Scientific paper

Synthesis and Reactions of Some Novel Nicotinonitrile Derivatives for Anticancer and Antimicrobial Evaluation

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Abstract

New diaryl-3-cyano-1*H*-pyridinone derivatives **2a–c** were synthesized. They were reacted with phosphorous oxychloride to give the chloro derivatives **3b**,**c**. On the other hand, the pyridine derivative **2a** was used for the preparation of thienopyridine derivative **4a**. Further **2b**,**c** were glycosidated with 2,3,4,6-tetra-*O*-acetyl-α-glucopyranosyl bromide (α-ABG) to afford the corresponding nucleosides **5b**,**c**. Also **2a**,**b** reacted with ethyl chloroacetate to afford the *O*-ethyl glycolate derivatives **6a**,**b**. Compounds **6a**,**b** upon treatment with hydrazine hydrate, gave the hydrazide derivatives **7a**,**b** which condensed with the appropriate aldehyde to afford the arylmethylene hydrazone derivatives **8a–d**. The latter compounds were cyclised with thioglycolic acid or acetic anhydride to afford **9c**,**d** and **10c**, respectively. The hydrazone derivatives **11a–c** were prepared by reaction of hydrazide derivative **7b** with some monosaccharides. The behaviour of compounds **7a**,**b** towards phenyl isothiocyanate has been investigated and gave **12a**,**b**, the latter compounds were condensed with chloroacetic acid to produce **13a**,**b**. Also compound **14b** was prepared by the reaction with acetylacetone. Additionally, compounds **7a**,**b** were reacted with aliphatic acids namely, formic and acetic acid to afford compounds **15a–d**. Some of the newly prepared products showed potent anticancer and antimicrobial activity.

Keywords: Pyridinones, nicotinonitriles, cyclic and acyclic nucleosides, anticancer and antimicrobial activity.

1. Introduction

Numerous thieno[2,3-*b*]pyridines have been investigated in relation with their biological and pharmacological activities. Some of them proved to possess antibacterial,[1,2] antiviral,[3] antihypertensive and immunostimulating activities.[4,5] Others are useful as gonadotropin releasing hormone antigonists[6–12] and as lipoxygenases inhibitors.[13] Recently, certain thieno[2,3-*b*]pyridine derivatives were prepared as antiinflammatory agents, particularly for treating arthritis and as bone-resorption agents.[14] Pyridothienopyrimidine derivatives have found applications as analgesics[15] and antipyretics.[16] In view of all these facts and as the continuation of our work on the synthesis of new heterocyclic derivatives,[17,18] we undertook the synthesis and investigated reactions of some new pyridine derivatives, which might have good biological and medicinal applications.

2. Results and Discussion

Enones are excellent starting materials for the synthesis of pyridine derivatives *via* the reaction of enones **1** with ethyl cyanoacetate in the presence of ammonium acetate.[19,20] This procedure is time consuming and the reported yield does not exceed 30% (scheme 1). Here, a method for one step synthesis of the new naphthyl-2(1*H*)-pyridinone **2** is carried out;[21] the method is easy to perform and uses almost all of the available starting materials to give product in high yield. Thus, heating an equimolar mixture of 2-acetylnaphthalene as ketone part and aroma-

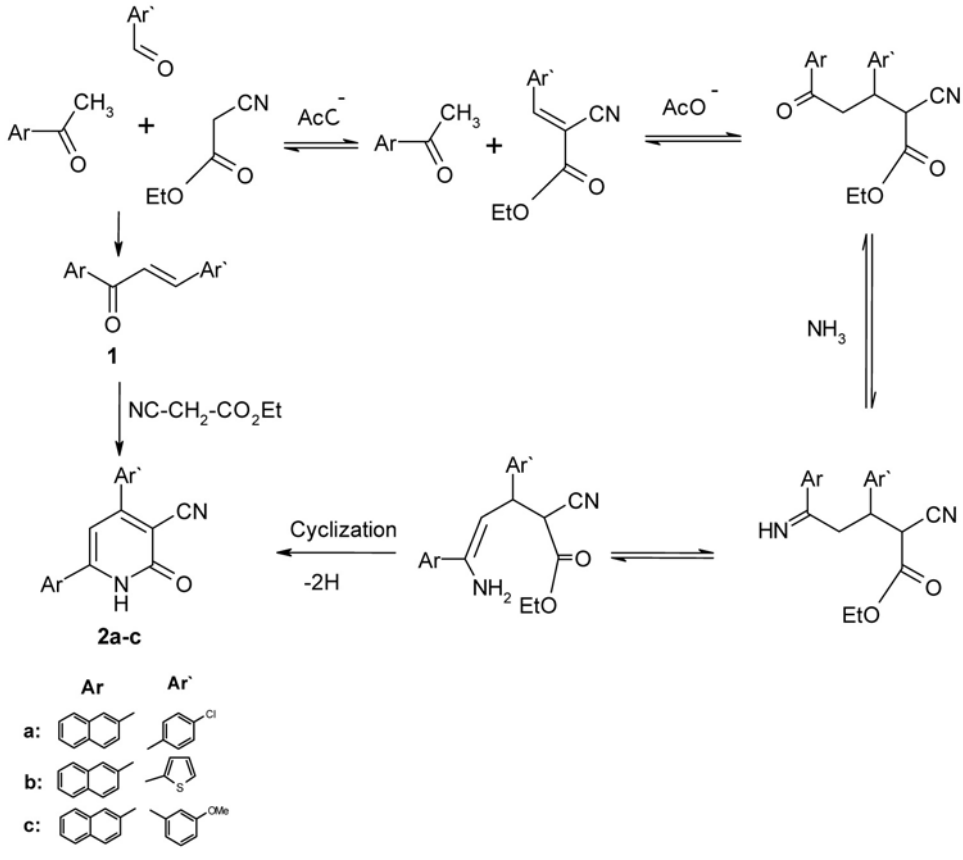
tic aldehyde (4-chlorobenzaldehyde, 2-thiophenecarboxaldehyde or 3-methoxybenzaldehyde) with ethyl cyanoacetate in the presence of ammonium acetate afforded nicotinonitrile derivatives **2a**,[20] **b**,**c**, respectively. The formation of compounds **2a**–**c** by this method takes place in high yields (around 80%). The elemental analyses and spectroscopic data are consistent with the assigned structures. IR spectrum of **2c** exhibited absorption bands at 3200, 2217 and 1651 cm^{-1} due to NH (keto-enol),[22] CN and C=O groups, respectively. ^{1}H NMR spectrum of compound **2b** showed signals at δ 7.12 (s, 1H, pyridine 5-H), 7.34 (d, *J* = 5.4 Hz, 1H, thiophene H), 7.63–7.66, 8.00–8.12 (2 × m, 8H, Ar-H), 8.55 (s, 1H Ar-H) and 12.85 (s, 1H, NH, D_2O exchangeable). The mass spectrum of compound **2b** showed molecular ion peak, as the base peak, at *m/z* 328 (100%).

