolies-

8-substituted 4-anilino-2-phenylquinoline derivatives were synthesized by Chen and his colleagues (91). Compound **113** and its oxime derivative **114**, the two most active compounds of the series with GI_{50} of 0.07, <0.01, <0.01μM and 1.48, 0.35, 0.25μM against HCT-116, MCF-7 and MDA-MB-435 cell lines respectively found to induced cell cycle arrest in S-phase. It was also proved that these compounds (mean GI_{50}=1.20 and 2.88 μM) are more potent than their respective methoxy derivatives (mean GI_{50}=8.91 and 6.31 μM). Similarly, Zhao group described the synthesis and cell growth inhibition of certain 6-substituted 4-anilino-2-phenylquinoline derivatives (92). The most active compound **115**, especially against the growth of NCI-H226 (non-small cell lung cancer), MDA-MB-231/ATCC (breast cancer), and SF-295 (CNS cancer) cancer cells with GI_{50} values of 0.94, 0.04, and < 0.01 μM respectively, its oxime **116a**, and its methyloxime **116b**, also exhibited significant cytotoxicity against all 60 cancer cells with mean GI_{50} values of 3.02, and 3.89 μM, respectively.

Robert Mallon and his colleagues, identified 4-anilino-3-quinolinecarbonitrile as inhibitors of mitogen-activated protein/extracellular signal-regulated kinase 1 kinase (93). Compound **117** the most potent inhibitor of human tumor cell growth in vitro with IC_{50} of 5nmol/L against LoVo cell line, inhibits kinase activity upstream of Raf, and thereby affects MEK1 phosphorylation in cells with IC_{50} of 1nmol/L. Even with the dual effect of **117** on MEK and MAPK phosphorylation, this compound was well tolerated and significantly inhibited growth of the human colon tumor cell line LoVo (at 50 and 100 mg/kg BID, i.p.) in a nude mouse xenograft model. Recently, Thota Ganesh group discovered a series of aminoquinolines as a new class of potent inhibitors of heat shock protein 90 (Hsp90), which exerts high-affinity interactions with multiple oncoproteins, which are essential for the growth of tumor cells (94). Among all, the best compound **118** (SID: 24724290), exhibits low micromolar activities in both primary FP and cell-based Western blot (WB) assays with IC_{50} of 1.3 and 1.0μM respectively.

10.Quinazolines as anticancer agents

The quinazoline ring system along with many alkaloids is a widely recognized moiety in organic syntheses and medicinal application. It has been reported that

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modification of quinazoline structure could be applied in many biological studies, such as anticonvulsant, antibacterial, antidiabetic, and anticancer. Interest in quinazolines as anticancer agents has further increased since the discovery of raltitrexed and thymitaq and their activity as thymidylate enzyme inhibitors (95, 96). 4-Anilinoquinazolines represent as a new class of antitumor drugs, which were found to inhibit the epidermal growth factor receptor (EGFR) tyrosine kinase over expression through the inhibition of EGFR autophosphorylation and EGF-stimulated signal transduction. Furthermore, quinazolines exert their antitumor activity through inhibition of the DNA repair enzyme system. Several amino/anilinoquinazolines discovered as potent anticancer agents in the past few years are discussed below.

4-Anilinoquinazolines-

Sirisoma and his colleagues identified a novel series of 4-anilinoquinazolines as inducers of apoptosis (97). Among all, compound **119** (EP128265, MPI-0441138) found to be the most active inducer of apoptosis (EC_{50} for caspase activation of 2 nM) and as a potent inhibitor of cell proliferation (GI_{50} of 2 nM) in T47D cells. Compound **119** inhibited tumor growth dose dependently and produced >95% tumor growth inhibition with once weekly intravenous (iv) dosing at 10 mg/kg in MX-1 breast cancer model. It was also proved that the methyl group on the nitrogen linker was essential for the apoptosis-inducing activity of 4-anilinoquinazolines and substitution in the 6- and 7-positions of the quinazoline core structure decreased potency. On other hand, Ballard and his colleagues synthesized a series of 5-Substituted 4-anilinoquinazolines as potent, selective and orally active inhibitors of erbB2 receptor tyrosine (98). Among all, the most potent compound **120** with favorable erbB2 kinase selectivity versus EGFR (IC_{50}=0.002µM vs 0.14µM) showed a clean selectivity profile versus in-house and external kinase panels and gave selectivity ratios of >3800 and >11,500, respectively, versus the receptor tyrosine kinases Kdr and Src. It also gave statistically significant inhibition of phospho-erbB2 (>90% inhibition 4 and 24 h after the last dose at 100 mg/kg b.i.d.) in the mouse BT474C xenograft model. Similarly, Smaill and his colleagues synthesized a series of 4-(phenylamino**)**quinazolines as irreversible inhibitors of the EGFR (99). Quinazoline **121**, bearing cationic side chain, showed excellent potency for inhibition of *erb*B2 autophosphorylation in MDA-MB 453 cells with IC_{50} of 9.0 nM and inhibition of phosphorylation of the isolated EGFR enzyme in A431cells with IC_{50} of 1.5nM. It also showed impressive activity when dosed orally (5mg/kg/day) for 14 days, against A431 xenografts in mice and has been selected for clinical evaluation.

Ple discovered a new class of anilinoquinazoline inhibitors with high affinity and specificity for the tyrosine kinase domain of the c-Src enzyme (100). Aminobenzodioxoles were shown to be potent inhibitors of tumor growth in a c-Src-transformed 3T3 xenograft model in vivo for e.g compound **122**, which showed maximum Src enzyme inhibition with IC_{50} <0.004µM and Src3T3 cell inhibition with IC_{50} of 0.11µM, resulted more than 90% growth inhibition at doses as low as 6mg/kg po once daily. While, Hennequin and his colleagues synthesized a series of 4-Anilinoquinazolines with C-7 basic side as potent, orally active, VEGF receptor tyrosine kinase inhibitors (101).

It was found that compound **123** (ZD6474) in recombinant enzyme assays revealed excellent selectivity for the inhibition of KDR tyrosine kinase (IC_{50} =0.04 μM) vs the kinase activity of erbB2, MEK, CDK-2, Tie-

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2, IGFR-1R, PDK, PDGFR*â*, and AKT (IC_{50} range: 1.1 to >100µM). Compound **123** demonstrated a very attractive in vitro profile combined with excellent solubility (330 *µ*M at pH 7.4) and good oral bioavailability in rat and dog (>80 and >50%, respectively) and also demonstrated highly significant, dose-dependent, antitumor activity in athymic mice. It was found that compound **123** on oral administration at a dose of 100mg/kg/day, inhibited the growth of established Calu-6 lung carcinoma xenografts by 79% after 21 days (P<0.001) and substantial inhibition (36%, $P < 0.02$) was evident with 12.5 mg/kg/day

Tsou and his group synthesized a series of 6-substituted-4-**(**3-bromophenylamino) quinazoline derivatives as irreversible inhibitors of epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor (HER-2) tyrosine kinases, which can interact covalently with these target enzymes (102). Among all, compound **124**, which showed inhibition of EGFR, HER-2 kinases and Inhibition of SKBR cells with IC_{50} of 0.011, 0.301 and 0.002µM respectively, when administered orally at 40 mg/kg every day for days 1-10, found to be inhibited tumor growth greater than 90%, even 12 days after stopping the drug treatment in a nude mouse xenograft model bearing A431 human tumors that overexpress EGFR. On the other hand, Gaul and his group synthesized a class of 6-thiazolylquinazolines as potent and selective inhibitors of both ErbB-2 and EGFR tyrosine kinase activity. The most promising compound **125**, showed EGFR and ErbB-2 TK dual inhibition with average IC_{50} of 0.012µM and several fold selectivity for tumor cells over normal cells with selectivity ratio >210. This compound was proved as the most efficacious compound of the series, which displayed approximately 80% tumor inhibition in both the HN5 and BT474 xenograft models (103).

