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Microwave-Assisted Synthesis of Certain Pyrrolylpyridines, Some derived Ring Systems and Their Evaluation as Anticancer and Antioxidant Agents.

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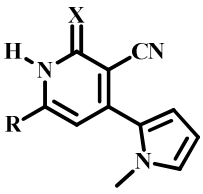
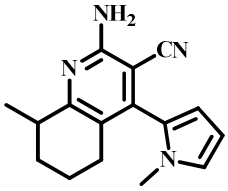
Several pyrrolylpyridines (**A**) and some derived fused rings (**B-D**) were synthesized using both conventional and MW heating techniques. Some pyridines, tetrahydroquinolines. and tetrahydropyrimido[4,5-*b*]quinolines exhibited promising antitumor and antioxidant activities.



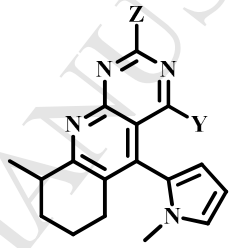
(A)

X = O or NH

R = aryl or hetaryl



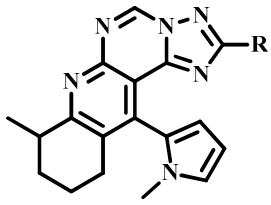
(B)



(C)

Y = amino, imino, oxo

Z = CH_3, thio, alkylthio



(D)

R = H or CH_3

Microwave-Assisted Synthesis of Certain Pyrrolylpyridines, Some derived Ring Systems and Their Evaluation as Anticancer and Antioxidant Agents.

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Abstract

The synthesis of 18 novel pyrrolylpyridines and some derived bi-, tri- and tetracyclic ring systems using both the conventional heating and MW irradiation techniques is described. Fourteen compounds; **2-9, 10-12, 14, 17** and **18** were evaluated for their antitumor activity according to the National Cancer Institute (NCI), *in vitro* disease oriented antitumor screening. Distinctive antitumor activity was conjugated with compounds **3** and **7** (R = 3,4-di-OCH_3-C_6H_3). The analogs **3, 6, 7, 9, 10, 11** and **12** which exhibited prominent antitumor activity, were further evaluated for their antioxidant potential using the DPPH radical scavenging assay. The substituted 6-(3,4-dimethoxyphenyl)pyridine-3-carbonitriles **3** and **7** were nearly equipotent to BHT the standard antioxidant utilized in this assay (scavenging activity 31 and 33 %, respectively, vs 36 %). Accordingly, compounds **3** and **7** can be considered as lead structures for dual antitumor and antioxidant activities.

Keywords:

Pyridines, Tetrahydroquinolines, Pyrimido[4,5-*b*]quinolines, Antitumor activity, Antioxidant activity.

1. Introduction

Despite the persistent efforts and prominent accomplishments achieved in many domains of cancer treatment, effective control of this complicated disease continues to be a major quarrel for medicinal chemistry researchers. This aspect refers to the fact that cancer is a complex pathological condition with a diversity of manifestations distinguished by rapid proliferation and spreading of anomalous cells [1]. To date, therapeutic management of cancer is a conjunction of surgery, radiotherapy together with chemotherapy, which remains one of the most reliable tools in the control and even recovery from different types of tumors. However, administration of anticancer drugs usually accompanied by several complications among which toxicity of healthy cells and the possible evolution of drug resistance [2]. Consequently, the need for designing novel unparalleled antitumor agents becomes an urgent demand.

On the other hand, oxidative stress caused by the prevalence of high levels of reactive oxygen species (ROS) such as hydroxyl free radical and superoxide radical anion that drastically attack and damage cells throughout the body [3], has been linked with the etiology of a variety of pathophysiological conditions such as rheumatoid arthritis, autoimmune diseases and definitely cancer [4]. Moreover, ROS was found to induce oxidative damage of DNA, which could result in mutations leading to carcinogenesis. Besides, ROS were shown to enhance tumor proliferation and progression through activation of signaling pathways involved in angiogenesis and metastasis [5]. Therefore, antioxidants that are able to scavenge free radicals and keep cell integrity have become currently an issue of growing interest, and their therapeutic utility would contribute significantly in the management of several types of cancer [6,7].

Among the diverse classes of heterocyclic compounds that are endowed with multiple biological efficiencies, pyridines and their derived fused ring structures have received profound attention since they are proved to be biological versatile compounds. A wide range of chemotherapeutic activities have been ascribed to pyridine derivatives including antimicrobial [8,9], antitubercular [10] and anticancer [11-15], and antiviral [16] activities. In particular, interest has been focused on pyridinecarbonitriles as they possess significant antibacterial [17], antifungal [18] and anticancer activities [19-21], in addition to their well-documented antioxidant potentials [22,23]. Consequently, pyridinecarbonitriles and their derived fused rings remain a promising template for the design of a new category of chemotherapeutic and antioxidant agents.

Along the past two decades, the utilization of microwave (MW) irradiation as a substitute of other conventional heating techniques has acquired popularity in contemporary synthetic medicinal chemistry research. Successful implementation of MW irradiation in various chemical reactions resulted in enhanced reaction rates with subsequent time-saving, fast and effective building up of libraries of compounds, improvement in products' purity and yields, in addition to being a suitable route towards the goal of echo-friendship and green chemistry [24].

[Figure 1]

Inspired by the aforementioned findings, and as an extension to our efforts devoted to the preparation of heterocycles with powerful chemotherapeutic potentials [25-43], it was attempted to synthesize some novel pyridines and some derived bi-, tri- and tetracyclic ring systems having the general structures (**A**-**D**; Fig. 1) using the MW irradiation technique, to be biologically evaluated as anticancer and antioxidant agents. Seeking synergistic biological efficiency, the targeted compounds are aimed to encounter basically a 1-methylpyrrolyl moiety owing to the reported role of the pyrrole ring in inducing many anticancer [44,45] and/or antioxidant [46,47] activities. In addition, the target compounds are supported with several functionalities that would assist the aimed biological actions. Therefore, this research work points to achieve new molecules that would be implemented as pioneers in the anticancer and/or antioxidant drug discovery area.

2. Results and Discussion

2.1. Chemistry

The pathways adopted for the preparation of the intermediate and target compounds are depicted in schemes 1 and 2. The reactions employed in these schemes were studied both under conventional heating conditions (fusion or reflux in the appropriate solvent), as well as single mode microwave (MW) irradiation technology. Optimization of the conditions of the performed reactions was accomplished via employment of various combinations of temperature and reaction time to achieve the maximum chemical yield at the shortest reaction time (TLC monitoring). The documented high heating efficiency of MW resulted in an observable

acceleration in reaction rates as revealed from the dramatic reduction in reaction times (from 0.5-8 hours to 10-20 minutes) and the observable improvement in reaction yields (Table 1).

[Scheme 1]

In scheme 1, the 4,6-disubstituted-2-oxo-1,2-dihydropyridine-3-carbonitriles **2-4** and the 2-oxo-1,2,5,6,7,8-hexahydroquinoline-3-carbonitrile **5** were prepared using Hantzsch-type synthesis via multi-component one-put cyclocondensation of 1-methyl-1*H*-pyrrole-2-carbaldehyde **1** with the appropriate ketone, ethyl cyanoacetate and ammonium acetate as a nitrogen source. In a similar fashion, when the aldehyde **1** was condensed with the appropriate ketone, malononitrile and ammonium acetate, the analogous 2-amino derivatives **6-9** were obtained. The latter pyrrolylhexahydroquinoline **9** was reacted with benzoyl isothiocyanate in the presence of K_2CO_3 in acetone to afford the corresponding thioureido derivative **10**. The IR spectrum of **10** revealed the characteristic CN absorption at 2220 cm^{-1}, in addition to the C=O and C=S bands at 1710 and 1170 cm^{-1} , respectively. Furthermore, direct condensation of the **9** with thiourea was attempted to produce the target pyrimidoquinoline-2-thione **11**. Its IR spectrum lacked the CN absorption, however it showed new absorption band at 1180 cm^{-1} attributed to the (C=S) group. A schematic presentation of the reaction mechanism involved in the synthesis of compounds **11** is illustrated in figure 2.

[Figure 2]

The synthesis of the the targeted alkylthio derivatives **12** and **13** was successfully achieved via two different approaches. The first method involved thioakylation of the 2-thione derivative **11** with the appropriate alkyl halide in 1N NaOH medium using conventional heating procedure. Whereas, MW irradiation of a mixture of the thioureido derivative **10,** the appropriate alkyl halide and 1N NaOH was utilized as a second method to produce the same alkylthio derivatives in shorter time and better yields.

[Scheme 2]

In scheme 2, the pyrrolylhexahydroquinoline **9** was utilized as a precursor for the preparation of the target compounds **14-19**. In this respect, reacting **9** with the phenyl isothiocyanate in a medium of pyridine gave rise to the substituted *N*-phenyl pyrimidoquinoline-2-thione **14**. Its IR spectrum exhibited a new band at 1635 cm^{-1} due to the (C=N) moiety and another one at 1210 cm^{-1} corresponding to the (C=S) group. Moreover, heating **9** with acetic anhydride resulted in the targeted 2-methyl pyrimidoquinoline analog **15**. The IR of **15** revealed a characteristic (C=O)

band at 1715 cm^{-1}, while its ^{1}H-NMR spectrum showed a new singlet at δ 2.56 ppm attributed to the newly introduced CH_3 group at C_2. On the other hand, reacting **9** with triethyl orthoformate yielded the 2-ethoxymethylidineamino derivative **16.** The IR spectrum of **16** showed in addition to the cyano group absorption at 2223 cm^{-1}, a new band at 1620 cm^{-1} due to the C=N moiety. Meanwhile, its ^{1}H-NMR exhibited a characteristic triplet and quartet at δ 1.25 and 3.69 ppm, respectively, owing to the CH_2CH_3 group, in addition to the CH=N singlet at δ 8.11 ppm. In its turn, compound **16** was reacted with $NH_2NH_2.H_2O$ in order to obtain the targeted tricyclic pyrimido[4,5-*b*]quinoline analog **17**. Its ^{1}H-NMR showed two new singlets at δ 5.1 and 7.91 ppm due to the novel NH_2 and NH protons, respectively. In its turn, compound **17** was subjected to cyclization reaction either with formic acid to afford the targeted tetracyclic pyrrolyl tetrahydropentaazacyclopenta[*a*]anthracene **18**, or acetic anhydride to give the corresponding 2-methyl analog **19**. The ^{1}H-NMR of **19** was characterised by the disappearance of the singlets of NH protons, and the appearance of a new singlet at 2.55 ppm attributed to the C_2-CH_3 group.

2.2. *In vitro* antitumor Screening

2.2.1. Preliminary *in vitro* one-dose antitumor screening

Out of the newly synthesized eighteen analogs, fourteen compounds namely: **2-12, 14, 17** and **18** were selected by the National Cancer Institute (NCI) *in-vitro* disease-oriented human cells screening panel assay to be evaluated for their *in-vitro* antitumor activity. An effective one-dose assay has been added to the NCI-60 cell screen in order to increase compound throughput and reduce data-turnaround time to suppliers while maintaining efficient identification of active compounds [48-50]. All compounds submitted to the NCI-60 cell screen are tested initially at a single high dose (10 μM) in the full NCI-60 cell panel including leukemia, non-small cell lung, colon, CNS melanoma, ovarian, renal, prostate, and breast cancer cell lines. For compounds **10-12, 14, 17** and **18** data are reported as a mean graph of the percent growth of treated cells, and presented as percentage growth inhibition (GI %) caused by the test compounds (Table 2). The analogs **2-9** that have successfully met threshold inhibition criteria determined by the Development Therapeutic Program (DTP), passed this primary anticancer assay, and were carried over to the 5-dose screen against a panel of about 60 different tumor cell lines.

The results recorded in table 2 showed that, some of the tested subpanel tumor cell lines displayed certain sensitivity profiles against most of the tested analogs **10-12, 14, 17** and **18.** Among these, the non-small cell lung cancer EKVX, HOP-92 and NCI-H522 cell lines exhibited a wide range of sensitivity towards all the tested compounds, with GI range 10.1-36.4%. Moreover, an observable activity with respect to breast cancer T-47D cell line was displayed by the analogs **10, 11** and **12** (GI values 40.6, 40.1 and 54.2%, respectively). Meanwhile, the ovarian cancer IGROV1 cell line showed mild to moderate sensitivity towards all the tested compounds, with special behavior towards compounds **10-12** with GI values range 34.4-38.8 %. Concerning the leukemia subpanel, most of the tested compounds revealed considerable growth inhibitory activities against most of the tested cell lines, especially the RPMI-8226 cell line. Particular high activities against this cell line were shown by compounds **11, 12** and **14** (GI values 51.9, 68.5 and 47.6%, respectively), whereas, the analogs **10** and **17** exerted nearly equipotent growth inhibition on the same cell line (GI values 36.7 and 38.6%, respectively). Furthermore, a reasonable sensitivity profile towards the tested compounds was shown by the leukemia MOLT-4 cell line, especially compound **12** (GI value 42.3%). Additionally, the rest of leukemia subpanel cell lines were moderately affected by the presence of the tested compounds with GI range of 8.5-35.9 %. Regarding the renal cancer subpanel, compounds **10-12** were able to remarkably inhibit the growth of the UO-31 cell line with GI values 51.4, 34.7 and 45.8%, respectively. Colon, melanoma, prostate and CNS cancer subpanels were the least affected by the presence of test compounds (GI range 6.3-31.9%), except the prostate PC-3 cancer cell line which showed remarkable growth inhibition with the analog **12** (GI value 57.1%).