The formation of compounds **2** possibly takes place as shown in Scheme 1, where the aldehyde condenses with the more reactive methylene group in ethyl cyanoacetate, rather than with the less reactive methyl group in 2-acetylnaphthalene. The Michael addition of the 2-acetylnaphthalene on the produced cyanoacrylate takes place, followed by the replacement of enolic OH by NH_2, then cyclization takes place with elimination of ethanol and finally dehydrogenation to produce compounds **2a**–**c**.

Compounds **2** have been utilized as key starting materials in the synthesis of many novel interesting heterocyclic compounds (Scheme 2), thus compounds **2b**,**c** reacted with phosphorous oxychloride to afford the corresponding chloro substituted nicotinonitriles **3b**,**c**. The structures of compounds **3b**,**c** were confirmed with microanalytical and spectroscopic data. The IR spectrum of the chloro derivative **3b** revealed the disappearance of the carbonyl band at 1651 cm^{-1} and the presence of absorption bands at 2223 (CN) and 1067 cm^{-1} (strong, C–Cl aryl). The mass spectrum of compound **3b** showed molecular ion peak ($C_{20}H_{11}ClN_2S$) at *m/z* 346 as the base peak.

When compound **2a** was treated with phosphorous pentasulfide, it afforded the corresponding pyridinethione derivative **4a**. The structure of the latter compound was in agreement with spectral data (elemental analysis), besides showing absorption bands in the IR spectrum at 3428 (NH), 2213 (CN) and 1405 cm^{-1} (C=S). Mass spectrum showed molecular ion peak ($C_{22}H_{13}ClN_2S$) at *m/z* 372.5 as the base peak.

It is well know that cyclic and acyclic nucleosides often enhance the biological activity of heterocyclic derivatives.[23,24] Thus, when compounds **2** were glycosidated with 2,3,4,6-tetra-*O*-acetyl-α-glucopyranosyl bromide (α-ABG) in the presence of dimethylformamide, β-glucopyranosyl derivatives **5b**,**5c** were isolated as shown by TLC analysis (Scheme 2). The structures of the new products were established according to their microanalytical and spectroscopic data. The IR spectrum of compound **5b**

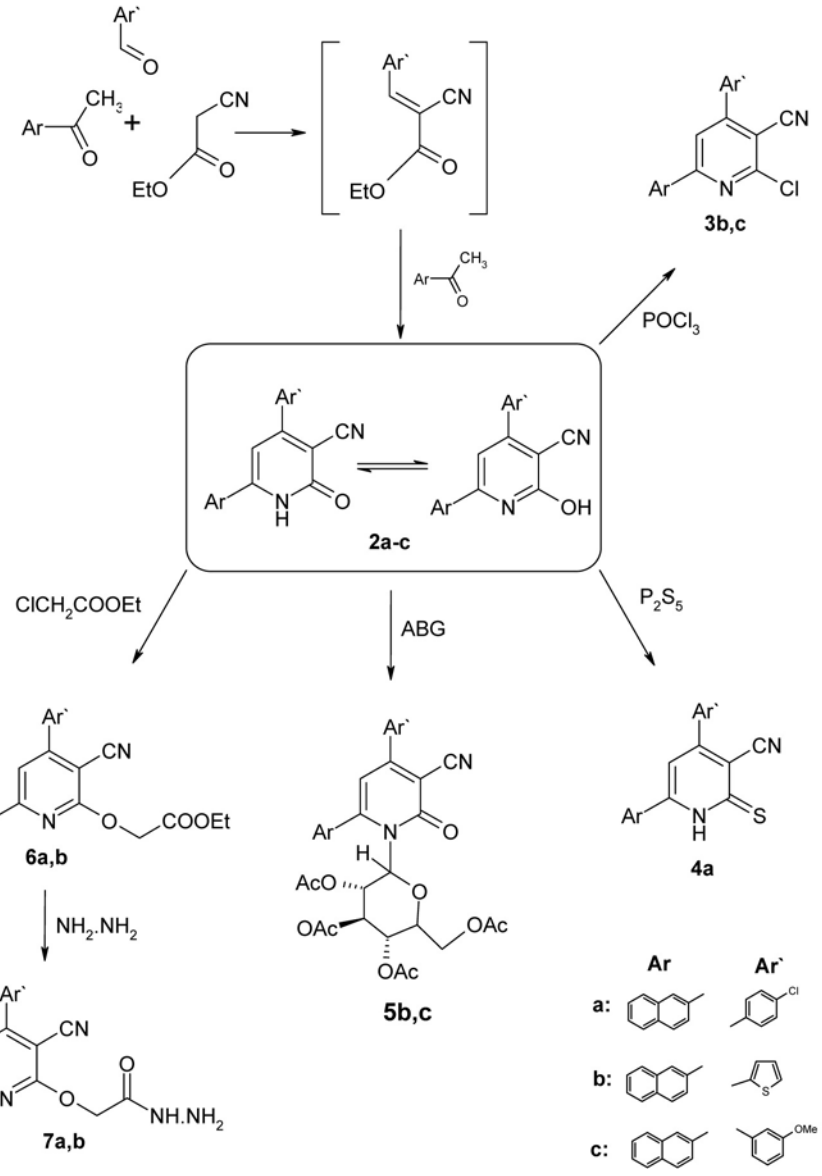


Schema 1

revealed the disappearance of NH group as well as the existence of C=O groups at 1747, 1658 and CN at 2222 cm^{-1}. ^1H NMR spectrum of compound **5c** showed signals at 2.08, 2.09, 2.10, 2.10 (4 × s, 12H, 4 × CH_3CO), 3.50 (s, 3H, OCH_3), 5.23 (m, 2H, 6'-CH_2), 4.25 (m, 2H, 5'-H, 4'-H), 5.28–5.48 (m, 2H, 3'-H, 2'-H), 6.03 (d, $J_{1',2'}$ = 9.0 Hz, 1H, 1'-H), 7.24 (s, 1H, pyridine 5-H), 7.39–7.65, 8.01–8.40 (2 × m, 10H, Ar-H) and 8.54 (s, 1H Ar-H). The mass spectrum of compound **5c** showed molecular ion peak ($C_{37}H_{34}N_2O_{11}$) at *m/z* 352 ($M^+ - C_{14}H_{19}O_9$, sugar molecule, 100%) and 331 ($M^+ - C_{23}H_{16}N_2O_2$, 90%).