Abouzid with his colleagues synthesized a series of 6-alkoxy-4-substituted-aminoquinazolines along with their bioisoteric quinoline congeners, targeting EGFR tyrosine kinase (104). Compound **126** displayed the highest activity among the tested compounds with IC_{50} = 0.13 nmol in vitro on human breast carcinoma cell line (MCF-7) in which EGFR was highly expressed. While in the quinoline series, compounds **127a** and **127b** were found as the most potent ones with IC_{50} of 1.67 and 2.84nmol respectively. Similarly, Gang Liu group synthesized a series of 6,7,8-trimethoxy-N-aryl-4-aminoquinazoline derivatives. Among all, **128** and **129** found as the most potent inhibitors, with IC_{50} value of 8.1, 9.8, 9.0, 9.9µM and 21.0, 12.6, 11.0, 12.1 µM against Bcap-37, PC3, A431, BGC823 tumor cells respectively (105).

Jung and his colleagues synthesized a novel series of quinazolines substituted at C4 by five-member ring amino heterocycles as a potent Aurora A and B inhibitors with excellent selectivity against a panel of various serine-threonine and tyrosine kinases, as exemplified by most potent compound which showed potent antiproliferative effect in SW620 cells, with an IC_{50} 0.002µmol and selectivity of EGFR kinase (IC_{50}=0.8µmol) against other kinase like JNK1A, P38A, PKA (IC_{50}>100µm). Compound **130** is a potent suppressor of the expression of phospho-histone H3 in tumor cells in vitro as well as in vivo, where **130**, administered as its phosphate prodrug **131**, suppresses the expression of phospho-histone H3 in subcutaneously implanted tumors in nude mice (106).

(ii) Pyrazolo quinazolines-

Foote and his group also synthesized a class of 1-acetanilide-4-aminopyrazole-substituted quinazolines as aurora kinase

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inhibitors (107). The most active phosphate derivative, **132** showed potent anti-proliferative activities against SW620 cells with IC_{50} < 0.001 μM, and also in pre-clinical in-vivo models it showed activity at lower doses compared with other series previously reported. In 2007, Mortlock and his colleagues discovered a series of pyrazoloquinazolines with attractive physicochemical and pharmacokinetic properties and some of them have shown show greater than 1000-fold selectivity for Aurora B over Aurora A kinase activity, in recombinant enzyme assays (108). At well-tolerated doses, inhibition of histone H3 phosphorylation was observed in SW620 tumors along with an increase in 4N DNA content and failure of cell division that leads to durable antitumor growth activity. Compound **133** (AZD1152) with striking *in vivo* activity has been selected for clinical evaluation and is currently in phase 1 clinical trials.

Kitano and his colleagues identified 4-alkynyl and 4-alkenylquinazolines as non-anilinoquinazolines potent EGFR tyrosine kinase inhibitors (109). The pyrazole derivative **134**, possessing a halogenated phenyl ring, was the most potent, with an IC_{50} of 1.8 nM. Chiral discrimination was also observed to occur in one of the 4-alkynylquinazoline derivatives **135**, (R)-isomer (IC_{50}=1.8 nM) being more than 150 times as potent as the (S)-isomer. With this result, future efforts will be directed toward understanding the interactions of the enantiomers from a structural point of view.

(iii) Piperazinyl quninazolines-

Anjali Pandey and her group identified orally active, potent, and selective 4-piperazinylquinazolines as antagonists of the platelet-derived growth factor receptor tyrosine kinase family (110). Among all, an optimized analogue **136** (CT53518), inhibits Flt-3, *β*PDGFR, and c-Kit receptor phosphorylation with IC_{50} values of 50-200 nM. This analogue also inhibits autophosphorylation of Flt-3 ligand-stimulated wild-type Flt-3 and a constitutively activated Flt-3/internal tandem duplication (ITD) with IC_{50} values of 30-100 nM. It was found to be metabolically stable with desirable pharmacokinetic properties in all animal species studied (F% > 50%, $T_{1/2}$ > 8 h). Oral administration of **136** promoted mice survival and significantly delayed disease progression in a Flt-3/ITD-mediated leukemia mouse model and showed efficacy in a nude mouse model of chronic myelomonocytic leukemia

11. Hybrids molecules as anticancer agents

A series of tetrahydro-β-carbolines and 1,3,5-triazine hybrids have been reported and evaluated for their cytotoxicity against a panel of eight human cancer cell lines and normal human fibroblasts (NIH3T3). The racemic compounds **138, 139** and **140,** which are selectively cytotoxic towards KB (oral cancer) cell line with IC_{50} values of 105.8, 664.7 and 122.2 nM, respectively; while their enantio pure forms are less active and not selective. Enantiopure compound **137** showed 2.5 times more selectivity towards MCF7 cells over normal fibroblast NIH3T3 cells with an IC_{50} value of 740 nM, also arrests cell cycle in G1 phase and induces apoptosis in MCF7 and MDA MB231cell lines(111).

Conclusions

Nitrogen heterocycles constitute an important class of anticancer agents as large numbers of structurally novel nitrogen heterocyclic derivatives have ultimately been reported to show substantial antitumor activity *in vitro* and/or *in vivo* via variety of mechanisms of their antitumor action, such

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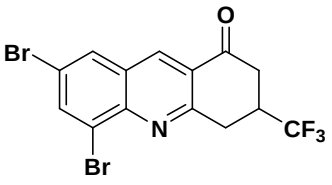
as DNA alkylation, carbonic anhydrase inhibition, cell cycle perturbation in the G1 phase, disruption of microtubule assembly, and angiogenesis (matrix metalloproteinase, MMP) Some of these derivatives are currently being evaluated in clinical trials, and there is much optimism that they may lead to novel types, alternative anticancer drugs, devoid of the side effects of the presently available pharmacological agents.



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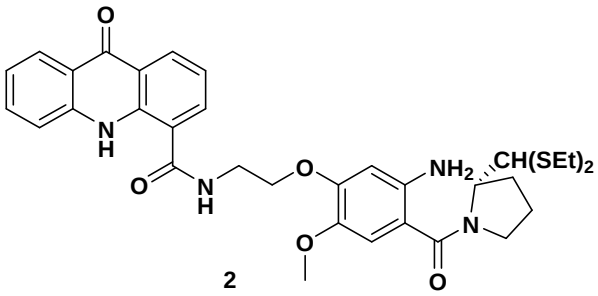

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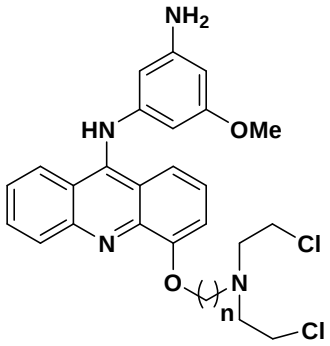
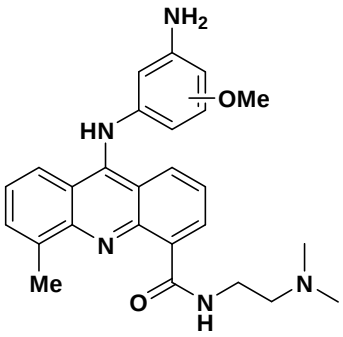
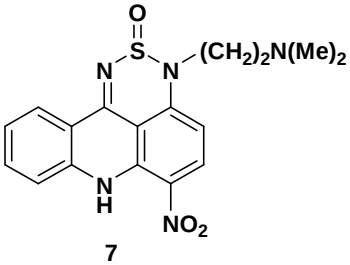


3a. n=2
3b. n=4



4. *0*-OMe
5. *m*-OMe
6. *p*-OMe



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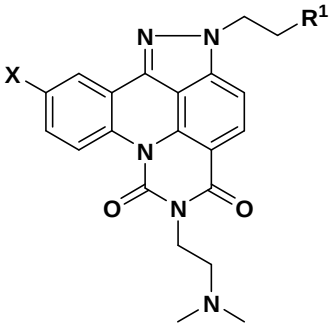