2.2.2. *In vitro* full panel (five-dose) 60-cell line assay for compounds 2-9

Eight compounds **2-9** which passed the primary one-dose screening, were selected to be evaluated for their antitumor activities according to the *in vitro* full panel (five-dose) 60-cell line assay [48-50]. About 60 cell lines of nine tumor subpanels, including leukemia, non-small cell lung, colon, CNS, melanoma, ovarian, renal, prostate and breast cancer cell lines, were incubated with five concentrations (0.01-100 μM) for each compound and were used to create log concentration-% growth inhibition curves. Three response parameters (GI_{50}, TGI, and LC_{50}) were calculated for each cell line. The GI_{50} value (growth inhibitory activity) corresponds to the

concentration of the compounds causing 50% decrease in net cell growth, the TGI value (cytostatic activity) is the concentration of the compounds resulting in total growth inhibition and the LC_{50} value (cytotoxic activity) is the concentration of the compounds causing net 50% loss of initial cells at the end of the incubation period (48h). Subpanel and full panel mean-graph midpoint values (MG-MID) for certain agents are the average of individual real and default GI_{50}, TGI, or LC_{50} values of all cell lines in the subpanel or the full panel, respectively. The NCI antitumor drug discovery was designed to distinguish between broad spectrum antitumor compounds and tumor or subpanel-selective agents. In this part of the present study, compounds **2-9** exhibited a wide range of antitumor activities against some of the tested subpanel tumor cell lines (GI_{50}, TGI and LC_{50} values <100 μM). These compounds showed particular sensitivity towards some individual cell lines, as well as a broad spectrum (MG-MID) of antitumor activity (Table 3).

With respect to the sensitivity against some individual cell lines, within the substituted 2-oxopyridine-3-carbonitriles **2-4**, compound **2** (R = C_6H_5) revealed mild to moderate growth inhibitory activity against 8 tumor cell lines belonging to 6 different subpanels (GI_{50} range 27.5-97.7 μM), with exceptional impact on the non-small cell lung Hop-92 cell line at both the growth inhibitory (GI_{50}) and cytostatic (TGI) levels (0.11 and 0.13 μM, respectively). Moreover, the methoxylated product **3** (R = 3,4-di-OCH_3-C_6H_3) showed better antitumor activity being able to inhibit the growth of 12 different cell lines, with a distinguished effect on the non-small cell lung HOP-92 cell line at both the GI_{50} (0.05 μM) and the TGI (9.77 μM) levels, and a peculiar efficiency against the leukaemia CCRF-CEM and SR cell lines (GI_{50} 5.01 and 0.48 μM, respectively), Additionally, the same analog **3** exhibited an observable antitumor activity against the leukaemia MOLT-4, non-small cell lung EKVX, CNS SNB-75 and breast BT-549 cell lines (GI_{50} values 22.9, 30.9, 23.9 and 34.7 μM, respectively). Replacement of the 6-aryl moiety with a 2-thienyl counterpart led to the moderately active compound **4** with variable growth inhibitory effect on 12 different cell lines (GI_{50} range 10.0-83.2 μM), and a particular effectiveness against the non-small cell lung HOP-92 and renal UO-31 cell lines at both the GI_{50} (10.0 and 13.8 μM, respectively) and the TGI (40.7 and 27.5 μM, respectively) levels. Moreover, a moderate cytotoxic effect was shown by the same analog **4** against the renal UO-31 cell line, expressed by LC_{50} value of 54.9 μM. On the other hand, the structurally related analog 2-oxotetrahydroquinoline-3-carbonitrile **5** revealed a dramatic reduction in the overall antitumor

activity as expressed by the weak antitumor profile against against only 2 cell lines, namely; the CNS SNB-75 and the ovarian OVCAR-4 cancer cell lines (GI_{50} 39.8 and 69.2 μM, respectively). Shifting to the 2-aminopyridine-3-carbonitriles **6-8,** compound **6** (R = C_6H_5) showed an observable antitumor spectrum against 16 different cell lines, with a distinctive growth inhibitory and cytostatic potentials against the leukaemia CCRF-CEM (GI_{50} 0.08 and TGI 0.38 μM) and HL-60 (TB) (GI_{50} 0.76 μM), the non-small cell lung HOP-92 (GI_{50} 0.01 and TGI 0.05 μM), and the CNS SNB-75 (GI_{50} 18.6 and TGI 77.6 μM) cell lines. Meanwhile, the methoxylated analog **7** (R = 3,4-di-OCH_3-C_6H_3) revealed a wide range of growth inhibitory potential against 21 cancer cell lines belonging to the 9 subpanels with a prominent effectiveness on all the tested leukaemia subpanel tumor cell lines. In particular, compound **7** displayed pronounced growth inhibitory, cytostatic and cytotoxic activities on the CCRF-CEM cell line (GI_{50}, TGI and LC_{50} values 0.01, 3.98 and 9.77 μM, respectively), in addition to a significant activity against the non-small cell lung HOP-92 cell line (GI_{50} 5.13 μM). Furthermore, the 2-thienyl analog **8** showed mild to moderate antitumor activity against 4 cell lines, with exceptional efficacy against the leukaemia SR cell line at both the GI_{50} (5.37 μM) and the TGI (67.6 μM) levels. Finally, the bicyclic 2-aminotetrahydroquinoline-3-carbonitrile derivative **9** was able to affect the growth of 14 different cell lines, with distinguished inhibitory action on the growth of the leukaemia HL-60(TB) (GI_{50} 0.42 μM) and SR (GI_{50}, TGI and LC_{50} values 3.39, 20.4 and 91.2 μM, respectively) cell lines.

Concerning the broad spectrum antitumor activity, the results revealed that the eight active compounds (**2-9**) exhibited effective growth inhibition GI_{50} (MG-MID) values of 77.6, 67.6, 83.2, 91.2, 79.7, 60.3, 93.3 and 75.9 μM, respectively. Moreover, six compounds namely; **2, 3, 4, 6, 7** and **9** were able to display a cytostatic activity with TGI (MG-MID) values of 85.1, 95.5, 95.5, 93.3, 79.4 and 97.7 μM, respectively (Table 3). However, only two compounds namely; **6** and **7** showed weak cytotoxic efficacy with LC_{50} (MG-MID) values 95.5 and 93.3 μM, respectively).

2.2.3. Structure-activity correlation

A close examination of the structures of the biologically active compounds revealed that they belong to four different series: monocyclic (2-oxo or 2-amino)pyridines (**2-4** and **6-8**), bicyclic

tetrahydroquinolines (**5, 9** and **10**), tricyclic tetrahydropyrimido[4,5-*b*]quinolines (**11, 12, 14** and **17**) and a tetracyclic tetrahydropentaazacyclopenta[*a*]anthracene (**18**) (Schemes 1,2). In general, the 2-oxo (or 2-amino)pyridines (**2-4** and **6-8**) exhibited significantly better antitumor spectrum and potential being passed the primary anticancer assay, and carried over to the 5-dose screen. According to the results recorded in table 3, it could be clearly recognized that better antitumor activity was bounded to the 2-aminopyridine-3-carbonitrile scaffold (**6-8**). The nature of the aryl moiety at C_6 seems to remarkably affect the antitumor activity of these compounds as evidenced by their $GI_{50,}$ TGI and LC_{50} values (Table 3). Among these, the 3,4-dimethoxyphenyl moiety (**7**; R = 3,4-di-OCH_3-C_6H_3) proved to be the most favourable substituent (GI_{50}, TGI, and LC_{50} (MG-MID) values 60.3, 79.4 and 93.3 μM, respectively), when compared with its congeners **6** (R = C_6H_5) and **8** (R = 2-thienyl). Analogously, the corresponding 6-(3,4-dimethoxyphenyl-2-oxopyridine-3-carbonitrile analog **3** showed the highest activity among the the 2-oxopyridine-3-carbonitrile series (**2-4**). With regard to the bicyclic tetrahydroquinolines (**5, 9** and **10**), the 2-aminotetrahydroquinoline-3-carbonitrile **9** displayed considerable antitumor efficacy in the 5-dose assay against 14 different cell lines, when compared with the 2-oxopyridine analog **5** which showed limited activity against only 2 cell lines (Table 3). Introduction of a benzoylthioureido counterpart at position 2, led to a less active compound **10** that couldn't be promoted to the 5-dose assay. However, it showed a broad spectrum of antitumor activity against 26 different tumor cell lines (Table 2). Annulation of the bicyclic tetrahydroquinoline **9** into variously substituted tricyclic tetrahydropyrimido[4,5-*b*]quinolines furnished 4 compounds namely; **11, 12, 14** and **17**. Among these, the 1*H*-pyrimido[4,5-*b*]quinoline-2-thione **11** and the ethyl thioether **12** exerted a noticeable broad spectrum of growth inhibitory activity on a variety of cell lines belonging to different tumor subpanels, with obvious effect on the leukaemia subpanel tumor cell lines. The N-phenylpyrimido[4,5-*b*]quinoline-2-thione **14** and iminopyrimido[4,5-*b*]quinoline **17** possessed moderate to weak antitumor activity, with special potency against the leukemia cell lines. However, conversion of the imino derivative **17** into the tetracyclic pentaazacyclopenta[*a*] anthracene **18** resulted in a reduction in the overall antitumor potency and spectrum.

2.3. Antioxidant Activity

DPPH radical scavenging assay

Compounds **3, 6, 7, 9, 10, 11** and **12** which exhibited prominent antitumor activity, were further evaluated for their antioxidant potential through scavenging of the 2,2-diphenyl-1-picrylhydrazyl

(DPPH) radical, according to a modified procedure from that described by Blois [51]. The principle of this assay is based on the fact that the odd electron in DPPH free radical gives a strong absorption maximum in the visible region at λmax 517 nm (violet in color). Upon reduction in the presence of an antioxidant, the violet color switches to yellow when such odd electron of DPPH radical conjugates with a hydrogen to form the reduced DPPH-H (2,2-diphenyl-1-picrylhydrazine). This color change is stoichiometric, where the degree of discoloration is proportional to the scavenging potential of the tested compound i.e. low absorbance refers to remarkable free radical scavenging potential. The antioxidant potential of the tested compounds was calculated as the percentage DPPH scavenging effect in relation to control and butylated hydroxyl toluene (BHT) was utilized as a reference standard antioxidant. The results recorded in table 4 revealed that all the tested seven compounds showed variable degree of DPPH scavenging activity. At the 10^{-3} M concentration level, the substituted 6-(3,4-dimethoxyphenyl)pyridine-3-carbonitriles **3** and **7** (scavenging activity 31 and 33 %, respectively) were nearly equiactive with BHT; the standard antioxidant utilized in this assay (scavenging activity 36 %), whereas, the substituted 6-phenyl-2-aminopyridine-3-carbonitrile analog **6** displayed an appreciable activity (scavenging activity 27 %). Nevertheless, the structurally related 2-aminotetrahydroquinoline-3-carbonitrile **9** displayed a relatively weak antioxidant activity (scavenging activity 16 %), when compared with compounds **3, 6** and **7**. On the other hand, the sulphur-containing benzoylthioureidoquinoline **10,** 1*H*-pyrimido[4,5-*b*]quinoline-2-thione **11** and the derived ethyl thioether **12** exhibited considerable activity (scavenging activity 23, 26 and 28 %, respectively). In a similar pattern, the same order of DPPH radical scavenging potential was expressed at the 10^{-4} M concentration level, with a scavenging activity range 9-19 %, when compared with BHT (scavenging activity 20 %).

3. Conclusion

The main aim of this investigation was to comparatively study the effect of utilizing both the conventional heating and MW irradiation techniques in the synthesis of some novel

pyrrolylpyridines and some derived bi-, tri- and tetracyclic ring systems, to be biologically evaluated as anticancer and antioxidant agents. The obtained NCI's *in vitro* one-dose antitumor data revealed that the analogs **10-12, 14, 17** and **18** showed various growth inhibitory (GI %) profiles against some of the tested subpanel tumor cell lines. Meanwhile, the analogs **2-9** have successfully passed the primary one-dose screening, and promoted to the *in vitro* full panel (five-dose) 60-cell line assay. The best antitumor activity was bounded to the 2-aminopyridine-3-carbonitrile scaffold (**6-8**) especially **7** (R = 3,4-di-OCH_3-C_6H_3), whereas the bicyclic tetrahydroquinolines (**5, 9** and **10**) displayed considerable antitumor efficacy. Further annulation of the bicyclic tetrahydroquinoline **9** into variously substituted tricyclic tetrahydropyrimido[4,5-*b*]quinolines (**11, 12, 14** and **17**) and the tetracyclic pentaazacyclopenta[*a*]anthracene **18** resulted in a reduction in the overall antitumor potency and spectrum, being not able to pass to the 5-dose assay. On the other hand, compounds **3, 6, 7, 9, 10, 11** and **12** which exhibited prominent antitumor activity, were further evaluated for their antioxidant potential using the DPPH radical scavenging assay. At the 10^{-3} M concentration level, the substituted 6-(3,4-dimethoxyphenyl)pyridine-3-carbonitriles **3** and **7** showed scavenging activity 31 and 33 %, respectively, which were nearly equiactive with BHT; the standard antioxidant utilized in this assay (scavenging activity 36 %). Finally, the broad spectrum antitumor activity and special efficacy against leukaemia together with the reliable antioxidant potential displayed by compounds **3** and **7** will be of interest for future derivatization in the hope of finding more active and selective lead structures for dual antitumor and antioxidant activities.