When compounds **2a**,**b** reacted with ethyl chloroacetate in dry acetone, in the presence of anhydrous potassium carbonate, they produced ethyl ester derivatives **6a**,**b** (Scheme 2), that gave correct elemental analysis besides displaying the expected carbonyl absorption bands in the IR spectrum. Compound **6b** showed absorption bands at 2215 (CN), 1739 (C=O of ester) and 1585 cm^{-1} (C=N). Its ^1H NMR spectrum showed signals at 1.18–1.23 (t, *J* = 7.5 Hz, 3H, CH_3), 4.14–4.21 (q, *J* = 7.5 Hz, 2H, OCH_2CH_3), 5.13 (s, 2H, OCH_2COO), 7.24 (s, 1H, pyridine 5-H), 7.36 (d, *J* = 5.4 Hz, 1H, thiophene H), 7.55–8.12, 8.21–8.36 (2 × m, 8H, Ar-H) and 8.48 (s, 1H Ar-H). Mass spectrum of compound **6b** showed molecular ion peak ($C_{24}H_{18}N_2O_3S$) at *m/z* 414, as the base peak.

Compounds **6a**,**b** reacted with hydrazine hydrate in ethanol to produce the hydrazide derivatives **7a**,**b** (Scheme 2). IR spectrum of compound **7a** displayed absorption bands near 3250, 3160 (NH_2, NH), 2220 (CN) and 1675 cm^{-1} (C=O). ^1H NMR spectrum of compound **7b** showed signals at 4.22 (s, 2H, NH_2, D_2O exchangeable), 5.12 (s, 2H, OCH_2), 7.33 (s, 1H, pyridine 5-H), 7.62 (d, *J* = 5.4 Hz, 1H, thiophene H), 7.90–8.25 (m, 7H, Ar-H), 8.35 (m, 1H, thiophene H), 8.91 (s, 1H Ar-H) and 9.63 (s, 1H, NH,

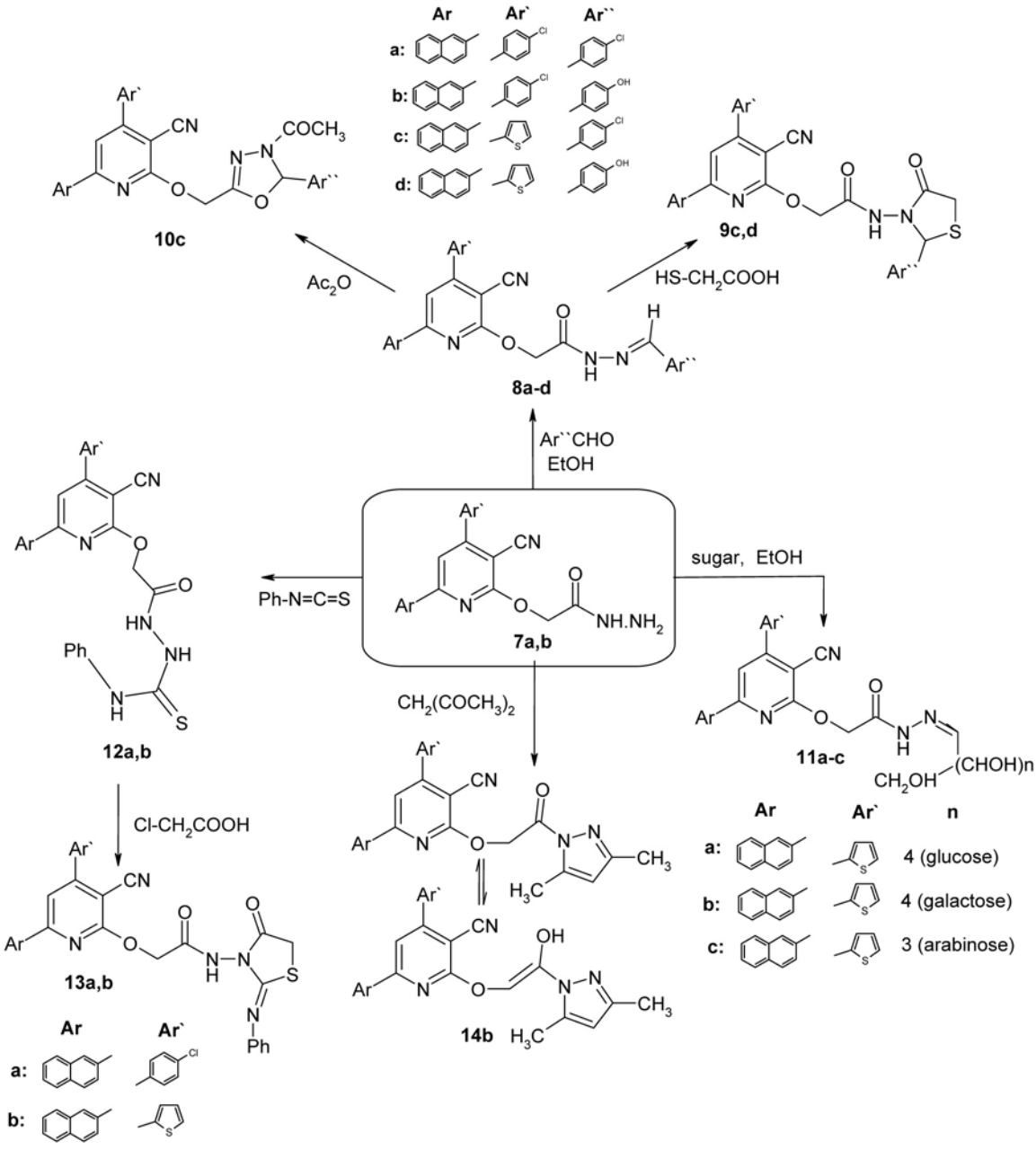


Schema 2

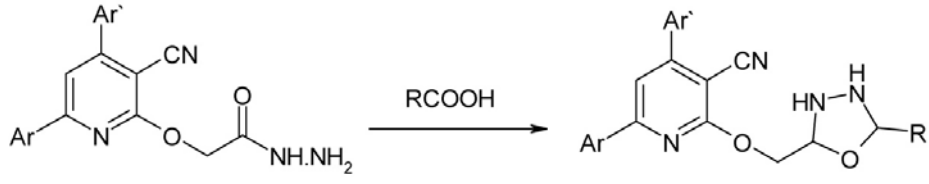
D_2O exchangeable). Its mass spectrum showed molecular ion peak at *m/z* 400 (25%) as well as the base peak at *m/z* 328 (M^+–CH-$CONHNH_2$).

Condensation of compounds **7a**,**b** with 4-chlorobenzaldehyde or 4-hydroxybenzaldehyde took place by heating under reflux in ethanol in the presence of piperidine, where substituted hydrazides **8a**–**d** were produced, which in turn underwent cyclocondensation with thioglycolic acid in dry benzene, according to the reported method, to obtain thiazolidine derivatives **9c**,**d** (Scheme 3).[25] Compound **8c** was refluxed in excess acetic anhydride for 3 h to give oxadiazole **10c** (Scheme 3).