8. X= OMe and R^1= piperidine
9. X= NO_2 and R^1= trimethylamine

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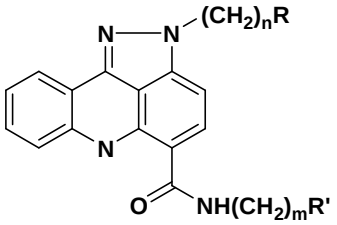
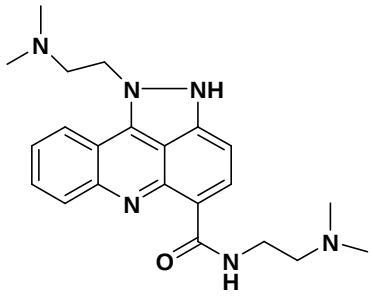


m=n=2

10. R =R'= $N(Me)_2$

11. R= piperadine, R'= $N(Me)_2$



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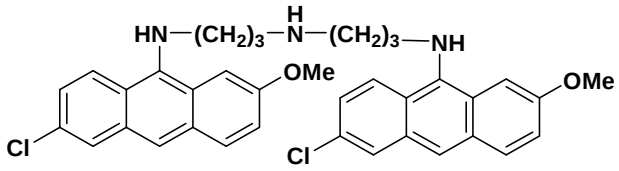

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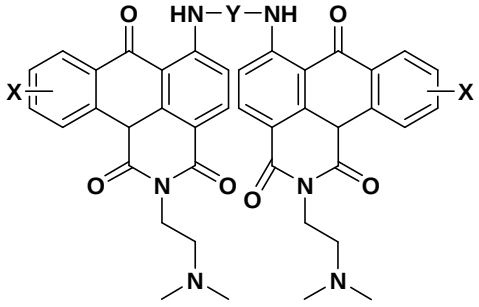


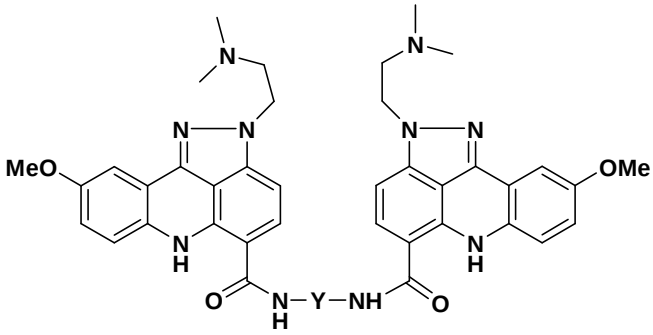
Y= $(CH_2)_3NMe(CH_2)_3$

14a. X= H

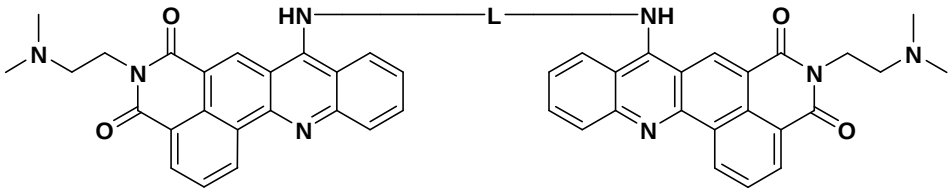
14b. X= 9, 9'-OMe

14c. X= OH

14d. X= NO_2



15. Y= $(CH_2)_3NMe(CH_2)_3$



16. L= $(CH_2)_3NMe(CH_2)_3$

17. L= $(CH_2)_2NH(CH_2)_3NH(CH_2)_2$

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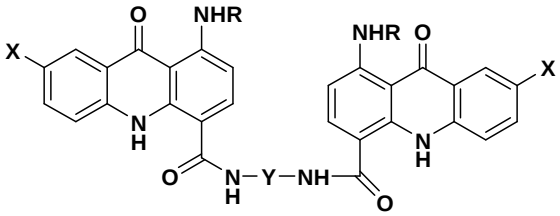
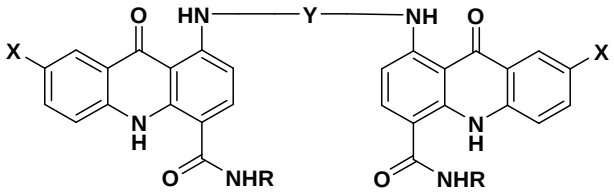
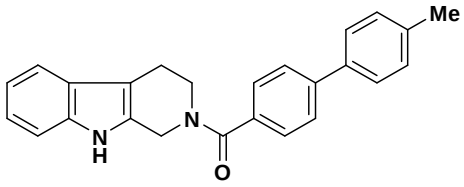


R= $(CH_2)_2N(CH_3)_2$
Y= $(CH_2)_3NMe(CH_2)_3$
18a. X=H
18b. X=OMe



Y= $(CH_2)_3NMe(CH_2)_3$
19a. X= NO_2
19b. X= OMe



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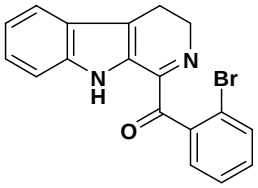

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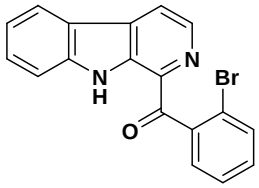

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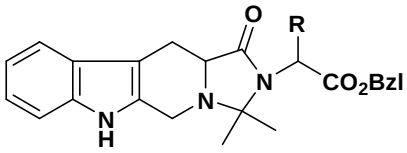
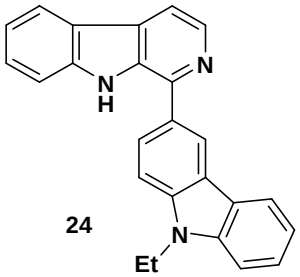


23a. R= $CH_2CH(Me)_2$
23b. R=$CH_2C_6H_5$,
23c. R=CH_2CO_2Bzl,
23d. R=$CH_2CH_2CO_2Bzl$,



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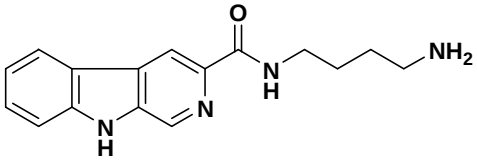

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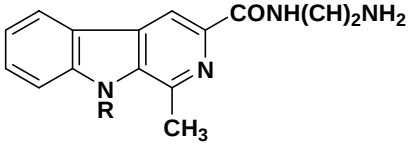

26a. R= n-C_4H_9
26b. R= -$CH_2C_6H_5$

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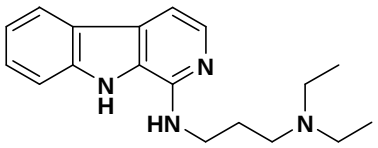
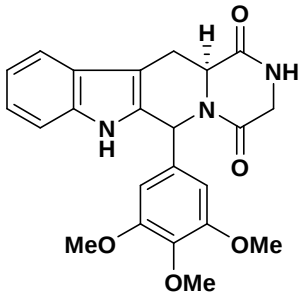
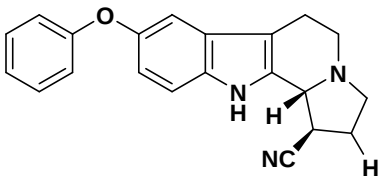


27



28



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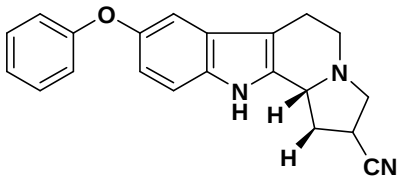

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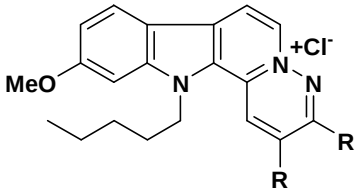
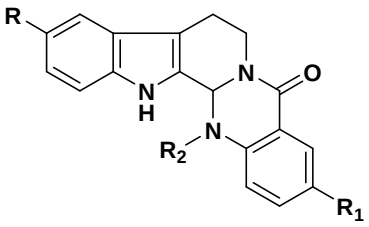