4. Experimental

4.1. Chemistry

Microwave-assisted syntheses were carried out in a (CEM Discover, 300W) microwave synthesizer using a pressure tube (10 mL) sealed with a plastic cap. Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. The infrared (IR) spectra were recorded on Shimadzu FT-IR 8400S infrared spectrophotometer using the KBr pellet technique. ^{1}H and ^{13}C-NMR spectra were recorded on a Bruker DPX-400 FT NMR spectrometer using tetramethylsilane as the internal standard and a mixture of $CDCl_3$ and

DMSO-d_6 as a solvent (Chemical shifts in δ, ppm). Splitting patterns were designated as follows: s: singlet; d: doublet; m: multiplet; q: quartet. Elemental analyses were performed on a 2400 Perkin Elmer Series 2 analyzer and the found values were within ±0.4% of the theoretical values. Follow up of the reactions and checking the homogeneity of the compounds were made by TLC on silica gel-protected aluminum sheets (Type 60 F254, Merck) and the spots were detected by exposure to UV-lamp at λ 254.

4.1.1. General procedure for the synthesis of 4-(1-methyl-1*H*-pyrrol-2-yl)-2-oxo-6-substituted-1,2-dihydropyridine-3-carbonitriles (2-4) and 8-methyl-4-(1-methyl-1*H*-pyrrol-2-yl)-2-oxo-1,2,5,6,7,8-hexahydroquinoline-3-carbonitrile (5)

Conventional heating: a one-pot mixture of 1-methyl-1*H*-pyrrole-2-carbaldehyde **1** (0.55 g, 5 mmol), the appropriate ketone (5 mmol), ethyl cyanoacetate (0.57 g, 5 mmol) and ammonium acetate (3.1 g, 40 mmol) in absolute ethanol (20 mL), was refluxed for 5-6 h. The reaction mixture was allowed to cool, and the formed solid product was filtered, washed with water, dried and recrystallized from ethanol.

Microwave irradiation: a thoroughly mixed solvent-free mixture of the aldehyde **1** (0.55 g, 5 mmol), the appropriate ketone (5 mmol), ethyl cyanoacetate (0.57 g, 5 mmol) and ammonium acetate (3.1 g, 40 mmol), was subjected to microwave irradiation at 100 ^{O}C for 15 min. After being cooled to room temperature, the residue was treated with water, filtered, dried and recrystallized from ethanol. IR (cm^{-1}): 3380-3220 (NH), 2220- 2210 (CN), 1685-1675 (C=O). Yields and melting points are recorded in table 1.

4.1.1.1. 4-(1-Methyl-1*H*-pyrrol-2-yl)-2-oxo-6-phenyl-1,2-dihydropyridine-3-carbonitrile (2). ^{1}H-NMR (δ, ppm): 3.46 (s, 3H, N-C*H*$_3$), 6.38 (s, 1H, pyridine C_5-*H*), 6.92-7.36 (m, 8H, 3 pyrrole-*H* and 5 Ar-*H*), 8.15 (s, 1H, N*H*). ^{13}C-NMR (δ, ppm): 45.6 (CH_3), 118.3 (CN), 89.2, 102.2, 110.8, 116.7, 121.4, 127.5, 128.8, 130.4, 132.8, 133.3, 144.3, 162.9, 166.1 (Ar C), 169.5 (CO). Anal. Calcd. for $C_{17}H_{13}N_3O$ (275.3): C, 74.17; H, 4.76; N, 15.26. Found: C, 73.94; H, 4.93; N, 15.11.

4.1.1.2. 6-(3,4-Dimethoxyphenyl)-4-(1-methyl-1*H*-pyrrol-2-yl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (3). ^{1}H-NMR (δ, ppm): 3.49 (s, 3H, N-C*H*$_3$), 3.85 (s, 3H, OC*H*$_3$), 3.90 (s, 3H, OC*H*$_3$), 6.47 (s, 1H, pyridine C_5-*H*), 6.76-7.41 (m, 6H, 3 pyrrole-*H* and 3 Ar-*H*), 8.18 (s, 1H, N*H*). ^{13}C-NMR (δ, ppm): 46.7 (CH_3), 55.3 (OCH_3), 56.9 (OCH_3), 117.9 (CN), 88.9, 102.3,

111.5, 116.6, 120.1, 125.8, 129.5, 130.7, 132.8, 133.9, 145.8, 162.9, 164.4 (Ar C), 169.7 (CO). Anal. Calcd. for $C_{19}H_{17}N_3O_3$ (335.36): C, 68.05; H, 5.11; N, 12.53. Found: C, 68.37; H, 5.02; N, 12.44.

4.1.1.3. 4-(1-Methyl-1*H*-pyrrol-2-yl)-2-oxo-6-(2-thienyl)-1,2-dihydropyridine-3-carbonitrile (4). ^{1}H-NMR (δ, ppm): 3.47 (s, 3H, N-C*H*$_3$), 6.40 (s, 1H, pyridine C_5-*H*), 6.81-7.24 (m, 6H, 3 pyrrole-*H* and 3 thiophene-*H*), 8.17 (s, 1H, N*H*). ^{13}C-NMR (δ, ppm): 48.1 (CH_3), 119.0 (CN), 88.9, 101.9, 110.8, 118.3, 122.5, 127.4, 131.2, 142.0, 146.3, 162.3, 166.4 (Ar C), 170.1 (CO). Anal. Calcd. for $C_{15}H_{11}N_3OS$ (281.33): C, 64.04; H, 3.94; N, 14.94; S, 11.4. Found: C, 63.87; H, 4.05; N, 14.82; S, 11.21.

4.1.1.4. 8-Methyl-4-(1-methyl-1*H*-pyrrol-2-yl)-2-oxo-1,2,5,6,7,8-hexahydroquinoline-3-carbonitrile (5) ^{1}H-NMR (δ, ppm): 1.38 (s, 3H, C*H*$_3$), 1.64-2.40 (m, 6H, $C_{5,6,7}$-*H*), 2.83 (m, 1H, C_8-*H*), 3.39 (s, 3H, N-C*H*$_3$), 6.89-7.21 (m, 3H, 3 pyrrole-*H*), 8.26 (s, 1H, N*H*). ^{13}C-NMR (δ, ppm): 16.1 (CH_3), 27.7, 27.9, 34.4, 34.9 (cyclohexyl C), 45.4 (CH_3), 118.4 (CN), 95.7, 102.2, 110.8, 116.5, 121.4, 126.3, 132.7, 169.4 (Ar C), 169.9 (CO). Anal. Calcd. for $C_{16}H_{17}N_3O$ (267.33): C, 71.89; H, 6.41; N, 15.72. Found: C, 72.06; H, 6.33; N, 15.48.

4.1.2. General procedure for the synthesis of 2-amino-4-(1-methyl-1*H*-pyrrol-2-yl)-6-substituted nicotinonitrile (6-8) and 2-amino-8-methyl-4-(1-methyl-1*H*-pyrrol-2-yl)-5,6,7,8-tetrahydroquinoline-3-carbonitrile (9).

Conventional heating: a one-put mixture of the aldehyde **1** (0.55 g, 5 mmol), the appropriate ketone (5 mmol), malononitrile (0.33 g, 5 mmol) and ammonium acetate (3.1 g, 40 mmol) in absolute ethanol (20 mL), was heated under reflux for 4-6 h. After cooling, the precipitated product was filtered, washed with water, dried and recrystallized from ethanol.

Microwave irradiation: a thoroughly mixed solvent-free mixture of the aldehyde **1** (0.55 g, 5 mmol), the appropriate ketone (5 mmol), malononitrile (0.33 g, 5 mmol) and ammonium acetate (3.1 g, 40 mmol), was subjected to microwave irradiation at 100 ^{O}C for 10 min. After being cooled to room temperature, the residue was treated with water, filtered, dried and recrystallized from ethanol. IR (cm^{-1}): 3390-3240 (NH), 2225-2210 (CN). Yields and melting points are recorded in table 1.

4.1.2.1. 2-Amino-4-(1-methyl-1*H*-pyrrol-2-yl)-6-phenylnicotinonitrile (6). ^{1}H-NMR (δ, ppm): 3.46 (s, 3H, N-C*H*$_3$), 5.09 (s, 2H, N*H*$_2$), 6.41 (s, 1H, pyridine C_5-*H*), 6.89-7.21 (m, 8H, 3 pyrrole-

H and 5 Ar-*H*). ^{13}C-NMR (δ, ppm): 48.3 (CH_3), 119.9 (CN), 89.1, 102.2, 110.8, 118.3, 121.4, 127.5, 128.8, 130.4, 132.8, 133.3, 146.3, 161.9, 167.2 (Ar C). Anal. Calcd. for $C_{17}H_{14}N_4$ (274.32): C, 74.43; H, 5.14; N, 20.42. Found: C, 74.80; H, 5.09; N, 20.12.

4.1.2.2. 6-(3,4-Dimethoxyphenyl)-2-amino-4-(1-methyl-1*H*-pyrrol-2-yl)-nicotinonitrile (7). ^{1}H-NMR (δ, ppm): 3.45 (s, 3H, N-C*H*$_3$), 3.89 (s, 6H, 2 OC*H*$_3$), 5.06 (s, 2H, N*H*$_2$), 6.44 (s, 1H, pyridine C_5-*H*), 6.81-7.26 (m, 6H, 3 pyrrole-*H* and 3 Ar-*H*). ^{13}C-NMR (δ, ppm): 47.9 (CH_3), 54.2 (OCH_3), 56.6 (OCH_3), 118.3 (CN), 89.7, 101.9, 111.2, 116.3, 120.9, 126.6, 129.1, 131.2, 133.6, 134.1, 145.6, 162.5, 167.9 (Ar C). Anal. Calcd. for $C_{19}H_{18}N_4O_2$ (334.37): C, 68.25; H, 5.43; N, 16.76. Found: C, 68.53; H, 5.23; N, 16.93.

4.1.2.3. 2-Amino-4-(1-methyl-1*H*-pyrrol-2-yl)-6-(2-thienyl)nicotinonitrile (8). ^{1}H-NMR (δ, ppm): 3.46 (s, 3H, N-C*H*$_3$), 5.07 (s, 2H, N*H*$_2$), 6.42 (s, 1H, pyridine C_5-*H*), 6.79-7.20 (m, 6H, 3 pyrrole-*H* and 3 thiophene-*H*). ^{13}C-NMR (δ, ppm): 48.1 (CH_3), 118.6 (CN), 89.1, 101.2, 110.2, 118.3, 121.9, 126.5, 130.4, 141.8, 146.3, 161.9, 167.2 (Ar C). Anal. Calcd. for $C_{15}H_{12}N_4S$ (280.35): C, 64.26; H, 4.31; N, 19.98; S, 11.44. Found: C, 64.41; H, 4.42; N, 20.28; S, 11.63.

4.1.2.4. 2-Amino-8-methyl-4-(1-methyl-1*H*-pyrrol-2-yl)-5,6,7,8-tetrahydroquinoline-3-carbonitrile (9). ^{1}H-NMR (δ, ppm): 1.36 (s, 3H, C*H*$_3$), 1.62-2.37 (m, 6H, $C_{5,6,7}$-*H*), 2.86 (m, 1H, C_8-*H*), 3.36 (s, 3H, N-C*H*$_3$), 5.06 (s, 2H, N*H*$_2$), 6.89-7.21 (m, 3H, 3 pyrrole-*H*). ^{13}C-NMR (δ, ppm): 21.1 (CH_3), 22.1, 27.6, 31.2, 38.4 ($C_{5,6,7,8}$), 46.2 (CH_3), 118.7 (CN), 88.1, 102.2, 110.8, 117.3, 121.4, 145.7, 163.8, 164.2, (Ar C). Anal. Calcd. for $C_{16}H_{18}N_4$ (266.34): C, 72.15; H, 6.81; N, 21.04. Found: C, 72.33; H, 7.06; N, 21.16.