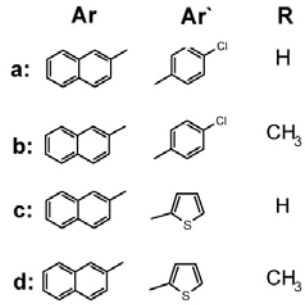
The IR spectrum of compound **8d** displayed absorption bands near 3186 (OH), 3054 (NH), 2215 (CN) and 1669 cm^{-1} (C=O). Compounds **9c**,**d** displayed absorption bands near 3225 (NH), 2220 (CN) and 1730, 1685 cm^{-1} (2C=O). ^1H NMR spectrum of compound **8b** showed signals at 5.12 (s, 2H, OCH_2), 7.75–8.55, 8.60–8.89 (2 × m, 17H, Ar-H, pyridine 5-H, benzylidine H), 10.12 and 10.40 (2 × s, 2H, NH, OH, D_2O exchangeable). The mass spectrum of **8d** showed molecular ion peak ($C_{29}H_{20}N_4O_3S$) at *m/z* 504 (32%) and the base peak at *m/z* 327 (100%) corresponding to the loss of $C_9H_8N_2O_2$. That of compound **9d** showed molecular ion peak ($C_{31}H_{22}N_4O_4S_2$) at *m/z* 578.



Schema 3



Schema 4



The hydrazone derivatives **11a–c** were prepared by the reaction of hydrazide derivative **7b** with some monosaccharides (D-glucose, D-galactose and arabinose), in ethanol and glacial acetic acid (Scheme 3). The products revealed absorption frequencies due to OH, NH and C=N in IR spectra, and their ^{1}H NMR spectra showed the presence of the sugar protons, NH and azo-methine (C*H*=N). The structures of nucleoside derivatives **11a–c** were elucidated on the basis of their elemental and spectral data. The IR spectrum of compound **11a** as displayed absorption bands at 3442–3320 (broad OH, NH), 2215 (CN) and 1676 cm^{-1} (C=O). The ^{1}H NMR spectrum of compound **11a** showed signals at 5.00 (s, 2H, OCH_2), 3.00–3.80 (m, 4H), 3.50–3.90 (m, 2H, CH_2OH), 4.30–4.50, 5.30–5.80 (2 × m, 5H, 5 × OH, D_2O exchangeable), 7.30 (s, 1H, pyridine 5-H), 7.64 (d, *J* = 5.4 Hz, 1H, thiophene H), 7.93–8.55 (m, 8H, Ar-H, HC=N), 8.88 (m, 1H, thiophene H), 9.10 (s, 1H, Ar-H) and 10.00 (s, 1H, NH, D_2O exchangeable). The IR spectrum of compound **11b** displayed absorption bands at 3400–3300 (broad OH, NH), 2215 (CN) and 1680 cm^{-1} (C=O). The ^{1}H NMR spectrum of compound **11b** showed signals at 3.30–3.80 (m, 4H), 4.20–4.60 (m, 5H, 5 × OH, D_2O exchangeable), 5.10 (s, 2H, CH_2), 5.60–5.80 (m, 2H, 6'-H, 6''-H), 7.30 (s, 1H, pyridine 5-H), 7.65 (d, *J* = 5.4 Hz, 1H, thiophene H), 7.92–8.55 (m, 9H, Ar-H, HC=N), 9.00 (s, 1H, Ar-H) and 11.40 (s, 1H, NH, D_2O exchangeable). The IR spectrum of compound **11c** showed absorption bands at 3400–3300 (broad OH, NH), 2215 (CN) and 1676 cm^{-1} (C=O). The ^{1}H NMR spectrum of compound **11c** showed signals at 3.35–3.80 (m, 3H of alditol), 4.40–4.80 (m, 4H, 4 × OH, D_2O exchangeable), 5.20 (s, 2H, OCH_2), 5.41 (m, 2H, 5'-H-, 5''-H), 7.38 (s, 1H, pyridine 5-H), 7.65 (d, *J* = 5.4 Hz, 1H, thiophene H), 8.00–8.40 (m, 9H, Ar-H, HC=N), 8.82 (s, 1H, Ar-H) and 11.60 (s, 1H, NH, D_2O exchangeable).

When compounds **7a**,**b** reacted with phenyl isothiocyanate in dry dioxane hydrazinecarbothioamide derivatives **12a,b** (Scheme 3) were obtained,[25–27] which showed besides correct values in elemental analysis, IR absorption bands near 3428, 3270 (NH), 2211 (CN), 1652 (C=O) and 1428 cm^{-1} (C=S). ^{1}H NMR spectrum of compound **12b** showed signals at 4.19 (s, 1H, NH, D_2O exchangeable), 5.76 (s, 2H, CH_2), 7.10 (s, 1H, pyridine 5-H), 7.23 (d, *J* = 5.4 Hz, 1H, Ar-H), 7.35 (d, *J* = 5.4 Hz, 1H, Ar-H), 7.58–8.25 (m, 12H, Ar-H), 8.84 (s, 1H, Ar-H) and 12.83 (s, 1H, NH, D_2O exchangeable). The mass spectrum of compound **12b** showed molecular ion peak ($C_{29}H_{20}N_5O_2S_2$) at *m/z* 534.

Compounds **12a**,**b** reacted with chloroacetic acid in ethanol to produce thiazolidine derivatives **13a**,**b** (Scheme 3). The IR spectrum of compounds **13a**,**b** displayed absorption bands near 3300, 3200 (NH), 2220 (CN) and 1720, 1685 cm^{-1} (2C=O). ^{1}H NMR spectrum of compound **13b** showed signals at 2.63 (s, 2H, methylene H), 5.35 (s, 2H, OCH_2), 7.20 (s, 1H, pyridine 5-H), 7.25–8.36 (m, 14H, Ar-H), 8.80 (s, 1H, Ar-H) and 10.81 (s, 1H, NH, D_2O exchangeable), while its mass spectrum showed molecular ion peak ($C_{31}H_{21}N_5O_3S_2$) at *m/z* 575.

Further condensation of the hydrazide derivative **7b** with acetylacetone in the presence of ethanol gave pyrazole **14b** (Scheme 3). The structure was confirmed by analytical and spectral data. The IR spectrum of compound **14b** displayed absorption bands at 3431 (OH), 2213 (CN) and 1665 cm^{-1} (C=O). ^{1}H NMR spectrum of compound **14b** showed signals at 1.74, 2.09 (2 × s, 6H, 2 × CH_3), 6.57 (s, 1H, OH, D_2O exchangeable), 7.36 (s, 1H, pyridine 5-H), 7.55 (s, 1H, pyrazole H), 7.64–8.33 (m, 10H, Ar-H, C=CO) and 8.75 (s, 1H, Ar-H). From ^{1}H NMR data it seems that compound **14b** really exists in keto-enol dynamic equilibrium in ratio 68:32 (17:8 or 2:1). Its mass spectrum showed molecular ion peak ($C_{27}H_{20}N_4O_2S$) at *m/z* 464.