31a. . R=Me
31b. R= Et



32a. R=Cl, R_1=H, R_2=H
32b. R=Cl, R_1=H, R_2=CH_3
32c. R=H, R_1=NO_2, R_2=H

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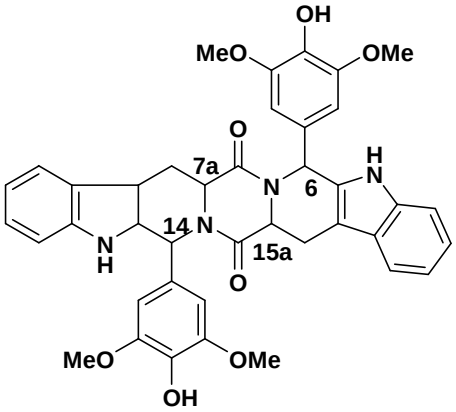
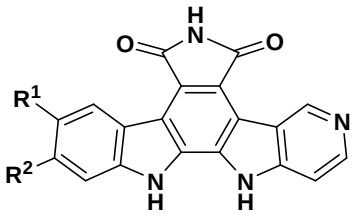
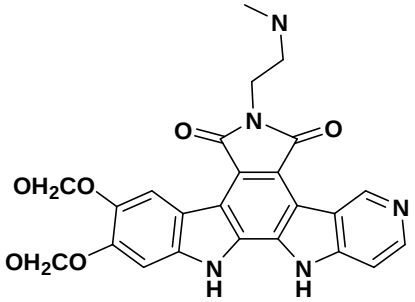


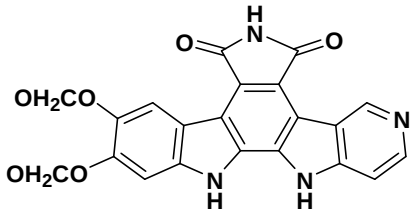
33a- 6(R), 7a(S), 14(R), 15a(S)
33b -6(S), 7a(R), 14(S), 15a(R)



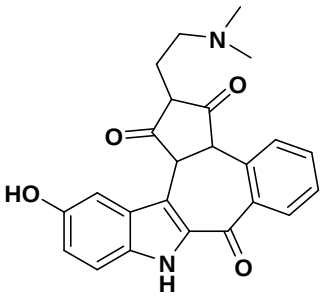
34a. R^1 = H, R^2 = OBn
34b. R^1 = OH, R^2 = H
34c. R^1 = H, R^2 = OH



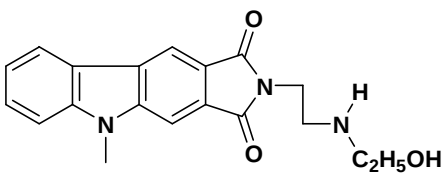
35



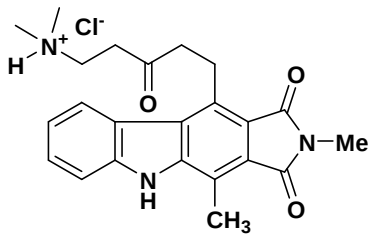
36



37



38



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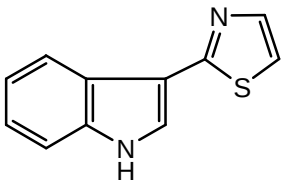
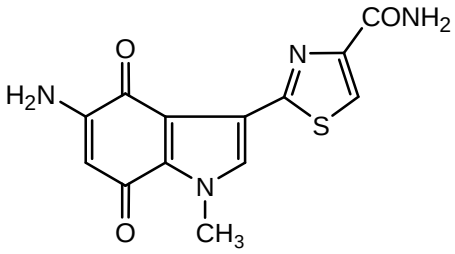
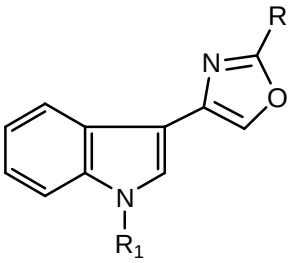


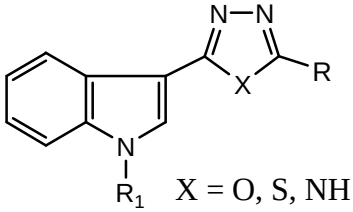
Camalexin (**39a**)



BE 10988 (**39b**)

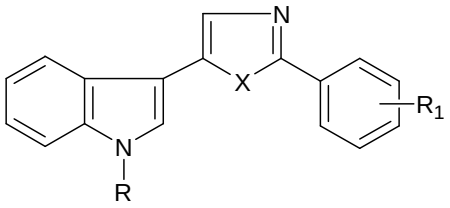


4-(3-Indolyl)oxazoles (**39c**)

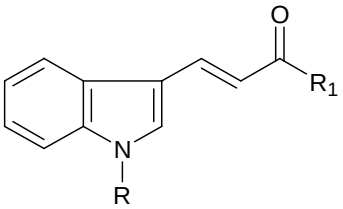


X = O, S, NH

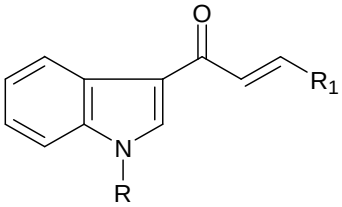
5-(3-Indolyl) azoles (**39d**)



(39e)



(39f)



(39g)

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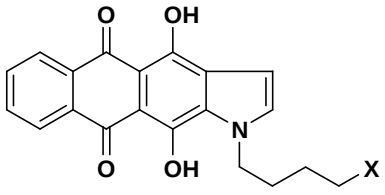
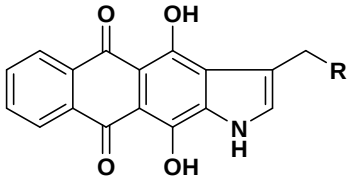
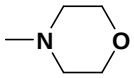
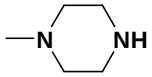
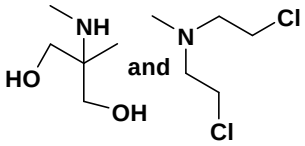
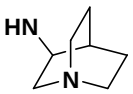


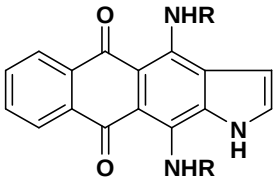


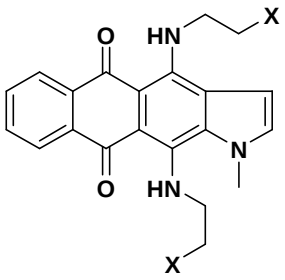
40a. X= 

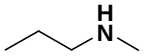
41a. R= 

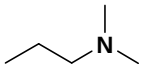
40b and 40c. X= 

41b. R= 





42a. R= 

42b. R= 

43a. X= NH_2
43b. X=NHMe
43c. X=NMe_2

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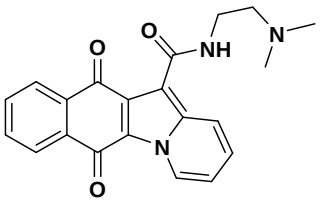
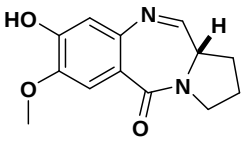
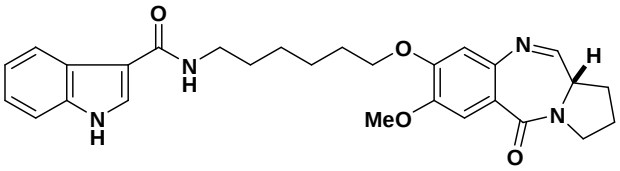