4.1.3. N-((3-cyano-8-methyl-4-(1-methyl-1*H*-pyrrol-2-yl)-5,6,7,8-tetrahydroquinolin-2-yl)carbamothioyl)benzamide (10).

Conventional heating: to a mixture of the 2-amino-8-methyl-4-(1-methyl-1*H*-pyrrol-2-yl)-5,6,7,8-tetrahydroquinoline-3-carbonitrile **9** (1.33 g, 5 mmol) and K_2CO_3 (0.9 g, 6.5 mmol) in dry acetone (20 mL), a solution of benzoyl isothiocyanate (0.82 g, 5 mmol) in dry acetone (5 mL) was added. The resultant reaction mixture was heated under reflux for 2 h, then left for an overnight at room temperature, concentrated to half its volume and allowed to cool in the refrigerator for 4 h. The separated solid product was filtered, washed with diethyl ether and crystallized from ethanol.

Microwave irradiation: a mixture of the tetrahydroquinoline **9** (1.33 g, 5 mmol), K_2CO_3 (0.9 g, 6.5 mmol), benzoyl isothiocyanate (0.82 g, 5 mmol) in dry acetone (10 mL), was subjected to microwave irradiation at 100 ^{O}C for 10 min. After being cooled to room temperature, the reaction mixture was worked up as described under the conventional heating procedure. Yields and melting point are recorded in table 1. IR (cm^{-1}): 3480-3330 (NH), 2220 (CN), 1710 (C=O), 1170 (C=S). ^{1}H-NMR (δ, ppm): 1.38 (s, 3H, C*H*$_3$), 1.64-2.64 (m, 6H, $C_{5,6,7}$-*H*), 3.05 (m, 1H, C_8-*H*), 3.40 (s, 3H, N-C*H*$_3$), 5.05 (s, 1H, N*H*), 7.09-7.73 (m, 8H, 3 pyrrole-*H* and Ar-*H*), 7.99 (s, 1H, N*H*). ^{13}C-NMR (δ, ppm): 21.4 (CH_3), 25.4, 31.5, 32.2, 39.1 ($C_{5,6,7,8}$), 56.1 (CH_3), 91.9, 104.5, 110.3, 121.7, 126.2, 128.8, 130.4, 131.8, 133.5, 156.7, 161.5, 163.7 (Ar C), 118.0 (CN), 180 (CS), 170.1 (CO). Anal. Calcd. for $C_{24}H_{23}N_5OS$ (429.54): C, 67.11; H, 5.40; N, 16.30; S, 7.47. Found: C, 67.38; H, 5.24; N, 16.42; S, 7.63.

4.1.4. 4-Amino-9-methyl-5-(1-methyl-1*H*-pyrrol-2-yl)-6,7,8,9-tetrahydro-1*H*-pyrimido[4,5-*b*]quinoline-2-thione (11).

Conventional method: the key intermediate **9** (1.33 g, 5 mmol) and thiourea (1.9 g, 25 mmol) were fused at 260-300 ºC using a sand bath for 1 h. The reaction mixture was allowed to attain room temperature, the crude solid product was rubbed with cold ethanol, filtered and recrystallized from DMF containing few drops of water.

Microwave method: a mixture of **9** (1.33 g, 5 mmol) and thiourea (1.9 g, 25 mmol), was subjected to microwave irradiation at 250 ^{O}C for 10 min. After being cooled to room temperature, the reaction mixture was worked up as described under the conventional heating procedure. Yields and melting point are recorded in table 1. IR (cm^{-1}): 3345-3280 (NH), 1180 (C=S). ^{1}H-NMR (δ, ppm): 1.39 (s, 3H, C*H*$_3$), 1.63-2.44 (m, 6H, $C_{6,7,8}$-*H*), 3.18 (m, 1H, C_9-*H*), 3.56 (s, 3H, N-C*H*$_3$), 5.06 (s, 2H, N*H*$_2$), 6.88-7.29 (m, 4H, 3 pyrrole-*H* and N-*H*). ^{13}C-NMR (δ, ppm): 21.1 (CH_3), 26.2, 32.5, 33.1, 38.6 ($C_{6,7,8,9}$), 52.0 (CH_3), 109.7, 114.4, 124.6, 127.8, 130.3, 149.6, 156.9, 162.5, 163.4, 164.3 (Ar C), 182.8 (CS). Anal. Calcd. for $C_{17}H_{19}N_5S$ (325.43): C, 62.74; H, 5.88; N, 21.52; S, 9.85. Found: C, 62.65; H, 5.94; N, 21.39; S, 10.07.

4.1.5. 2-Alkylthio-4-amino-9-methyl-5-(1-methyl-1*H*-pyrrol-2-yl)-6,7,8,9-tetrahydro-1*H*-pyrimido[4,5-*b*]quinolines (12 and 13).

Conventional heating: to a stirred solution of the thione **11** (0.98 g, 3 mmol) in a mixture of 1N NaOH (10 mL) and ethanol (5 mL), was added the appropriate alkyl halide (4.5 mmol). The reaction mixture was stirred at room temperature for 6 h, and the precipitated product was filtered, washed with aqueous ethanol, dried and recrystallized from ethanol.

Microwave irradiation: a solution of the thioureido derivative **10** (1.23 g, 3 mmol) and the appropriate alkyl halide (4.5 mmol) in a mixture of 1N sodium hydroxide (3 mL) and EtOH (7 mL), was subjected to microwave irradiation at 180 ^{O}C for 15 min. After being cooled to room temperature, the reaction mixture was worked up as described under the conventional heating procedure. Yield and melting point are recorded in table 1. IR (cm^{-1}): 3440-3150 (NH).

4.1.5.1. 4-Amino-2-ethylthio-9-methyl-5-(1-methyl-1*H*-pyrrol-2-yl)-6,7,8,9-tetrahydro-1*H*-pyrimido[4,5-*b*]quinoline (12). ^{1}H-NMR (δ, ppm): 1.25 (t, *J* = 9 Hz, 3H, ethyl-C*H*$_3$), 1.39 (s, 3H, C*H*$_3$), 1.41-2.23 (m, 6H, C$_{6,7,8}$-*H*), 3.21 (m, 1H, C$_9$-*H*), 3.52 (q, *J* = 9 Hz, 2H, ethyl-C*H*$_2$), 3.51 (s, 3H, N-C*H*$_3$), 5.28 (s, 2H, N*H*$_2$), 6.88-7.21 (m, 3H, pyrrole-*H*). ^{13}C-NMR (δ, ppm): 15.8 (CH$_3$), 22.1 (CH$_3$), 29.4 (CH$_2$), 25.8, 30.9, 32.7, 37.9 (C$_{6,7,8,9}$), 55.3 (CH$_3$), 102.3, 113.4, 128.9, 130.4, 135.4, 148.7, 151.4 158.0, 162.5, 164.2, 167.6 (Ar C). Anal. Calcd. for $C_{19}H_{23}N_5S$ (353.48): C, 64.56; H, 6.56; N, 19.81; S, 9.07. Found: C, 64.83; H, 6.37; N, 19.64; S, 9.33.

4.1.5.2. 4-Amino-2-benzylthio-9-methyl-5-(1-methyl-1*H*-pyrrol-2-yl)-6,7,8,9-tetrahydro-1*H*-pyrimido[4,5-*b*]quinoline (13). ^{1}H-NMR (δ, ppm): 1.36 (s, 3H, C*H*$_3$), 1.56-2.31 (m, 6H, C$_{6,7,8}$-*H*), 3.18 (m, 1H, C$_9$-*H*), 3.46 (s, 3H, N-C*H*$_3$), 4.25 (s, 2H, benzyl C*H*$_2$), 5.32 (s, 2H, N*H*$_2$), 6.82-7.58 (m, 8H, 3 pyrrole-*H* and Ar-*H*). ^{13}C NMR (δ-ppm): 15.4 (CH$_3$), 30.8 (N-CH$_3$), 44.9 (benzyl-CH$_2$), 27.6, 28.2, 32.2, 34.9 (C$_{6,7,8,9}$), 95.8, 104.0, 111.2, 119.7, 121.2, 122.6, 124.1, 125.3, 126.8, 128.8, 129.3, 132.7, 161.6 (Ar C). Anal. Calcd. for $C_{24}H_{25}N_5S$ (415.55): C, 69.37; H, 6.06; N, 16.85; S, 7.72. Found: C, 69.51; H, 6.32; N, 16.94; S, 7.91.

4.1.6. 4-Imino-9-methyl-3-phenyl-5-(1-methyl-1*H*-pyrrol-2-yl)-3,4,6,7,8,9-hexahydro-1*H*-pyrimido [4,5-*b*]quinoline-2-thione (14).

Conventional method: a mixture of **9** (1.33 g, 5 mmol), phenyl isothiocyanate (1 g, 7.5 mmol) in pyridine (10 mL) was refluxed for 3 h. After cooling, the separated solid product was filtered off, washed thoroughly with water, dried and recrystallized from acetic acid.

Microwave method: a mixture of **9** (1.33 g, 5 mmol), phenyl isothiocyanate (1 g, 7.5 mol) and pyridine (5 mL) was subjected to microwave irradiation at 180 ^{O}C for 15 min. After being cooled to room temperature, the reaction mixture was worked up as described under the conventional heating procedure. Yields and melting point are recorded in table 1. IR (cm^{-1}): 3330-3160 (NH), 1635 (C=N), 1210 (C=S). ^{1}H-NMR (δ, ppm): 1.39 (s, 3H, C*H*$_3$), 1.68-2.39 (m, 6H, $C_{6,7,8}$-*H*), 3.12 (m, 1H, C_9-*H*), 3.45 (s, 3H, N-C*H*$_3$), 4.98 (s, 1H, N*H*), 6.81-7.52 (m, 8H, 3 pyrrole-*H* and Ar-*H*), 8.05 (s, 1H, N*H*). ^{13}C-NMR (δ-ppm): 21.6 (CH_3), 26.4, 32.6, 34.5, 39.7 ($C_{6,7,8,9}$), 51.2 (CH_3), 91.3, 109.8, 114.4, 125.2, 127.6, 128.6, 130.5, 139.7, 148.8, 157.5 (Ar C), 165.2 (C=NH), 179.4 (CS). Anal. Calcd. for $C_{23}H_{23}N_5S$ (401.53): C, 68.8; H, 5.77; N, 17.44; S, 7.99. Found: C, 68.54; H, 5.37; N, 17.69; S, 8.16.

4.1.7. 2,9-Dimethyl-5-(1-methyl-1*H*-pyrrol-2-yl)-6,7,8,9-tetrahydro-3*H*-pyrimido[4,5-*b*]-quinolin-4-one (15). A mixture of **9** (1.33 g, 5 mmol), acetic anhydride (10 mL) and conc. H_2SO_4 (1 mL) was heated in a boiling water bath for 10 min. The reaction mixture was cooled, poured carefully onto ice-cold water, treated with 20% NaOH solution till alkaline. The precipitated crude solid product was filtered, washed with water, dried and recrystallized from ethanol. Yield and melting point are recorded in table 1. IR (cm^{-1}): 3430-3220 (NH), 1715 (C=O).^{1}H-NMR (δ, ppm): 1.38 (s, 3H, C*H*$_3$), 1.46-2.2 (m, 6H, $C_{6,7,8}$-*H*), 2.56 (s, 3H, C_2-C*H*$_3$), 3.14 (m, 1H, C_9-*H*), 3.88 (s, 3H, N-C*H*$_3$), 6.87-7.51 (m, 3H, 3 pyrrole-*H*), 8.03 (s, 1H, N*H*). ^{13}CNMR (δ, ppm): 18.9 (CH_3), 21.4 (CH_3), 22.1, 28.4, 31.2, 38.7 ($C_{6,7,8,9}$), 55.4 (CH_3), 113.1, 119.2, 131.5, 134.2, 139.5, 152.6, 159.0, 161.4, 162.5, 169.3 (Ar C), 174.5 (CO). Anal. Calcd. for $C_{18}H_{20}N_4O$ (308.38): C, 70.11; H, 6.54; N, 18.17. Found: C, 69.93; H, 6.31; N, 18.32.

4.1.8. 2-Ethoxymethylidineamino-3-cyano-8-methyl-4-(1-methyl-1*H*-pyrrol-2-yl)-5,6,7,8-tetrahydroquinoline (16).

Conventional method: a mixture of the tetrahydroquinoline **9** (1.33 g, 5 mmol), triethylorthoformate (5 mL) and acetic anhydride (3 mL), was heated for 10 h. The reaction mixture was allowed to cool then diluted with cold water. The precipitated solid was collected by filtration, washed with water and recrystallized from ethanol/benzene mixture 3:1.

Microwave method: a mixture of the tetrahydroquinoline **9** (1.33 g, 5 mmol), triethylorthoformate (5 mL) and acetic anhydride (3 mL), was subjected to microwave irradiation

at 180 ^{O}C for 20 min. After being cooled to room temperature, the reaction mixture was worked up as described in the conventional procedure. Yields and melting point are recorded in table 1. IR (cm^{-1}): 2223 (CN), 1620 (C=N). ^{1}H-NMR (δ, ppm): 1.25 (t, *J* = 8.6, 3H, ethyl-C*H*$_3$), 1.36 (s, 3H, C*H*$_3$), 1.69-2.31 (m, 6H, C$_{5,6,7}$-*H*), 3.09 (m, 1H, C$_8$-*H*), 3.69 (q, *J* = 8.6, 2H, ethyl-C*H*$_2$), 3.81 (s, 3H, N-C*H*$_3$), 6.87-7.29 (m, 3H, pyrrole-*H*), 8.11 (s, 1H, N=C*H*). ^{13}C-NMR (δ, ppm): 15.5 (CH$_3$), 21.2 (CH$_3$), 23.2, 28.4, 34.5, 38.6 (cyclohexyl C), 54.1 (CH$_3$), 58.3 (CH$_2$), 117.7 (CN), 103.1, 115.8, 127.2, 130.8, 134.2, 155.5, 162.3, 169.1, 171.8 (Ar C), 165.1 (N=C). Anal. Calcd. for $C_{19}H_{22}N_4O$ (322.4): C, 70.78; H, 6.88; N, 17.38. Found: C, 70.92; H, 6.57; N, 17.64.