Heating compounds **7a**,**b** under reflux with aliphatic acids (formic or acetic acid) resulted in the formation of 1,3,4-oxadiazolidine derivatives **15a–d** (Scheme 4). The structures of these compounds were confirmed according to their microanalytical and spectroscopic data. The IR spectrum of compound **15c** displayed absorption bands at 3441, 3177 (NH), 2215 cm^{-1} (CN), those of compound **15d** displayed absorption bands at 3190 (NH), 2215 cm^{-1} (CN). The ^{1}H NMR spectrum of compound **15c** showed signals at 5.05 (s, 1H, CH), 5.24, 5.18 (2 × s, 4H, 2 × CH_2), 7.24 (s, 1H, pyridine 5-H), 7.38–8.88 (m, 10H, Ar-H), 10.20 and 10.56 (2 × s, 2H, 2 × NH, D_2O exchangeable). Its mass spectrum showed molecular ion peak ($C_{23}H_{18}N_4O_2S$) at *m/z* 414. Those of compound **15d** sho-

wed signals at 1.88 (s, 3H, CH_3), 5.18 (s, 2H, CH_2), 7.38–8.90 (m, 11H, Ar H), 9.95 and 10.32 (2 × s, 2H, 2 × NH, D_2O exchangeable). The mass spectrum of compound **15d** showed molecular ion peak ($C_{24}H_{20}N_4O_2S$) at *m/z* 429.

3. Anticancer Evaluation

Six selected new compounds **1b**, **5b**, **5c**, **8c**, **11c** and **12a** were tested for cytotoxic activity against the McF_7 (Breast Carcinoma Cell Line) and $HEPG_2$ (Liver Carcinoma Cell Line). All new compounds tested were dissolved in DMSO in different concentrations (0, 1, 2.5, 5 and 10 μg/mL). Preliminary experiments were made using the human tumour cell line to identify the cytotoxicity of the selected compounds according to Skehan *et al.*[28]

***Material and Method*:** (i) Tumor (Human tumor cell); (ii) $HEPG_2$ (Liver Carcinoma Cell Line); (iii) McF_7 (Breast Carcinoma Cell Line).

***Measurement of Potential Cytotoxicity by (SRB) Assay*:**

– Cells were plated in 96-multiwell plates (10^4 cells/well) for 24 h before treatment with the compounds to allow attachment of cells to the wall of the plate.
– Different concentrations of the tested compound (0, 1, 2.5, 5 and 10 μg/mL) were added to the cell monolayer; triplicate wells were prepared for each individual dose.
– Monolayer cells were incubated with the compounds for 48 h at 37 °C and in atmosphere of 5% CO_2.
– After 48 h, cells were fixed, washed and stained with Sulfo-Rhodamine-B stain.
– Excess stain was washed with acetic acid and attached stain was recovered with Tris EDTA buffer.
– Color intensity was measured in an ELISA reader.
– The relation between surviving fraction and drug concentration is shown in Tables 1 and 2.

Results.

– IC50: dose of the compound which reduces survival to 50%.
– All tested compounds were proven to have cytotoxic activity against the McF_7 (Breast Carcinoma Cell Line) and $HEPG_2$ (Liver Carcinoma Cell Line) at the chosen drug concentrations (Tables 1 and 2). Only compound **11c** had no cytotoxic activity against the $HEPG_2$ (Table 2).

Table 1: Cytotoxic activity against the McF_7 of tested compounds

Tested Compounds	Concentration (μg/mL)/ Surviving fraction					
	0.0	1.0	2.5	5.0	10.0	IC50
1b	1.000	0.668	0.480	0.468	0.407	2.35
5b	1.000	0.960	0.831	0.412	0.413	4.50
5c	1.000	0.817	0.748	0.560	0.397	6.31
8c	1.000	0.682	0.530	0.273	0.270	3.02
11c	1.000	0.958	0.879	0.580	0.441	7.72
12a	1.000	0.903	0.806	0.662	0.321	7.32

Table 2: Cytotoxic activity against the $HEPG_2$ of tested compounds

Tested Compounds	Concentration (μg/mL)/ Surviving fraction					
	0.0	1.0	2.5	5.0	10.0	IC50
1b	1.000	0.636	0.468	0.352	0.351	2.01
5b	1.000	0.926	0.586	0.406	0.405	3.89
5c	1.000	0.789	0.700	0.476	0.365	4.77
8c	1.000	0.618	0.498	0.362	0.327	2.68
11c	1.000	0.958	0.584	0.541	0.636	–
12a	1.000	0.977	0.685	0.200	0.185	3.42

4. Antimicrobial Evaluation

The target compounds were tested for their antimicrobial activity against *Escherichia coli* NRRL B-210 (Gram negative bacteria), *Bacillus subtilis* NRRL B-543 (Gram positive bacteria), *Aspergillus niger* and *Candida albicans* NRRL Y-477 (fungi). These microorganisms were obtained from Northern Utilisation Research and Development Division, U. S. Department of Agriculture, Peoria, Illionis, USA. Chloramphenicol and Fluconazole were purchased from Egyptian market and used at the concentration of 25 mg/mL as references for antibacterial and antifungal activities. These compounds were assayed by the agar diffusion method.[29] The assay medium flasks containing 50 mL of nutrient agar medium for bacteria and Czapek's-Dox agar media for fungi, respectively were allowed to reach 40–50 °C and then inoculated with 0.5 mL of the last organism cell suspension.

The flasks were mixed well and then the content of each flask was poured into a Petri dish (15 × 2 cm) and allowed to solidify. Thereafter, holes (1 cm diameter) were made in the agar plate by the aid of a sterile corkborer. In these holes, 100 μL of the 1.8 mg/mL DMSO of each compound was placed using an automatic micropipette. The Petri dish were left at 5 °C for 1 h to allow diffusion of the samples through the agar medium and retard the growth of the test organism, then incubated at 30 °C for 24 h for bacteria and 72 h of incubation at 28 °C for fungi. The diameter of the resulted inhibition zone was measured in cm.

4. 1. Antibacterial Activity:

DMSO showed no inhibition zones. Result of antibacterial activity test against *Escherichia coli* (Gram negative bacteria) and *Bacillus subtilis* (Gram positive bacteria) showed that compounds **5c**, **7b**, **8c**, **10c** and **15a** of fifteen compounds have an antibacterial activity while the other tested compounds were generally inefficient.

4. 2. Antifungal Activity

The prepared compounds were evaluated in vitro against two strains of fungi, *Candida albicans and Aspergillus niger.* Results of antimicrobial activity showed that

compounds **2b** and **10c** have an antifungal activity while the other tested compounds were generally inefficient.