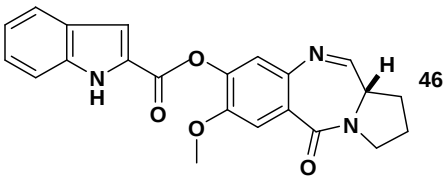
44



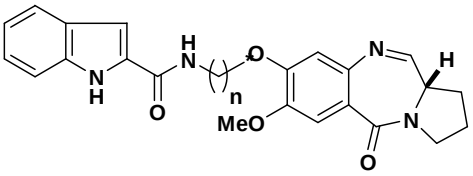
45



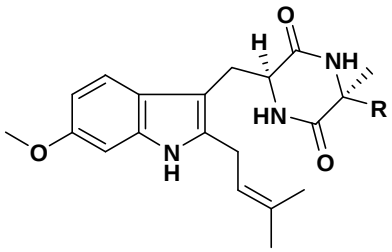
46



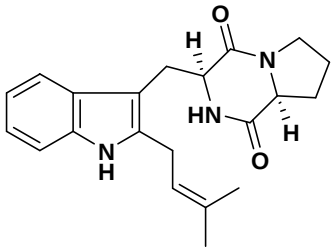
47



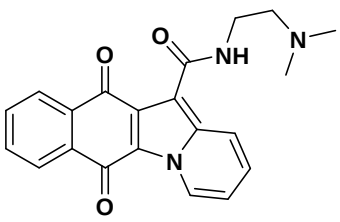
48. n=3



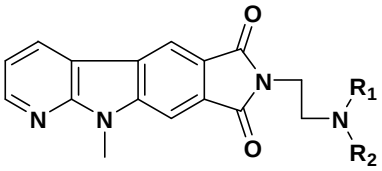
49a. R= isopropyl
49b. R= benzyl



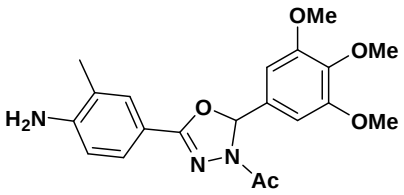
50



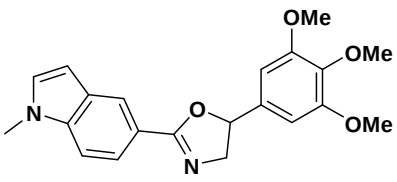
51



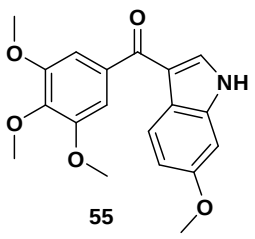
52a. R_1= Me, R_2= Me
52b. R_1= H, R_2= EtOH



53



54



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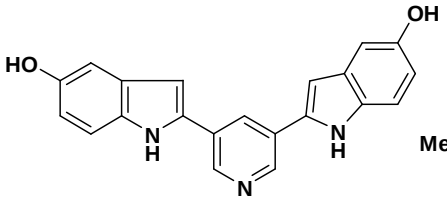
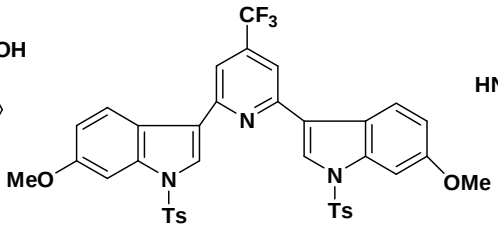
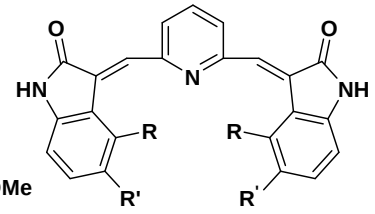


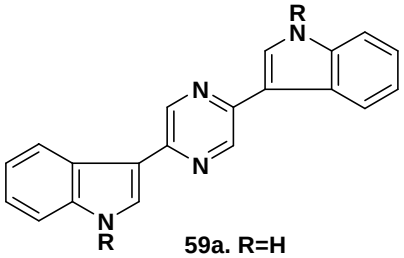
56



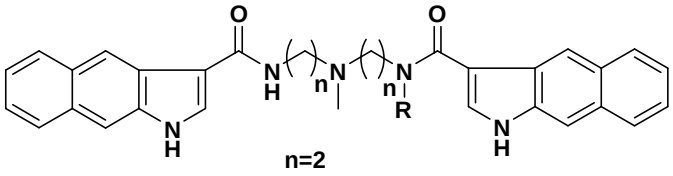
57



58a. R=Cl, R'=H
58b. R=H, R'= OCH_3

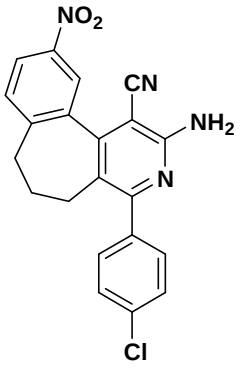


59a. R=H
59b. R=CH_3

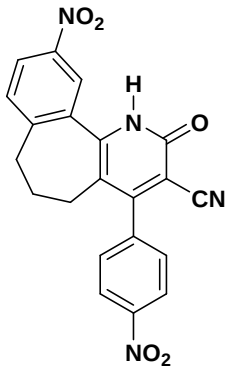


n=2

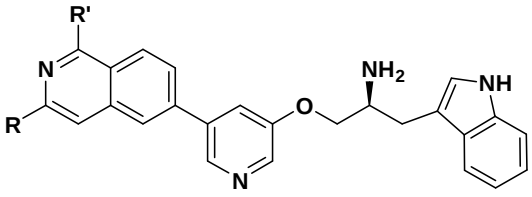
60a. R= CH_3
60b. R= H



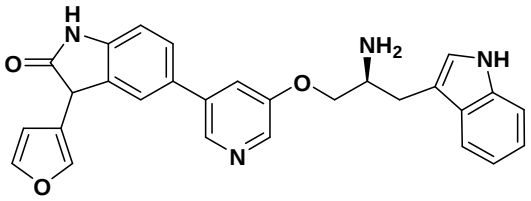
61



62



63. R= R'= H
63a. R=H, R'= Cl
63b. R=NH_2, R'=H



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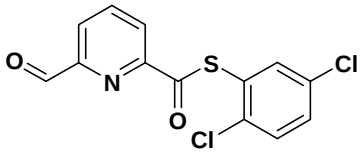
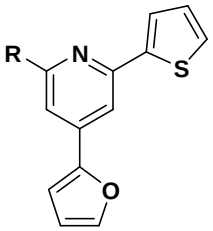
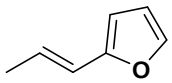


65

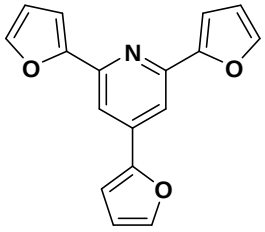


66a. R=



66b. R=

66c. R=H



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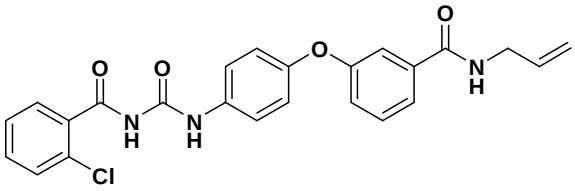

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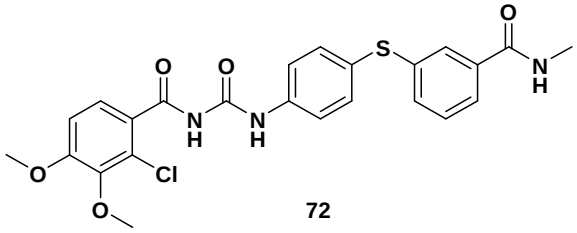

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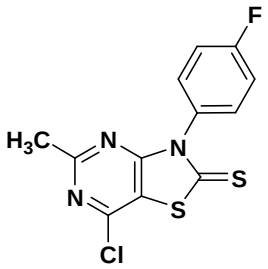

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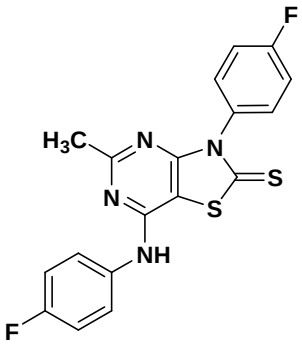