4.1.9. 3-Amino-4-imino-9-methyl-5-(1-methyl-1*H*-pyrrol-2-yl)-6,7,8,9-tetrahydro-4*H*-pyrimido[4,5-*b*]quinoline (17).

Conventional method: a mixture of the intermediate tetrahydroquinoline **16** (1.6 g, 5 mmol) and hydrazine hydrate 99% (1 g, 20 mmol) in dry benzene (30 mL), was heated under reflux for 4 h. On cooling, the solid product thus obtained was filtered, dried and recrystallized from toluene.

Microwave method: a solvent-free mixture of the intermediate tetrahydroquinoline **16** (1.6 g, 5 mmol) and hydrazine hydrate 99% (1 g, 20 mmol) was subjected to microwave irradiation at 150 ^{O}C for 10 min. After being cooled to room temperature, the reaction mixture was worked up as described under the conventional heating procedure. Yields and melting point are recorded in table 1. IR (cm^{-1}): 3350-3235 (NH), 1640 (C=N). ^{1}H-NMR (δ, ppm): 1.38 (s, 3H, C*H*$_3$), 1.58-2.31(m, 6H, C$_{6,7,8}$-*H*), 2.85 (m, 1H, C$_9$-*H*), 3.81 (s, 3H, N-C*H*$_3$), 5.1 (s, 2H, N*H*$_2$), 6.84-7.31 (m, 4H, pyrrole-*H* and C$_2$-*H*), 7.91 (s, 1H, N*H*). ^{13}C-NMR (δ, ppm): 21.1 (CH$_3$), 22.4, 27.4, 32.2, 39.4 (C$_{6,7,8,9}$), 56.6 (CH$_3$), 113.8, 119.3,2, 127.8, 130.4, 134.2, 147.1, 159.4, 161.7, 162.1, 164.0, 167.8 (Ar C). Anal. Calcd. for $C_{17}H_{20}N_6$ (308.38): C, 66.21; H, 6.54; N, 27.25. Found: C, 66.13; H, 6.87; N, 27.61.

4.1.10. 7-Methyl-11-(1-methyl-1*H*-pyrrol-2-yl)-7,8,9,10-tetrahydro-1,3,3a,5,6-pentaazacyclopenta[*a*]anthracene (18).

Conventional heating: a solution of the pyrimido[4,5-*b*]quinoline **17** (1.54 g, 5 mmol) in formic acid (10 mL) was heated under reflux for 6 h. The reaction mixture was cooled to room temperature, diluted with cold water and the precipitated solid was collected by filtration, washed with water, dried and recrystallized from benzene. IR (cm^{-1}): 1630 (C=N).

Microwave irradiation: a mixture of **17** (1.54 g, 5 mmol) and formic acid (10 mL) was subjected to microwave irradiation at 150 ^{O}C for 20 min. After being cooled to room temperature, the reaction mixture was worked up as described under the conventional heating procedure. Yields and melting point are recorded in table 1. IR (cm^{-1}): 1640 (C=N). ^{1}H-NMR (δ, ppm): 1.38 (s, 3H, C*H*$_3$), 1.54-2.41 (m, 6H, C$_{8,9,10}$-*H*), 3.1 (m, 1H, C$_7$-*H*), 3.86 (s, 3H, N-C*H*$_3$), 6.91-7.41 (m, 3H, pyrrole-*H*), 8.69 (s, 1H, C$_2$-*H*), 9.18 (s, 1H, C$_4$-*H*). ^{13}C-NMR (δ, ppm): 21.8 (CH$_3$), 22.4, 27.9, 32.9, 40.2 (C$_{7,8,9,10}$), 55.2 (CH$_3$), 115.6, 122.3, 126.5, 131.7, 136.1, 145.3, 147.1, 155.3, 158.6, 162.5, 163.8 (Ar C). Anal. Calcd. for $C_{18}H_{18}N_6$ (318.38): C, 67.9; H, 5.7; N, 26.4. Found: C, 68.08; H, 5.52; N, 26.51.

4.1.11. 2,7-Dimethyl-11-(1-methyl-1*H*-pyrrol-2-yl)-7,8,9,10-tetrahydro-1,3,3a,5,6-pentaazacyclopenta[*a*]anthracene (19).

Conventional heating: a mixture of **17** (1.54 g, 5 mmol) and acetic anhydride (10 mL) was heated under reflux for 8 h. The reaction mixture was allowed to attain room temperature, diluted with cold water, and the precipitated solid was filtered, washed with water, dried and recrystallized from acetic acid.

Microwave irradiation: a mixture of **17** (1.54 g, 5 mmol) and acetic anhydride (10 mL) was subjected to microwave irradiation at 200 ^{O}C for 20 min. After being cooled to room temperature, the reaction mixture was worked up as described under the conventional heating procedure. Yields and melting point are recorded in table 1. IR (cm^{-1}): 1626 (C=N). ^{1}H-NMR (δ, ppm): 1.41 (s, 3H, C*H*$_3$), 1.49-2.47 (m, 6H, C$_{8,9,10}$-*H*), 2.55 (s, 3H, C$_2$-C*H*$_3$), 3.07 (m, 1H, C$_7$-*H*), 3.85 (s, 3H, N-C*H*$_3$), 6.91-7.41 (m, 3H, pyrrole-*H*), 9.01 (s, 1H, C$_4$-*H*). ^{13}C-NMR (δ, ppm): 14.8 (CH$_3$), 20.9 (CH$_3$), 21.8, 27.3, 32.2, 38.9 (C$_{7,8,9,10}$), 56.8 (CH$_3$), 113.2, 122.4, 127.8, 132.4, 136.5, 147.6, 148.9, 155.4, 158.1, 162.2, 163.9 (Ar C). Anal. Calcd. for $C_{19}H_{20}N_6$ (332.4): C, 68.65; H, 6.06; N, 25.28. Found: C, 68.34; H, 6.22; N, 25.39.

4.2. In vitro antitumor screening

Out of the newly synthesized compounds, fourteen derivatives namely: **2-12, 14, 17** and **18**; were selected by the National Cancer Institute (NCI) *in-vitro* disease-oriented human cells screening panel assay [48-50] to be evaluated for their *in-vitro* antitumor activity. Primary *in vitro* one dose anticancer assay was performed using the full NCI 60 cell panel in accordance with the current

protocol of the Drug Evaluation Branch, NCI, Bethesda, Maryland, USA. These cell lines were incubated with one concentration (10 μM) for each tested compound. A 48h continuous drug exposure protocol was used, and a sulphorhodamine B (SRB) protein assay was employed to estimate cell viability or growth. Data are reported as a mean graph of the percent growth of treated cells, and presented as percentage growth inhibition (GI %) caused by the test compounds (Table 2).

Compound **2-9**, passed this primary anticancer assay and consequently was carried over to the 5-dose screen against a panel of about 60 different tumor cell lines of nine tumor subpanels, including leukemia, non-small cell lung, colon, CNS, melanoma, ovarian, renal, prostate and breast cancer cell lines. These cell lines were incubated with five concentrations (0.01-100 μM) for the tested compound and were used to create log concentration % growth inhibition curves. Three response parameters: GI_{50} (growth inhibitory activity), TGI (cytostatic activity), and LC_{50} (cytotoxic activity) were calculated for each cell line, using 5-flourouracil (5-FU) as a positive control. Subpanel and full panel mean-graph midpoint values (MG-MID) for certain agents are the average of individual real and default GI_{50}, TGI, or LC_{50} values of all cell lines in the subpanel or the full panel, respectively. (Table 3).

4.3. DPPH radical scavenging antioxidant assay

Compounds **3, 6, 7, 9, 10, 11** and **12** which exhibited prominent antitumor activity, were tested for their ability to show antioxidant effect through scavenging of the 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical, according to a modified procedure from that described by Blois [51]. Two concentrations of the tested compounds (10^{-3} and 10^{-4} M) were mixed with a methanolic solution of DPPH (0.1 mL of 1 mM) at room temperature, so that the total volume of the reaction mixture is 3 mL. The mixture was shaken vigorously and allowed to stand in the dark for 30 min at room temperature. Thereafter, the absorbance (A) of the obtained solution was measured spectrophotometrically in the visible region at λ_{max} 517 nm. The same procedure was performed for a control which is DPPH radical solution in methanol alone. BHT was utilized as a reference standard antioxidant in this experiment. Each experiment was carried out in triplicate.

The capability of the tested compounds to scavenge DPPH radical was calculated according to the following equation:

DPPH scavenging effect (%) = ($A_C - A_S$) / A_C × 100

Where A_C is the absorbance of control (DPPH radical solution in methanol), and A_S represents the value of the absorbance of the sample (solution of DPPH radical and tested compound in methanol). The obtained data are presented in table 4.

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Table and Figure Captions

Scheme 1. Synthesis of the target compounds **2-13.**

Scheme 2. Synthesis of the target compounds **4-19.**

Table 1. Reaction times, yields and melting points of compounds **2-19** using conventional heating and/or microwave irradiation modes.

Table 2. *In vitro* growth inhibition percentage (GI%) of compounds **10, 11, 12, 14, 17** and **18** against some selected tumor cell lines at the single-dose assay.[a]

Table 3. *In vitro* growth inhibitory concentrations (GI_{50}, μM) for compounds **2-9** against some selected tumor cell lines.[a]

Table 4. DPPH radical-scavenging activity of compounds **3, 6, 7, 9, 10, 11** and **12**

Figure 1. General structures (**A-D**) for the newly synthesized compounds.

Figure 2. A schematic presentation of the reaction mechanism involved in the synthesis of compound **11.**

Table 1. Reaction times, yields and melting points of compounds **2-19** using conventional heating and/or microwave irradiation modes.

Cpd. No.	R	Reaction Time		Yield (%)		M.P.
		C.H.[a] (h)	MW[b] (min.)	C.H.[a] (h)	MW[b] (min.)	(^{o}C)
2	C_6H_5	5	10	71	88	127-9
3	3,4-di OCH_3-C_6H_3	5	10	47	76	117-9
4	2-Thienyl	5	10	55	79	122-4
5	-	6	10	66	81	126-8
6	C_6H_5	4	15	59	78	132-4
7	3,4-di OCH_3-C_6H_3	4	15	38	65	146-8
8	2-Thienyl	5	15	32	62	156-8
9	-	6	15	48	71	150-2
10	-	2	10	52	83	152-4
11	-	1	10	49	74	207-9
12	CH_2CH_3	6	15	43	59	201-3
13	CH_2-C_6H_5	6	15	48	66	192-4
14	-	3	15	59	83	136-8
15	-	0.5	NA[c]	36	NA[c]	>300
16	-	4	20	45	73	155-7
17	-	4	10	53	84	134-6
18	-	6	20	57	76	>300
19	-	8	20	50	79	209-11

a: C.H.: Conventional heating mode (h: hours).

b: MW: Microwave irradiation mode (min.: minutes).

c: NA: Not applied.

Table 2. *In vitro* growth inhibition percentage (GI%) of compounds **10, 11, 12, 14, 17** and **18** against some selected tumor cell lines at the single-dose assay.[a]

Cell Lines	10	11	12	14	17	18
NSCLC[b]						
EKVX	14.2	18.9	34.1	-[c]	16.2	-
HOP92	32.0	36.4	28.7	23.6	11.3	10.1
NCI-H522	22.4	29.7	33.8	21.5	10.4	-
Colon Cancer						
HCT-116	19.5	22.6	35.3	-	11.7	-
HCT-15	20.1	13.4	10.8	14.1	13.4	6.3
Breast Cancer						
HS 578T	38.1	-	15.2	-	10.7	-
MDA-MB-468	32.7	-	15.4	11.4	-	-
T-47D	40.6	40.1	54.2	19.3	17.5	11.8
Ovarian Cancer						
IGROV1	38.8	34.4	35.3	10.6	12.4	7.9
OVCAR-4	27.6	13.8	23.4	-	-	6.1
Leukemia						
CCRF-CEM	27.5	26.7	21.6	15.6	30.1	10.3
HL-60(TB)	35.9	33.2	25.8	-	11.6	8.5
K-562	33.5	29.6	37.4	12.1	18.3	-
MOLT-4	31.4	32.6	42.3	23.8	29.2	20.4
RPMI-8226	36.7	51.9	68.5	47.6	38.6	12.2
Renal Cancer						
A 498	22.6	41.3	26.5	8.6	14.6	5.7
ACHN	31.4	15.2	11.9	12.3	-	-
CAKI-1	31.9	-	21.7	13.8	-	-
UO-31	51.4	34.7	45.8	-	7.3	-
Melanoma						
LOX IMVI	29.6	10.7	12.9	-	-	-

SK-MEL-5	12.8	18.4	13.1	16.3	10.5	-
UACC-62	24.7	23.5	24.1	18.4	16.9	8.3
Prostate Cancer						
PC-3	28.4	19.8	57.1	12.5	20.4	-
CNS Cancer						
SNB-75	31.9	17.5	21.4	-	10.7	-
U251	15.8	21.4	16.7	-	-	-

[a] Data obtained from NCI's *in vitro* disease-oriented human tumor cell screen at 10 μM conc.