Table 3: In vitro antimicrobial activity by agar diffusion method of tested compounds

Tested Compounds and Standards	Inhibition Zone (mm) Microorganism			
	Bacteria		Fungi	
	Gram-negative	Gram-positive		
	Eschericha coli	*Bacillus subtilsi*	*Aspergillus niger*	*Candida albicans*
Chloramphenicol	+++	+++	+	+
Fluconazole	–	–	+++	+++
2a	–	–	–	–
2b	–	–	+	+
5b	–	–	–	–
5c	–	++	–	–
6b	–	–	–	–
7a	–	–	–	–
7b	–	++	–	–
8a	–	–	–	–
8b	–	–	–	–
8c	–	++	–	–
9c	–	++	–	–
10c	++	++	+	–
11a	–	++	–	–
11b	–	++	–	–
11c	–	++	–	–
12a	–	–	–	–
14a	–	–	–	–
14b	–	–	–	–
15a	++	++	–	–
15b	–	–	–	–
15d	–	–	–	–

+++ Highly sensitive (inhibition zone 21–25 mm).
++ Fairly sensitive (inhibition zone 16–20 mm).
+ Slightly sensitive (inhibition zone 10–15 mm).
– Not sensitive.

5. Experimental

All melting points are uncorrected and measured using Electro-thermal IA 9100 apparatus (Shimadzu, Tokyo, Japan). IR spectra were recorded as KBr pellets on a Perkin–Elmer 1650 spectrophotometer (Perkin–Elmer, Norwalk, CT, USA). ^{1}H NMR was determined on a Jeol-Ex-300 NMR spectrometer (JEOL, Tokyo, Japan) and chemical shifts are expressed as ppm (δ values) against TMS as internal reference. Mass spectra were recorded on VG 2AM-3F mass spectrometer (Thermo electron corporation, USA). Microanalyses were obtained by Mario El Mentar apparatus, Organic Microanalysis Unit, and the results were within the accepted range (± 0.20) of the calculated values. Reaction progress and purity checks of the compounds were made by TLC on silica gel-precoated aluminum sheets (Type 60 F254, Merck, Darmstadt, Germany).

*General procedures for the synthesis of compounds **1a–c***

A mixture of 2-acetylnaphthalene (0.01 mol) and aromatic aldehydes (4-chlorobenzaldehyde, 2-thiophenecarboxaldehyde or 3-methoxybenzaldehyde (0.01 mol)) in ethanol (30 mL) and 10% NaOH (15 mL) was added dropwise within 15 min. The reaction mixture was stirred for 3 h and left overnight at room temperature. The mixture was poured onto ice cold water and the obtained precipitate was filtered off and recrystallized from ethanol to give the corresponding derivatives **1a–c**, respectively. Compounds **1a**,**c** were identified via their melting points.[30,31]

1-(2-Naphthyl)-3-(2-thienyl)-2-propen-1-one (1b)

Yield 80%; mp 100–101°C (EtOH). IR (KBr) ν 1640 (C=O), 1606 (C=C) cm^{-1}. ^{1}H NMR (DMSO-d_6) δ 7.21 (d, J = 5.4 Hz, 1H, thiophene H), 7.55–8.30 (m, 10H, Ar-H), 8.88 (s, 1H, Ar-H). MS *m/z* 264 (M$^+$, 100%). Anal. Calcd for $C_{17}H_{12}OS$: C, 77.24; H, 4.58; S, 12.13. Found: C, 77.18; H, 4.61; S, 12.16.

*General procedures for the synthesis of compounds **2a–c***

Method A:

A mixture of 2-acetylnaphthalene (0.01 mol), aromatic aldehydes (4-chlorobenzaldehyde, 2-thiophene-carboxaldehyde or 3-methoxybenzaldehyde (0.01 mol)), ethyl cyanoacetate (0.01 mol) and ammonium acetate (0.08 mol) in ethanol (40 mL) was refluxed for 8 h. The obtained precipitate was filtered off, washed successively with water and recrystallized from DMF to give the corresponding derivatives **2a–c**, respectively.

Method B:

A mixture of enones **1** (0.01 mol), ethyl cyanoacetate (0.01 mol) and ammonium acetate (0.08 mol) in ethanol (40 mL) was refluxed for 10 h. The obtained precipitate was filtered off and recrystallized from DMF to give products identical in all aspects with compounds **2a–c** obtained before.

4-(4-Chlorophenyl)-6-(2-naphthyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (2a)[20]

Yield 60% (method A), 40% (method B); mp 340–341 °C (EtOH). IR (KBr) ν 3300 (NH), 2210 (CN), 1650 (C=O) cm^{-1}. ^{1}H NMR (DMSO-d_6) δ 7.16 (s, 1H, pyridine 5-H), 7.53–7.67 (m, 4H, Ar-H), 7.87–8.54 (m, 4H, Ar-H), 8.68 (d, J = 7.5 Hz, 2H, Ar-H), 8.89 (s, 1H, Ar-H), 12.91 (s, 1H, NH, D_2O exchangeable). MS *m/z* 356 (M$^+$, 100%). Anal. Calcd for $C_{22}H_{13}ClN_2O$: C, 74.06; H, 3.67; N, 7.85; Cl, 9.94. Found: C, 73.99; H, 3.66; N, 7.87; Cl, 9.97.

6-(2-Naphthyl)-2-oxo-4-(2-thienyl)-1,2-dihydropyridine-3-carbonitrile (2b)

Yield 60% (method A), 30% (method B); mp 328–329 °C (EtOH). IR (KBr) ν 3350 (NH), 2220 (CN),

1660 (C=O) cm^{-1}. ^1H NMR (DMSO-d_6) δ 7.12 (s, 1H, pyridine 5-H), 7.34 (d, *J* = 5.4 Hz, 1H, thiophene H), 7.63–7.66 (m, 2H, Ar-H), 8.00–8.12 (m, 6H, Ar-H), 8.55 (s, 1H Ar-H), 12.85 (s, 1H, NH, D_2O exchangeable). MS *m/z* 328 (M^+, 100%). Anal. Calcd for $C_{20}H_{12}N_2OS$: C, 73.15; H, 3.68; N, 8.53; S, 9.76. Found: C, 73.00; H, 3.60; N, 8.49; S, 10.03.

4-(3-Methoxyphenyl)-6-(2-naphthyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (2c)

Yield 70% (method A), 35% (method B); mp 280–281 °C (EtOH). IR (KBr) ν 3320 (NH), 2218 (CN), 1651 (C=O) cm^{-1}. ^1H NMR (DMSO-d_6) δ 3.69 (s, 3H, OCH_3), 7.11 (s, 1H, pyridine 5-H), 7.35–7.63 (m, 4H, Ar-H), 7.92–8.45 (m, 6H, Ar-H), 8.88 (s, 1H, Ar-H), 12.90 (s, 1H, NH, D_2O exchangeable). MS *m/z* 351 (M^+–H). Anal. Calcd for $C_{23}H_{16}N_2O_2$: C, 78.39; H, 4.58; N, 7.95. Found: C, 78.47; H, 4.66; N, 7.91.