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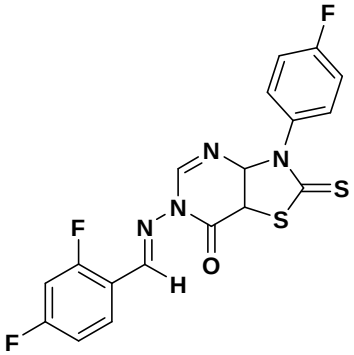

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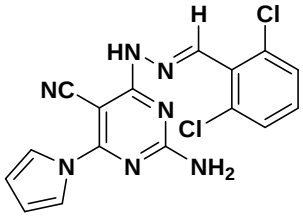

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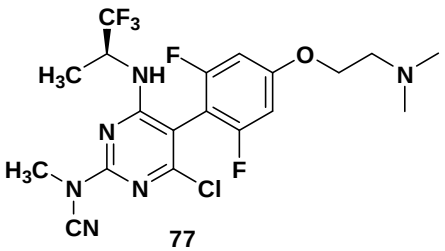

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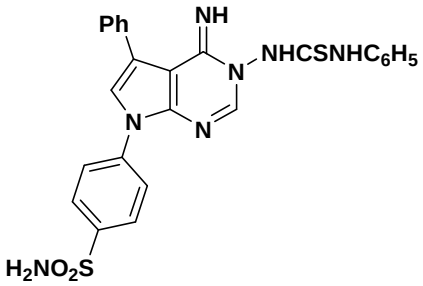

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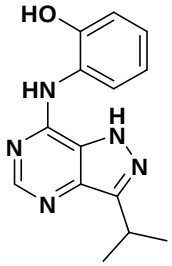

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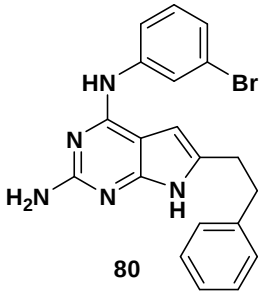

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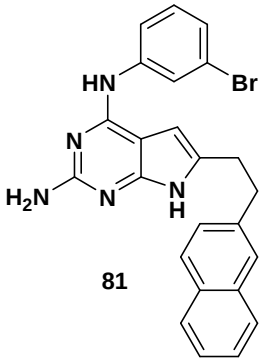

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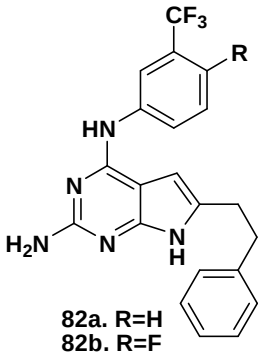
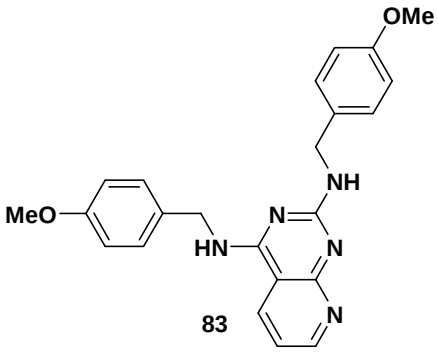


82a. R=H
82b. R=F



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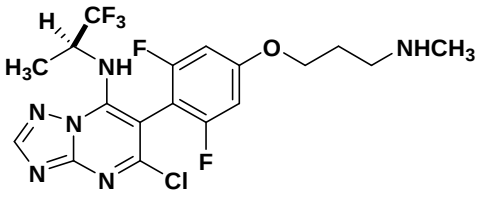

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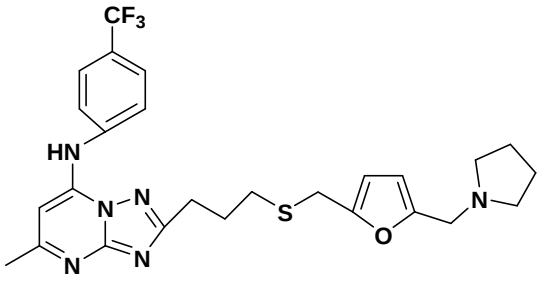

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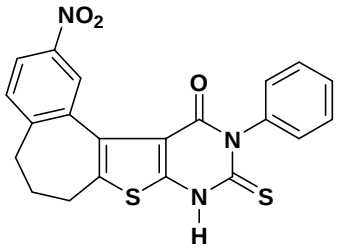

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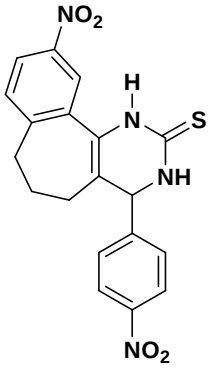

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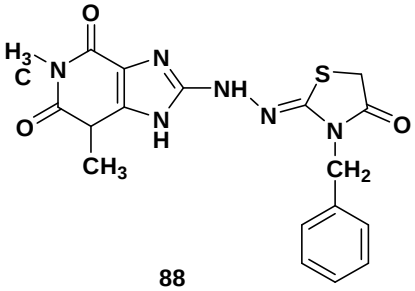

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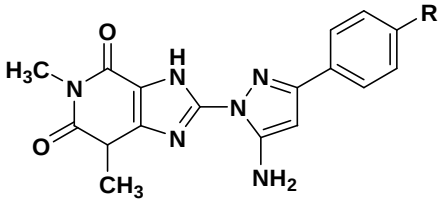
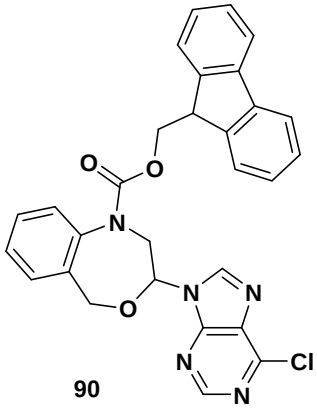


89a. R= CH_3
89b. R= H



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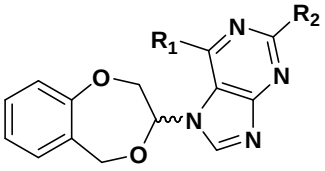

91a. R_1=Cl, R_2= H
91b. R_1=I, R_2= H
91c. R_1= R_2= Cl

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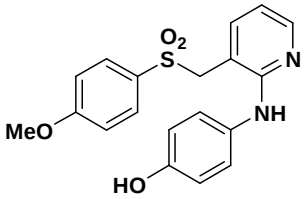

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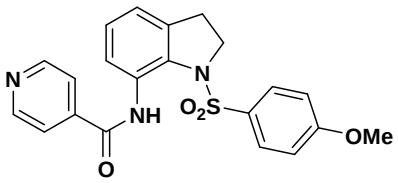

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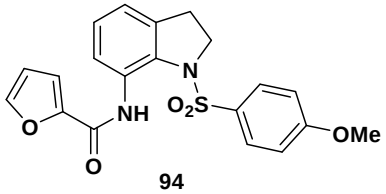

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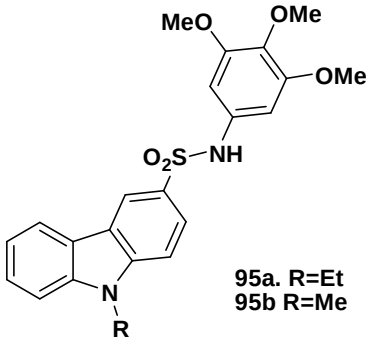
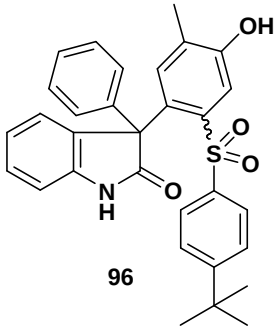


95a. R=Et
95b R=Me



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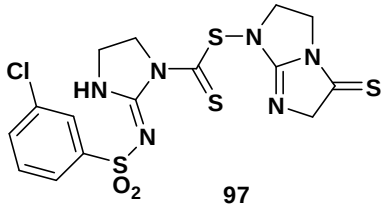