[b] NSCLC: Non-Small Cell Lung Cancer.

[c] Totally inactive.

Table 3. *In vitro* growth inhibitory concentrations (GI_{50}, μM) for compounds **2-9** against some selected tumor cell lines.[a]

Cell Line	2	3	4	5	6	7	8	9
Leukemia								
CCRF-CEM	-[b]	5.01	-	-	0.08	0.01	-	-
	-	-	-	-	(0.38)[c]	(3.98)[c]	-	-
	-	-	-	-	(3.55)[d]	(9.77)[d]	-	-
HL-60(TB)	-	-	-	-	0.76	19.5	-	0.42
MOLT-4	29.1	22.9	-	-	-	46.8	-	-
	(57.4)[c]	-	-	-	-	-	-	-
RPMI-8226	-	-	-	-	53.7	38.9	-	79.4
SR	-	0.48	-	-	35.5	56.2	5.37	3.39
	-	-	-	-	-	-	(67.6)[c]	(20.4)[c]
	-	-	-	-	-		-	(91.2)[d]
NSCLC[e]								
EKVX	31.7	30.9	52.5	-	95.5	-	-	-
HOP-62	-	-	83.2	-	81.3	-	-	-
HOP-92	0.11	0.05	10.0	-	0.01	5.13	-	47.9
	(0.13)[c]	(9.77)[c]	(40.7)[c]	-	(0.05)[c]	-	-	-
NCI-H226	-	-	69.2	-	-	-	-	64.6
NCI-H522	-	-	25.7	-	61.6	40.7	-	66.1
Colon Cancer								
HCT-116	-	91.2	-	-	-	89.1	-	-
CNS Cancer								
SF-268	-	-	-	-	79.4	83.2	-	-
SF-539	-	-	-	-	33.9	83.2	-	-
SNB-75	47.4	23.9	38.1	39.8	18.6	20.9	45.7	22.4
	-	-	-	-	(77.6)[c]	(70.8)[c]	-	(85.1)[c]
Melanoma								
UACC-62	97.7	66.1	72.4	-	44.7	87.1	87.1	33.1
Ovarian Cancer								
IGROV1	-	91.2	22.9	-	-	95.5	-	70.8
OVCAR-4	-	-	-	69.2	46.8	40.7	85.1	77.6

Renal Cancer								
A498	27.5	56.2	17.8	-	91.2	83.2	-	91.2
SN12C	-	-	-	-	-	67.6	-	30.2
UO-31	-	85.1	13.8	-	-	97.7	-	-
	-	-	(27.5) [c]	-	-	-	-	-
	-	-	(54.9) [d]	-	-	-	-	-
Prostate Cancer								
DU-145	-	-	-	-	-	91.2	-	-
Breast Cancer								
MCF7	-	-	-	-	-	93.3	-	-
MDA-MB-231/ATCC	83.2	-	-	-	67.6	38.0	-	69.2
BT-549	85.1	34.7	-	-	60.2	64.6	-	69.1
GI_{50} (MG-MID)[f]	77.6	67.6	83.2	91.2	79.7	60.3	93.3	75.9
TGI (MG-MID)[g]	85.1	95.5	95.5	-	93.3	79.4	-	97.7
LC_{50} (MG-MID)[h]	-	-	-	-	95.5	93.3	-	-

[a] Data obtained from NCI's *in vitro* disease-oriented human tumor cell screen (5-dose assay).

[b] Values > 100 μM.

[c] Total growth inhibitory concentration value (TGI, μM).

[d] Lethal concentration 50 value (LC_{50}, μM).

[e] Non-small Cell Lung Cancer.

[f] GI_{50} (μM) full panel mean-graph mid point (MG-MID) = the average sensitivity of all cell lines towards the test agent.

[g] TGI (μM) full panel mean-graph mid point (MG-MID) = the average sensitivity of all cell lines towards the test agent.

[h] LC_{50} (μM) full panel mean-graph mid point (MG-MID) = the average sensitivity of all cell lines towards the test agent.

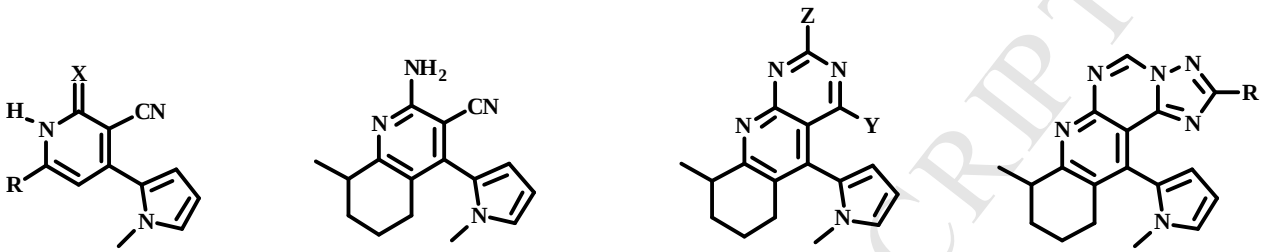
Table 4. DPPH radical-scavenging activity of compounds **3, 6, 7, 9, 10, 11** and **12**

Compound no.	Concentration (M)	DPPH radical scavenging activity (% of control) [a]
Control [b]	---	100 ± 0.05
BHT [c]	10^{-4}	20 ± 0
	10^{-3}	36 ± 1
3	10^{-4}	17 ± 1
	10^{-3}	31 ± 2
6	10^{-4}	12 ± 1
	10^{-3}	27 ± 1
7	10^{-4}	19 ± 0
	10^{-3}	33 ± 2
9	10^{-4}	9 ± 1
	10^{-3}	16 ± 2
10	10^{-4}	11 ± 2
	10^{-3}	23 ± 1
11	10^{-4}	14 ± 2
	10^{-3}	26 ± 1
12	10^{-4}	16 ± 0
	10^{-3}	28 ± 2

[a] Values are recorded as the mean of three independent experiments ± SD.

[b] Control: DPPH radical solution in methanol.

[c] BHT: Butylated hydroxyl toluene (reference standard antioxidant).



(A) **(B)** **(C)** **(D)**

X = O or NH

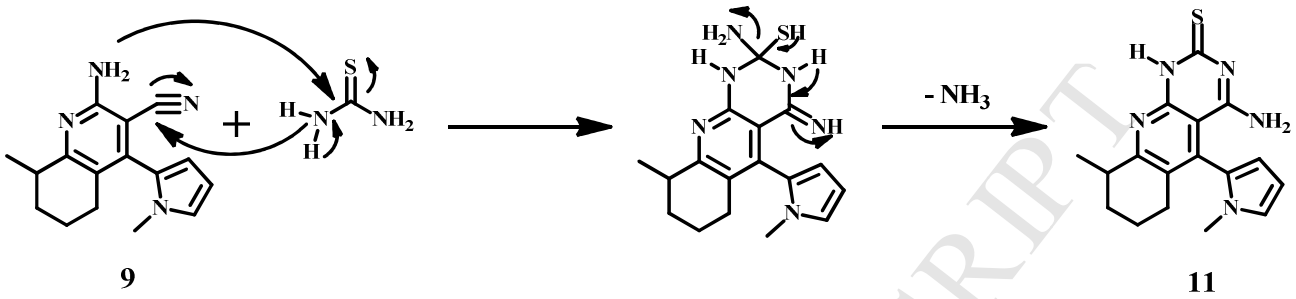
R = aryl or hetaryl

Y = amino, imino, oxo

Z = CH_3, thio, alkylthio

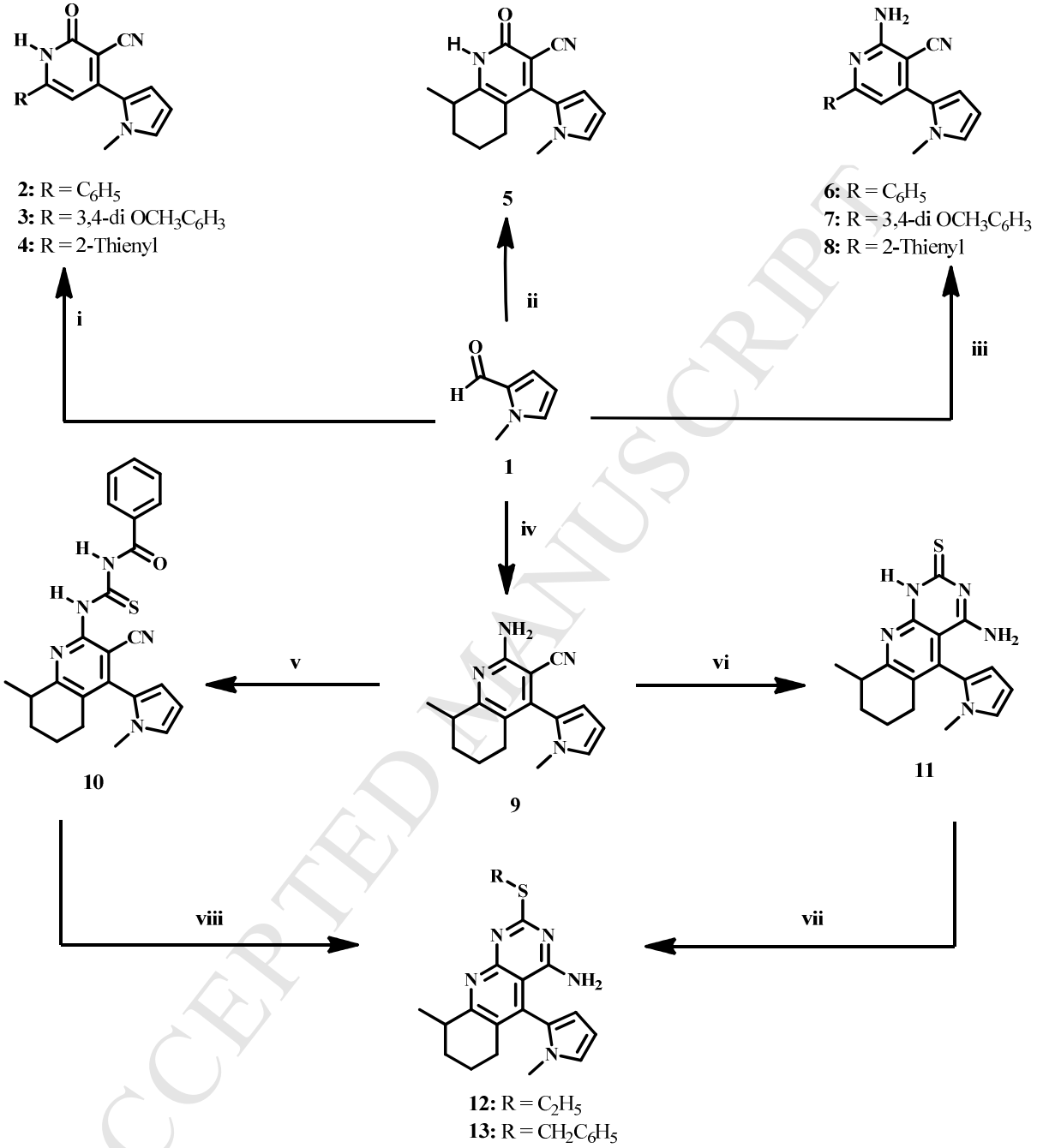
R = H or CH_3

Figure 1. General structures (**A-D**) for the newly synthesized compounds



9 11

Figure 2. A schematic presentation of the reaction mechanism involved in the synthesis of compound 11.