*General procedure for the synthesis of compounds **3b**,**c**.*

A suspension of compound **2b** or **2c** (0.01 mol) and $POCl_3$ (5 mL) was heated on a water bath for 3 h. The reaction mixture was poured gradually into ice-cold water and neutralized by diluted ammonia solution. The separated solid was filtered off and recrystallized from ethanol/DMF to afford the corresponding derivatives **3b**,**c**.

2-Chloro-6-(2-naphthyl)-4-(2-thienyl)nicotinonitrile (3b)

Yield 61%; mp 170–171 °C (EtOH/DMF). IR (KBr) ν 2223 (CN), 1066 (C-Cl) cm^{-1}. ^1H NMR (DMSO-d_6) δ 7.75–8.12 (m, 4H, Ar-H), 8.21–8.56 (m, 6H, Ar-H), 8.69 (s, 1H, Ar-H). MS *m/z* 348 (M^+, Cl^{37}, 33), 346 (M^+, Cl^{35}, 100), 312 (70). Anal. Calcd for $C_{20}H_{11}ClN_2S$: C, 69.26; H, 3.20; Cl, 10.22; N, 8.08; S, 9.24. Found: C, 69.19; H, 3.22; Cl, 10.24; N, 8.10; S, 9.25.

2-Chloro-4-(3-methoxyphenyl)-6-(2-naphthyl)nicotinonitrile (3c)

Yield 64%; mp 169–170 °C (EtOH/DMF). IR (KBr) ν 2220 (CN), 1066 (C-Cl) cm^{-1}. ^1H NMR (DMSO-d_6) δ 3.32 (s, 3H, OCH_3), 7.78–8.13 (m, 5H, Ar-H), 8.23–8.70 (m, 6H, Ar-H), 8.82 (s, 1H, Ar-H). MS *m/z* 372 (M^+, Cl^{37}, 34), 370 (M^+, Cl^{35} 100). Anal. Calcd for $C_{23}H_{15}ClN_2O$: C, 74.49; H, 4.08; Cl, 9.56; N, 7.55. Found: C, 74.58; H, 4.05; Cl, 9.54; N, 7.52.

4-(4-Chlorophenyl)-6-(2-naphthyl)-2-thioxo-1,2-dihydropyridine-3-carbonitrile (4a)

A mixture of compound **2a** (0.01 mol) and P_2S_5 (2 g) in pyridine (10 mL) was refluxed for 6 h. The product was poured into ice-cold diluted HCl. The separated solid was filtered off and recrystallized from DMF to afford the corresponding thione derivative **4a**. Yield 70%; mp 240–241 °C (DMF). IR (KBr) ν 3428 (NH), 2213 (CN), 1405 (C=S) cm^{-1}. ^1H NMR (DMSO-d_6) δ 7.12 (s, 1H, pyridine 5-H), 7.55–7.69 (m, 4H, Ar-H), 7.88–8.64 (m, 4H, Ar-H), 8.67 (d, *J* = 7.5 Hz, 2H, Ar-H), 8.87 (s, 1H, Ar-H), 12.55 (s, 1H, NH, D_2O exchangeable). MS *m/z* 372 (M^+, 100%), 337 (20). Anal. Calcd for $C_{22}H_{13}ClN_2S$: C, 70.87; H, 3.51; Cl, 9.51; N, 7.51; S, 8.60. Found: C, 70.80; H, 3.53; Cl, 9.55; N, 7.49; S, 8.63

*General procedure for the synthesis of compounds **5b**,**c***

To a solution of compound **2b** or **2c** (0.01 mol) in 1 mL triethylamine, a solution of 2,3,4,6-tetra-*O*-acetyl-α-glucopyranosyl bromide (0.02 mol) in 5 mL DMF was added, then the reaction mixture was stirred for 3 h at room temperature, evaporated under reduced pressure at 40 °C, the residue washed with distilled water, filtered off and dried to afford compounds **5b**,**c**.

1-(2,3,4,6-Tetra-*O*-acetyl-β-glucopyranosyl)-6-(2-naphthyl)-2-oxo-4-(2-thienyl)pyridine-3-carbonitrile (5b)

Yield 64%; mp 170–171 °C (DMF). IR (KBr) ν 2222 (CN), 1658 (C=O), 1747 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.87 (s, 3H, CH_3CO), 2.08 (s, 3H, CH_3CO), 2.10 (s, 3H, CH_3CO), 2.10 (s, 3H, CH_3CO), 4.11 (m, 2H, 6'-CH_2), 4.22–4.30 (m, 2H, 5'-H, 4'-H), 5.23–5.48 (m, 2H, 3'-H, 2'-H), 6.03 (d, $J_{1',2'}$ = 9.0 Hz, 1H, 1'-H), 7.26 (s, 1H, pyridine 5-H), 7.36 (d, *J* = 5.4 Hz, 1H, thiophene H), 7.59–8.01 (m, 6H, Ar-H), 8.12–8.22 (m, 2H, Ar-H), 8.54 (s, 1H Ar-H). MS *m/z* 328 ($M^+ - C_{14}H_{19}O_9$, 30%). Anal. Calcd for $C_{34}H_{30}N_2O_{10}S$ (658): C, 62.00; H, 4.59; N, 4.25; S, 4.87. Found: C, 61.95; H, 4.60; N, 4.30; S, 4.84.

1-(2,3,4,6-Tetra-*O*-acetyl-β-glucopyranosyl)-4-(3-methoxyphenyl)-6-(2-naphthyl)-2-oxopyridine-3-carbonitrile (5c)

Yield 67%; mp 170–171 °C (DMF). IR (KBr) ν 2222 (CN), 1658 (C=O), 1747 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.08 (s, 3H, CH_3CO), 2.09 (s, 3H, CH_3CO), 2.10 (s, 3H, CH_3CO), 2.10 (s, 3H, CH_3CO), 3.50 (s, 3H, OCH_3), 5.23 (m, 2H, 6'-CH_2), 4.25 (m, 2H, 5'-H, 4'-H), 5.28–5.48 (m, 2H, 3'-H, 2'-H), 6.03 (d, $J_{1',2'}$ = 9.0 Hz, 1H, 1'-H), 7.24 (s, 1H, pyridine 5-H), 7.39–7.65 (m, 4H, Ar-H), 8.01–8.40 (m, 6H, Ar-H), 8.54 (s, 1H Ar-H). MS *m/z* 352 ($M^+ - C_{14}H_{19}O_9$, 100%), 331 ($M^+ - C_{23}H_{16}N_2O_2$, 90%). Anal. Calcd for $C_{37}H_{34}N_2O_{11}$ (682): C, 65.10; H, 5.02; N, 4.10. Found: C, 65.15; H, 4.95; N, 4.07.