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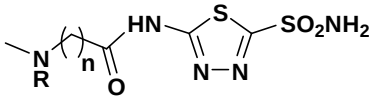
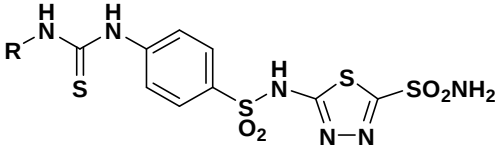


98a. R= morpholine, n=1
98b. R=pyridyl, n=1
98c. R=n-benzyl piperazinyl, n=1
98d. R=piperazine, n=1
98e. R= piperazine, n=2



99a. R= N'N dimethyl aminopropyl
99b. R= piperazine
99c. R= 2-fluoro phenyl
99d. R= 2,3,4,5,6 tetrafluoro aniline
99e. R= 2-methyl-1-(4-nitrophenyl)propane-1,3-diol

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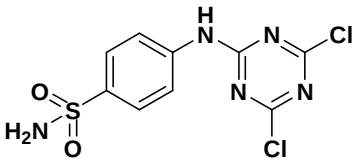

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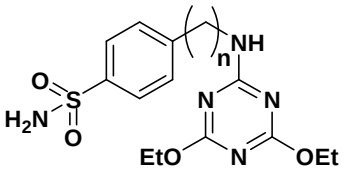
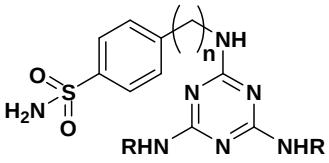
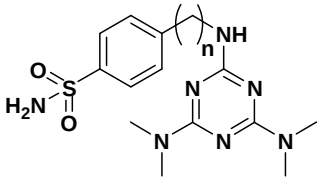


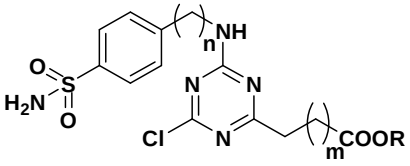
101a. n=0
101b. n=1



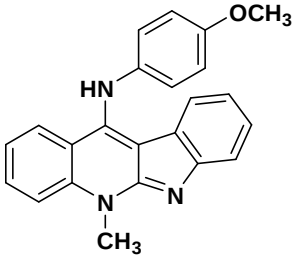
102a. n=1, R=H
102b. n=2, R=H
102c. n=0, R=NH_2
102d. n=1, R=NH_2
102e. n=2, R=NH_2
102f. n=1, R=Et
102g. n=2, R=Et



103a. n=0
103b. n=1
103c. n=2



104a. n=m=1, R=H
104b. n=2, m=1, R=H
104c. n=2, m=1, R=Me
104d. n=m=2, R=H



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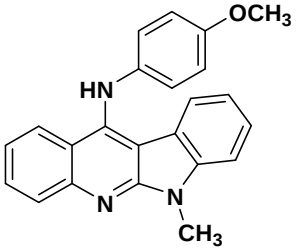

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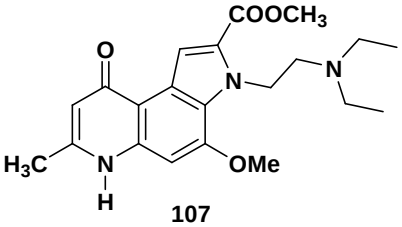

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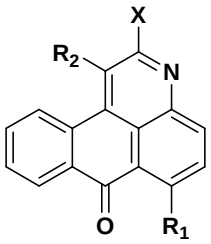
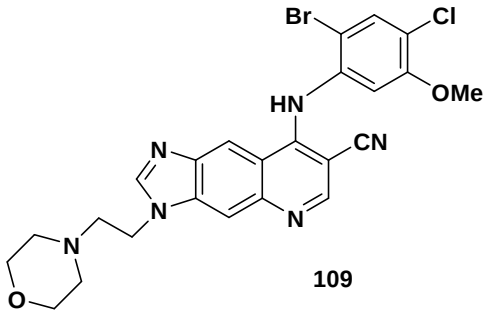


108a. R_1=$NH(CH_2)_2NMe_2$, R_2=COOEt, X=OH
108b. R_1=$NH(CH_2)_2NMe_2$, R_2=$CONH(CH_2)_2NMe_2$, X=OH
108c. R_1=$NH(CH_2)_2NMe_2$, R_2=H X=Cl



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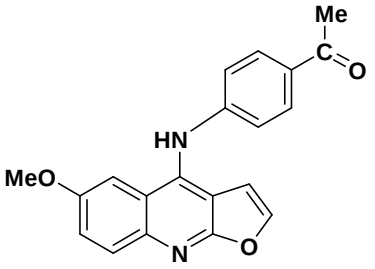

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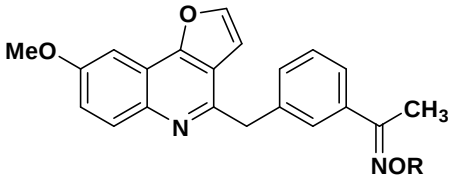
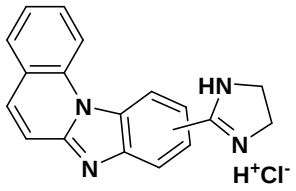


111a. R=H
111b. R=CH_3



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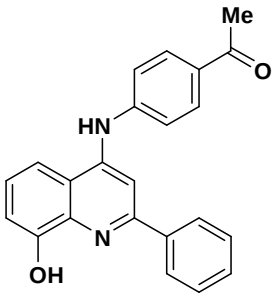

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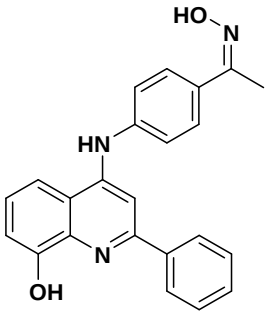

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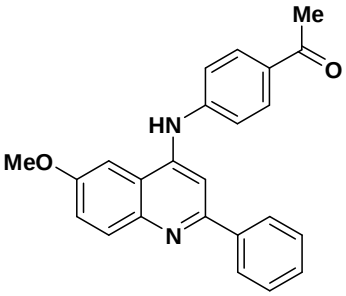

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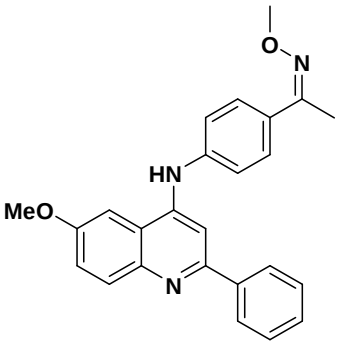
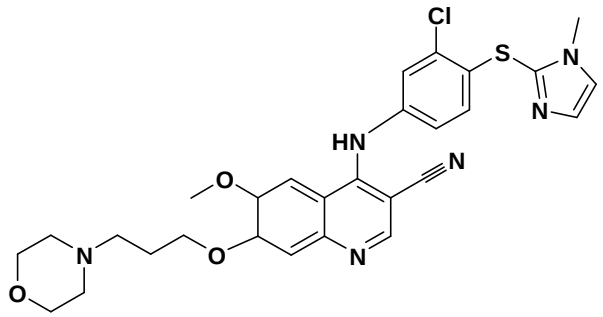


116a. R=H
116b. R=Me



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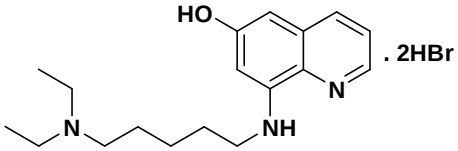

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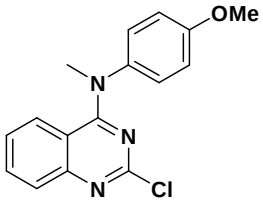