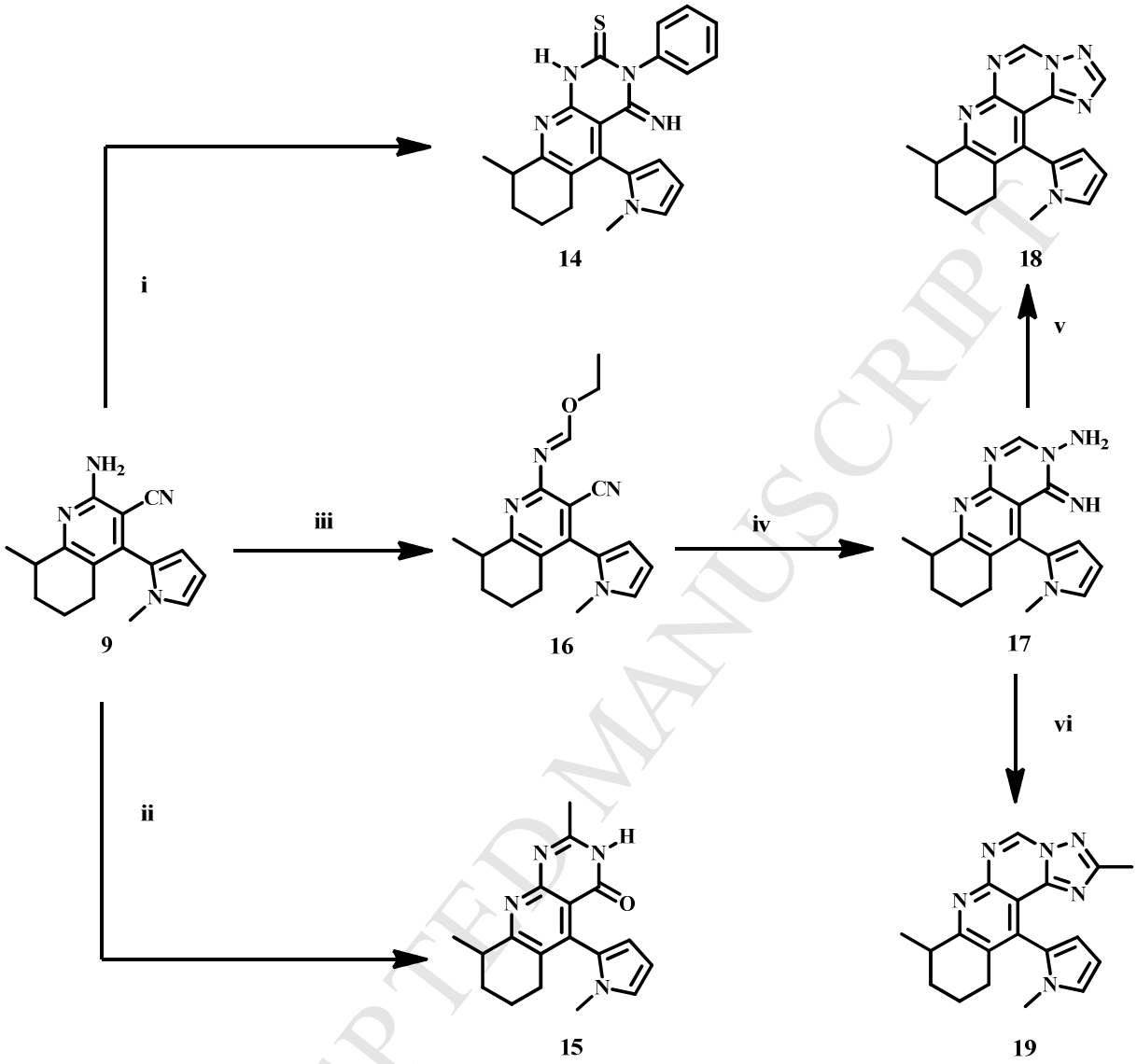


Reagents and reaction conditions:

A: Conventional heating: i,ii: ketone, ethyl cyanoacetate, ammonium acetate, reflux, 5-6h; **iii,iv:** ketone, malononitrile, ammonium acetate, reflux, 4-6h; **v:** benzoyl isothiocyanate, K_2CO_3, acetone, reflux, 2h; **vi:** thiourea, 260-300^{O}C, 1h; **vii:** RX, 1N NaOH, ethanol, r.t., 6h; **viii:** RX, 1N NaOH, MW, 180 ^{o}C, 15 min.

B: Microwave irradiation: the same reagents were put in a glass tube sealed with a plastic cap and irradiated in a CEM 300W MW synthesizer for 10-15 min.

Scheme 1. Synthesis of the target compounds **2-13**



Reagents and reaction conditions:

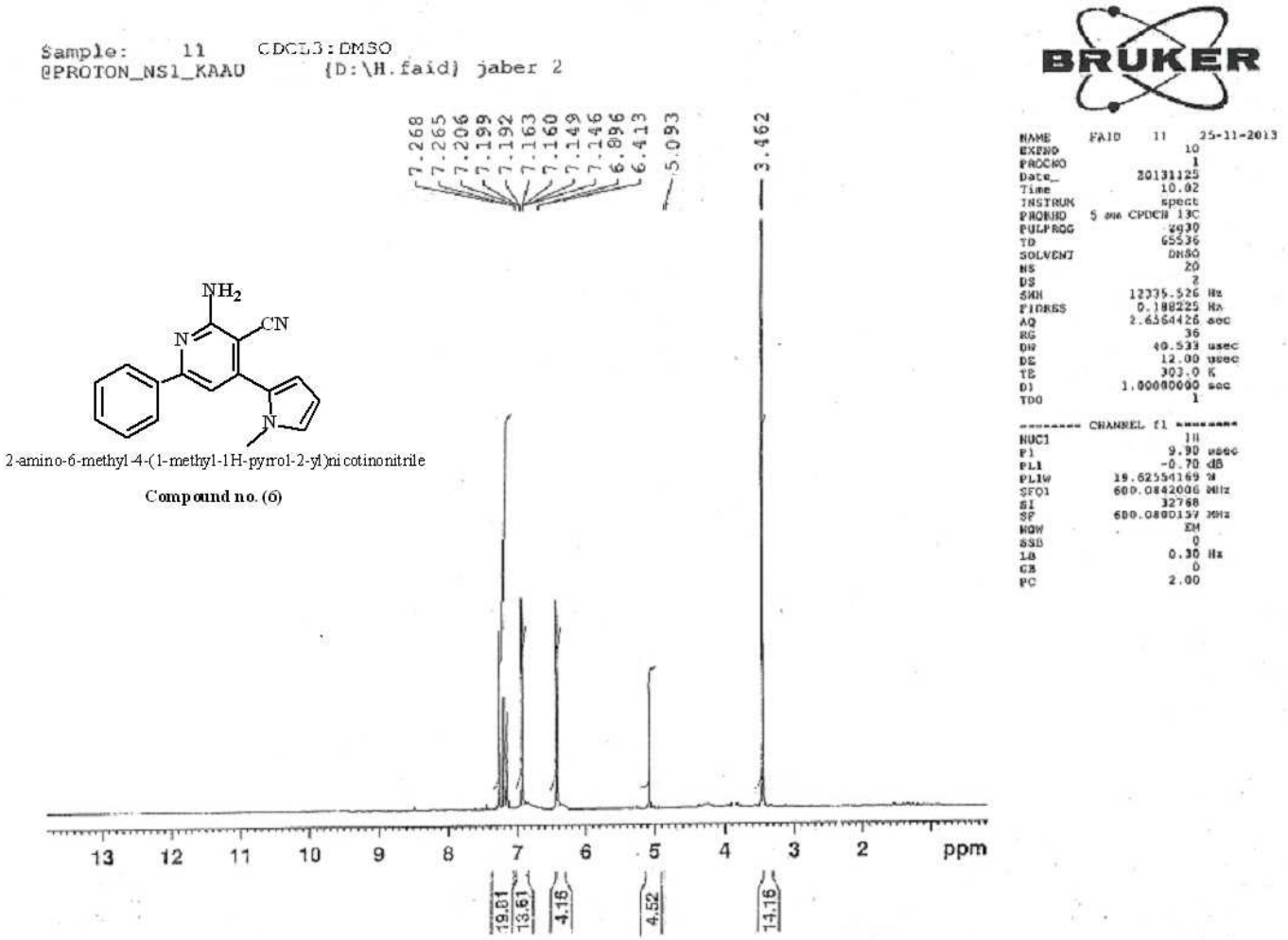
A: Conventional heating: i: PhNCS, pyridine, reflux, 3h; **ii:** acetic anhyhydride, heating, 10 min.; **iii:** triethyl orthoformate, acetic anhydride, reflux, 10h; **iv:** $NH_2NH_2.H_2O$ 99%, benzene, reflux, 3h; **v:** HCOOH, reflux, 6h; **vi:** acetic anhydride, reflux, 8h.

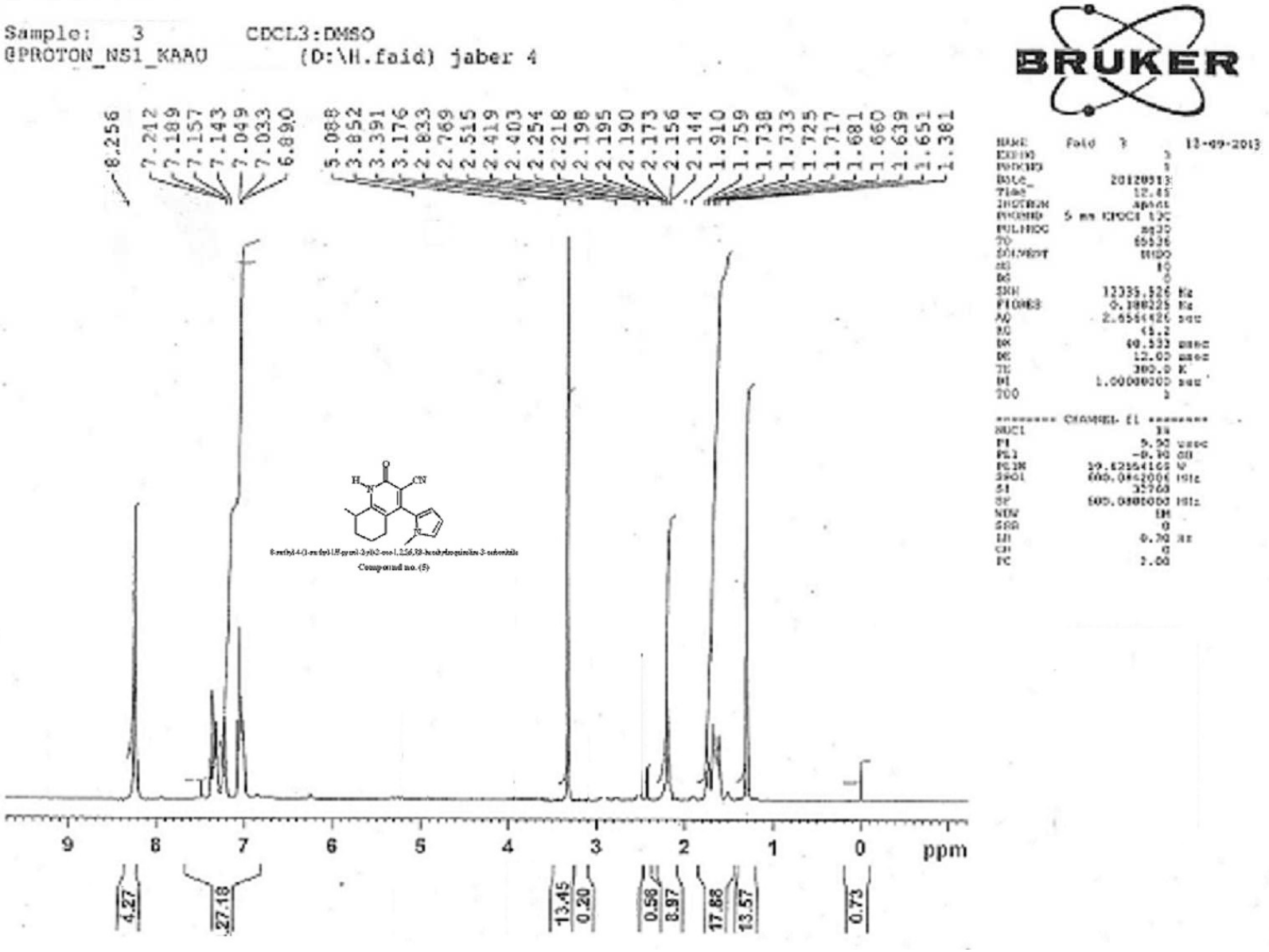
B: Microwave irradiation: reactions i-v: the same reagents are put in a glass tube sealed with a plastic cap and irradiated in a CEM 300W MW synthesizer for 10-20 min.

Scheme 2. Synthesis of the target compounds **14-19**

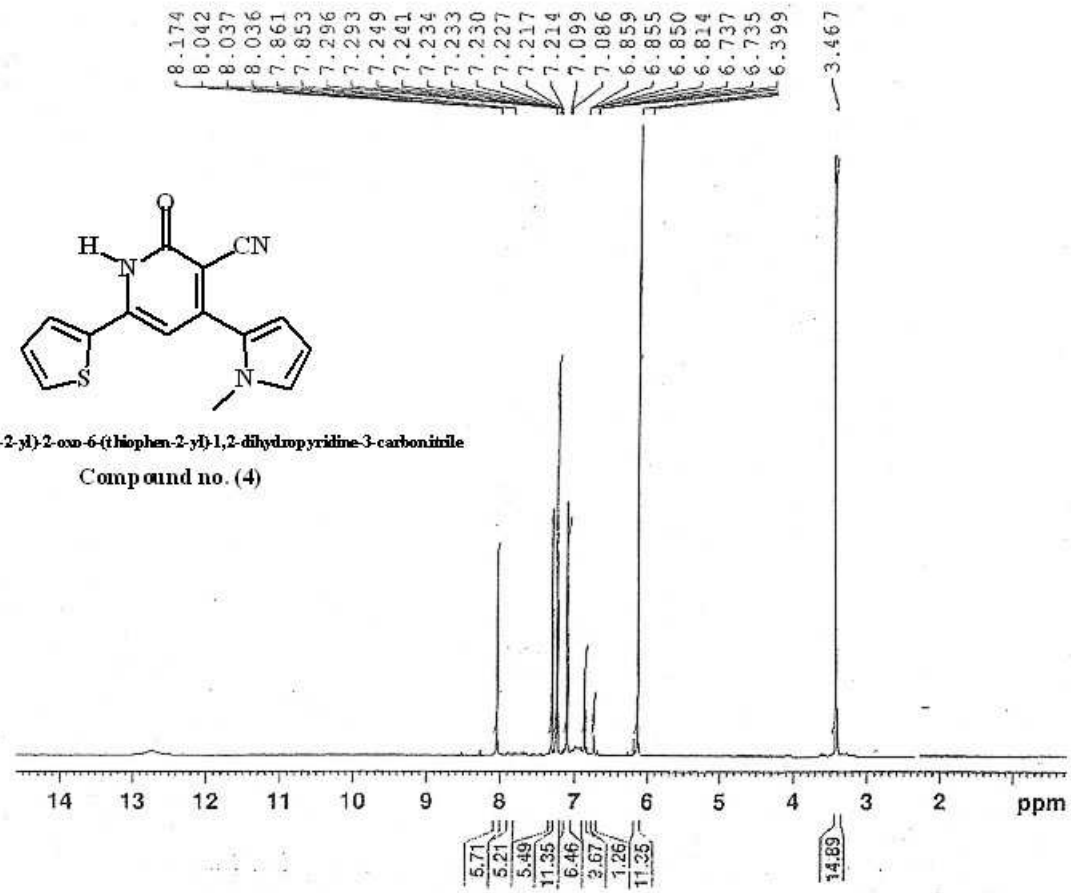
Highlights

- Synthesis of some new pyrrolylpyridines and some derived ring systems.
- *In vitro* antitumor evaluation according to the NCI's protocol.
- Fourteen compounds displayed broad spectrum of antitumor activity.
- Seven analogs showed reliable antioxidant potential.
- Compounds **3** and **7** can be considered as dual antitumor and antioxidant agents.




Sample: 3 CDCL3:DMSO
@PROTON_NS1_KAAU (D:\H.faid) jaber 4
8.256
7.212
7.189
7.157
7.143
7.049
7.033
6.890
5.068
3.852
3.391
3.176
2.833
2.769
2.515
2.419
2.403
2.254
2.218
2.198
2.195
2.190
2.173
2.156
2.141
1.910
1.759
1.738
1.733
1.725
1.717
1.681
1.660
1.639
1.651
1.381
BRUKER
Compound no. (5)
9
8
7
6
5
4
3
2
1
0
ppm
4.27
27.18
13.45
0.20
0.58
8.97
17.88
13.57
0.73

Sample: 8 CDCL3:DMSO
@PROTON_NS1_KAAU (D:\H.faid) jaber 8



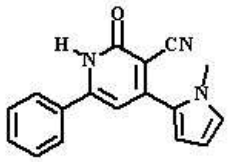
4-(1-methyl-1*H*-pyrrol-2-yl)-2-oxo-6-(thiophen-2-yl)-1,2-dihydropyridine-3-carbonitrile

Compound no. (4)

BRUKER

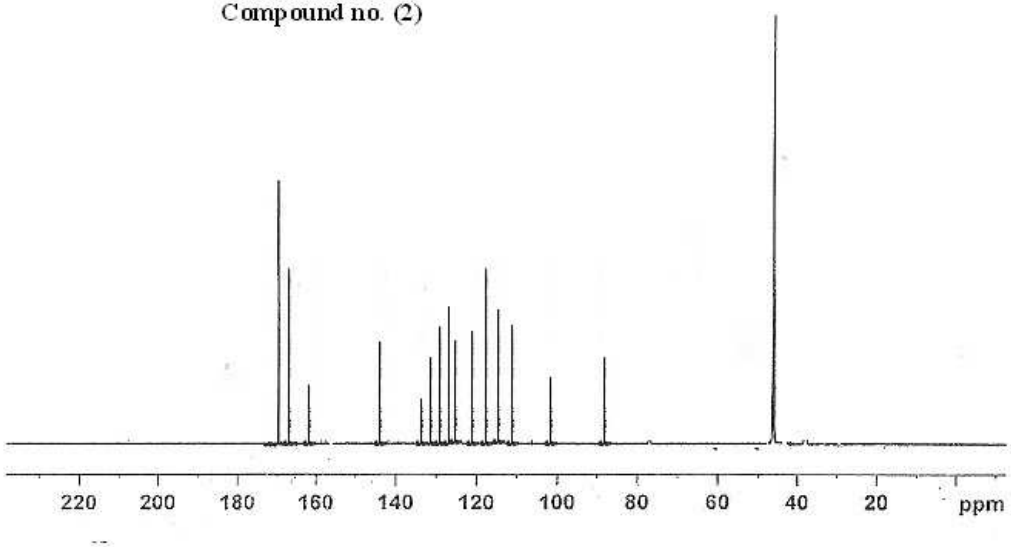
NAME	Faid	8	17-11-2013
EXPNO		10	
PROCNO		1	
Date_		20131117	
Time		12.45	
INSTRUM		spect	
PROBHD	5 mm CPDCH 13C		
PULPROG		zg30	
TD		65536	
SOLVENT		DMSO	
NS		20	
DS		2	
SWH		12335.526	Hz
FIDRES		0.188225	Hz
AQ		2.6564426	sec
RG		57	
DW		40.533	usec
DE		12.00	usec
TE		303.0	K
D1		1.00000000	sec
TD0		1	
======== CHANNEL f1 ========			
NUC1		1H	
P1		9.90	usec
PL1		-0.70	dB
PL1W		19.62554169	W
SFO1		600.0842006	MHz
SI		32768	
SF		600.0800149	MHz
WDW		EM	
SSB		0	
LB		0.30	Hz
GB		0	
PC		2.00	

Sample: CDCL3:DMSO
@C13_NS256_KAAU DMSO (D:\H.faid) jaber 2



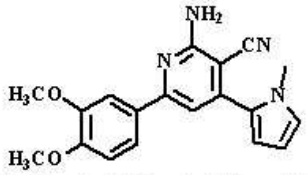
4-(1-methyl-1*H*-pyrrol-2-yl)-2-oxo-6-phenyl-1,2-dihydropyridine-3-carbonitrile

Compound no. (2)



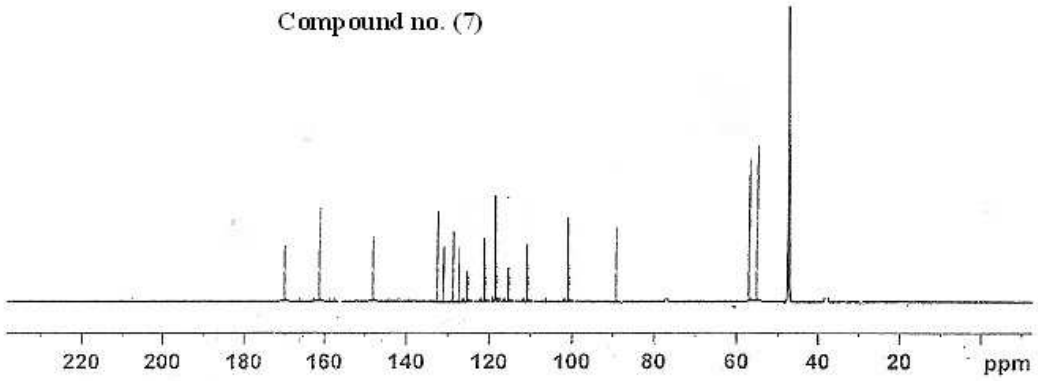
NAME	FAID	2	26-09-2013
EXPNO		10	
PROCNO		1	
Date_		20120926	
Time		13.29	
INSTRUM		spect	
PROBHD	5 mm	CPDCH 13C	
PULPROG		zgpg30	
TD		131072	
SOLVENT		DMSO	
NS		102	
DS		4	
SWH		37878.789	Hz
FIDRES		0.288992	Hz
AQ		1.7302004	sec
RG		203	
DW		13.200	usec
DE		71.32	usec
TE		300.0	K
D1		1.50000000	sec
D11		0.03000000	sec
TD0		1	
========	CHANNEL f1	========	
NUC1		13C	
P1		9.90	usec
PL1		2.80	dB
PL1W		37.96579361	W
SFO1		150.9075884	MHz
========	CHANNEL f2	========	
CPDPRG2		waltz16	
NUC2		1H	
PCPD2		70.00	usec
PL2		-0.70	dB
PL12		16.29	dB
PL13		19.29	dB
PL2W		19.62554169	W
PL12W		0.39248362	W
PL13W		0.19670779	W
SFO2		600.0824003	MHz
SI		131072	
SF		150.8905427	MHz
WDW		EM	
SSB		0	
LB		1.00	Hz
GB		0	
PC		1.40	

Sample: CDCL3:DMSO
@C13_NS256_KAAU DMSO (D:\H.faid) jaber 6



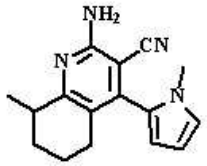
2-amino-6-(3,4-dimethoxyphenyl)-4-(1-methyl-1*H*-pyrrol-2-yl)nicotinonitrile

Compound no. (7)



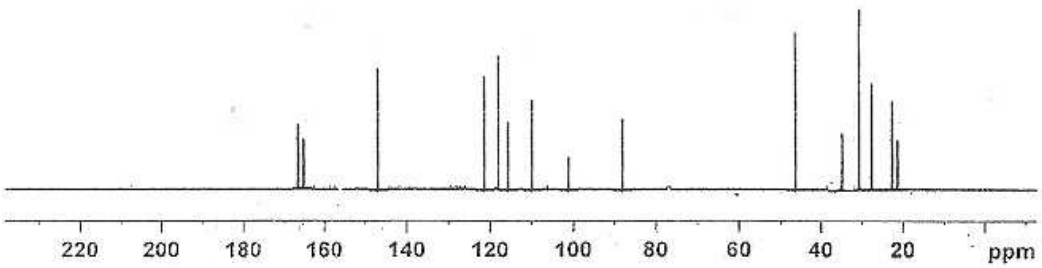
NAME	FAID 6	26-10'-2013
EXPNO	10	
PROCNO	1	
Date_	201.....	
Time	13.29	
INSTRUM	spect	
PROBHD	5 mm CPDCH 13C	
PULPROG	zgpg30	
TD	131072	
SOLVENT	DMSO	
NS	102	
DS	4	
SWH	37878.789	Hz
FIDRES	0.288992	Hz
AQ	1.7302004	sec
RG	203	
DW	13.200	usec
DE	71.32	usec
TE	300.0	K
D1	1.50000000	sec
D11	0.03000000	sec
TD0	1	
========	CHANNEL f1	========
NUC1	13C	
P1	9.90	usec
PL1	2.00	dB
PL1W	37.96579361	W
SFO1	150.9075884	MHz
========	CHANNEL f2	========
CPDPRG2	waltz16	
NUC2	1H	
PCPD2	70.00	usec
PL2	-0.70	dB
PL12	16.29	dB
PL13	19.29	dB
PL2W	19.62554169	W
PL12W	0.39248362	W
PL13W	0.19670779	W
SFO2	600.0824003	MHz
SI	131072	
SF	150.8905427	MHz
WDW	EM	
SSB	0	
LB	1.00	Hz
GB	0	
PC	1.40	

Sample: CDCL3:DMSO
@C13_NS256_KAAU DMSO (D:\H.faid) jaber 5



2-amino-8-methyl-4-(1-methyl-1*H*-pyrrol-2-yl)-5,6,7,8-tetrahydroquinoline-3-carbonitrile

Compound no. (9)



NAME	FAID	5	26-05-2013
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PROCNO		1	
Date_		20130526	
Time		13 29	
INSTRUM		spect	
PROBHD	5 mm CPDCH 13C		
PULPROG		zgpg30	
TD		131072	
SOLVENT		DMSO	
NS		102	
DS		4	
SWH		37878.789	Hz
FIDRES		0.288992	Hz
AQ		1.7302004	sec
RG		203	
DW		13.200	usec
DE		71.32	usec
TE		300.0	K
D1		1.50000000	sec
D11		0.03000000	sec
TD0		1	
========	CHANNEL f1	========	
NUC1		13C	
P1		9.90	usec
PL1		2.80	dB
PL1W		37.96579361	W
SFO1		150.9075884	MHz
========	CHANNEL f2	========	
CPDPRG2		waltz16	
NUC2		1H	
PCPD2		70.00	usec
PL2		-0.70	dB
PL12		16.29	dB
PL13		19.29	dB
PL2W		19.62554169	W
PL12W		0.39248362	W
PL13W		0.19670779	W
SFO2		600.0824003	MHz
SI		131072	
SF		150.8905427	MHz
WDW		EM	
SSB		0	
LB		1.00	Hz
GB		0	
PC		1.40	