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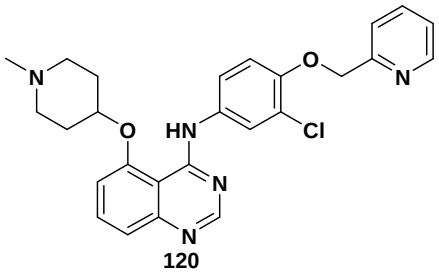

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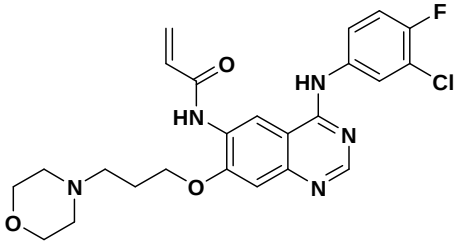

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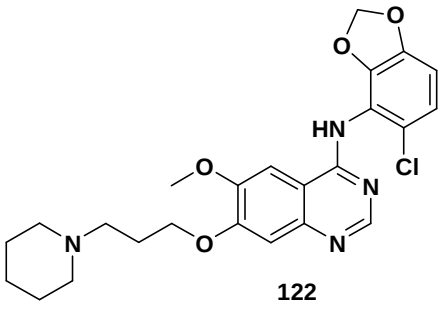

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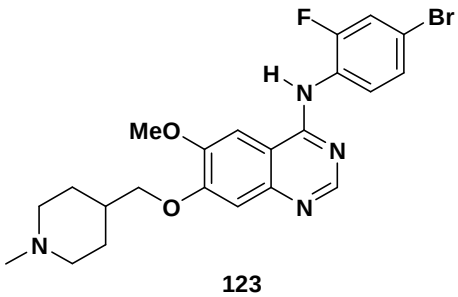

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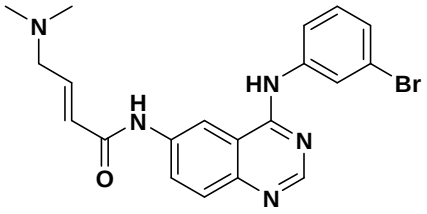

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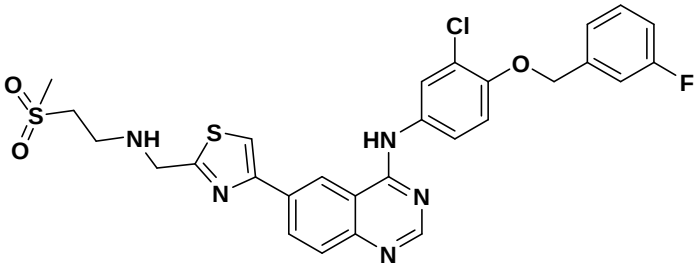
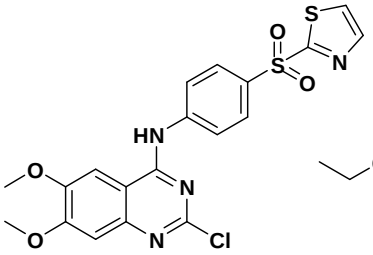
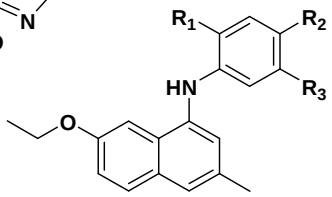


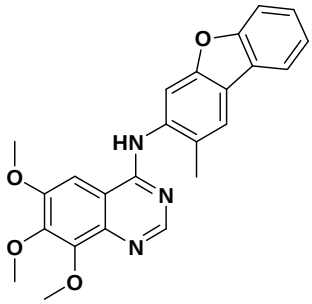
125



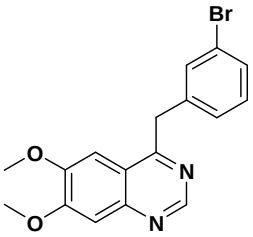
126



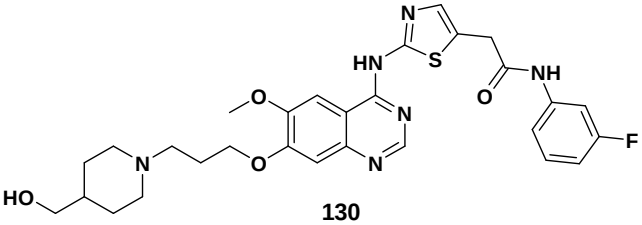
127a. R_1=CH_3OCO, R_2=R_3=OCH_3
127b. R_1=R_2=H, R_3=OH



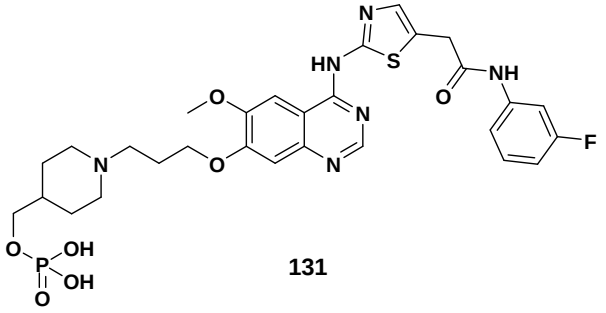
128



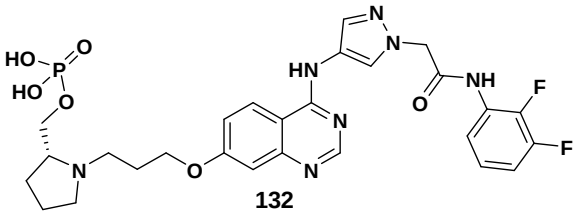
129



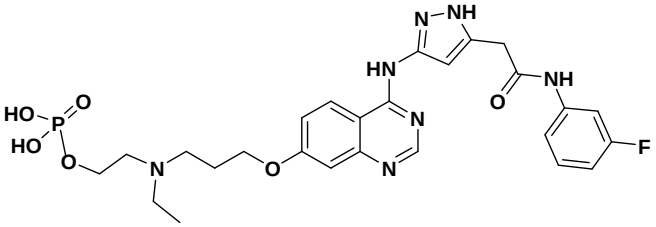
130



131



132



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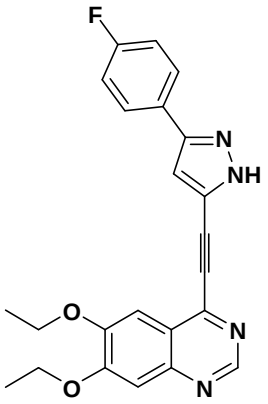
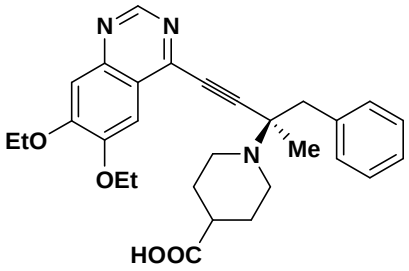
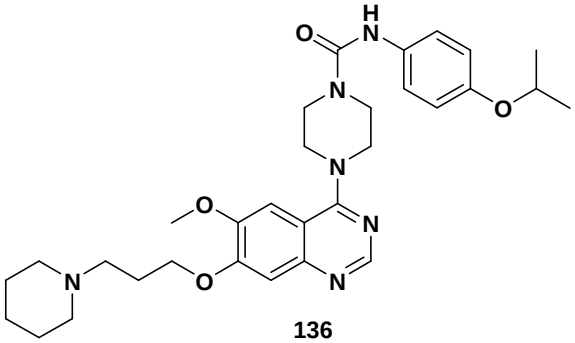


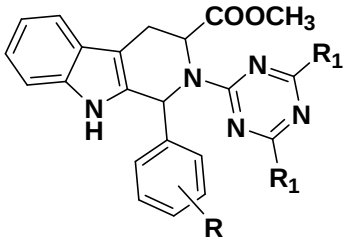
134



135



136



137,138,139,140

Compounds No	Isomer	R	R1
137	L, Trans	4-methoxy	N-methylpiperazine
138	DL, Trans	4-methyl	N-methylpiperazine
139	DL, Trans	4-methyl	propylamine
140	DL, Trans	4-methoxy	propylamine

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