*General procedure for the synthesis of compounds **6a**,**b***

A mixture of compound **2a** or **2b** (0.01 mol), ethyl chloroacetate (0.01 mol), anhydrous potassium carbonate (0.04 mol) in dry acetone (30 mL) was refluxed for 30 h, on a water bath. The solvent was removed under reduced pressure, then water was added to the mixture and the solid formed was filtered off, recrystallized from appropriate solvent to afford the corresponding derivatives **6a**,**b**.

Ethyl {[4-(4-Chlorophenyl)-3-cyano-6-(2-naphthyl)-2-pyridinyl]oxy}acetate (6a)

Yield 69%; mp 190–191°C (AcOH). IR (KBr) ν

2214 (CN), 1743 (C=O) cm^{-1}. ^1H NMR (DMSO-d_6) δ 1.17–1.21 (t, J = 7.5 Hz, 3H, CH_3), 4.15–4.22 (q, J = 7.5 Hz, 2H, OCH_2CH_3), 5.12 (s, 2H, OCH_2COO), 7.27 (s, 1H, pyridine 5-H), 7.55–7.68 (m, 4H, Ar-H), 7.88–8.15 (m, 6H, Ar-H), 8.51 (s, 1H, Ar-H). MS *m/z* 442 (M^+, 100%), 369 (90), 339 (20). Anal. Calcd for $C_{26}H_{19}ClN_2O_3$: C, 70.51; H, 4.32; Cl, 8.00; N, 6.32. Found: C, 70.44; H, 4.54; Cl, 8.08; N, 6.30.

Ethyl {[3-Cyano-6-(2-naphthyl)-4-(2-thienyl)-2-pyridinyl]oxy}acetate (6b).

Yield 70%; mp 160–161°C (EtOH). IR (KBr) ν 2214 (CN), 1739 (C=O) cm^{-1}. ^1H NMR (DMSO-d_6) δ 1.18–1.23 (t, J = 7.5 Hz, 3H, CH_3), 4.14–4.21 (q, J = 7.5 Hz, 2H, OCH_2CH_3), 5.13 (s, 2H, OCH_2COO), 7.24 (s, 1H, pyridine 5-H), 7.36 (d, J = 5.4 Hz, 1H, thiophene H), 7.55–8.12 (m, 4H, Ar-H), 8.21–8.36 (m, 4H, Ar-H), 8.48 (s, 1H Ar-H). MS *m/z* 414 (M^+, 100%), 341 (90), 369 (10), 311 (30). Anal. Calcd for $C_{24}H_{18}N_2O_3S$: C, 69.55; H, 4.38; N, 6.76; S, 7.74. Found: C, 69.50; H, 4.30; N, 6.81; S, 7.75.

*General procedure for the synthesis of compounds **7a**,**b***

A solution of compound **6a** or **6b** (0.01 mol) in ethanol (20 ml) and hydrazine hydrate (0.01 mol) was refluxed for 8 h. The separated solid after cooling was recrystallized from dioxane to afford the corresponding hydrazides **7a**–**b**.

2-{[4-(4-Chlorophenyl)-3-cyano-6-(2-naphthyl)-2-pyridinyl]oxy}acetohydrazide (7a)

Yield 50%; mp 210–211°C (dioxane). IR (KBr) ν 3250, 3160 (NH_2, NH), 2220 (CN), 1675 (C=O) cm^{-1}. ^1H NMR (DMSO-d_6) δ 4.43 (s, 2H, NH_2, D_2O exchangeable), 5.11 (s, 2H, OCH_2), 7.13 (s, 1H, pyridine 5-H), 7.72 (d, J = 7.5 Hz, 2H, Ar-H), 7.83 (d, J = 7.5 Hz, 2H, Ar-H), 7.95–7.45 (m, 6H, Ar-H), 8.79 (s, 1H, Ar-H), 9.60 (s, 1H, NH, D_2O exchangeable). MS *m/z* 428 (M^+, 30%), 356 (100), 328 (40). Anal. Calcd for $C_{24}H_{17}ClN_4O_2$: C, 67.21; H, 4.00; Cl, 8.27; N, 13.06. Found: C, 67.33; H, 3.92; Cl, 8.20; N, 13.05.

2-{[3-Cyano-6-(2-naphthyl)-4-(2-thienyl)-2-pyridinyl]oxy}acetohydrazide (7b)

Yield 50%; mp 240–241 °C (dioxane). IR (KBr) ν 3250, 3160 (NH_2, NH), 2221 (CN), 1635 (C=O) cm^{-1}. ^1H NMR (DMSO-d_6) δ 4.22 (s, 2H, NH_2, D_2O exchangeable), 5.12 (s, 2H, OCH_2), 7.33 (s, 1H, pyridine 5-H), 7.62 (d, J = 5.4 Hz, 1H, thiophene H), 7.90–8.25 (m, 7H, Ar-H), 8.35 (m, 1H, thiophene H), 8.91 (s, 1H Ar-H), 9.63 (s, 1H, NH, D_2O exchangeable). MS *m/z* 400 (M^+, 25%), 369 (80), 328 (100), 311 (25). Anal. Calcd for $C_{22}H_{16}N_4O_2S$: C, 65.99; H, 4.03; N, 13.99; S, 8.01. Found: C, 66.08; H, 3.99; N, 14.02; S, 7.99.

*General procedure for the synthesis of compounds **8a**–**d***

A mixture of compound **7a** or **7b** (0.01 mol) and equimolar amount of the aromatic aldehydes (4-chlorobenzaldehyde or 4-hydroxybenzaldehyde) in ethanol (20 mL) was refluxed for 8 h. The solution was cooled, the precipitate formed was filtered off and recrystallized from the DMF to give compounds **8a**–**d**.

2-{[4-(4-Chlorophenyl)-3-cyano-6-(2-naphthyl)-2-pyridinyl]oxy}-*N*'-[(4-chlorophenyl)methylidene]acetohydrazide (8a)

Yield 60%; mp 280–281 °C (DMF). IR (KBr) ν 3200 (NH), 2217 (CN), 1672 (C=O) cm^{-1}. ^1H NMR (DMSO-d_6) δ 5.12 (s, 2H, OCH_2), 7.75–8.55 (m, 13H, Ar-H), 8.60–8.89 (m, 4H, Ar-H, pyridine 5-H, benzylidine H), 10.12 (s, 1H, NH, D_2O exchangeable). MS *m/z* 550 (M^+, 30%). Anal. Calcd for $C_{31}H_{20}Cl_2N_4O_2$: C, 67.52; H, 3.66; Cl, 12.86; N, 10.16. Found: C, 67.59; H, 3.61; Cl, 12.84; N, 10.10.

2-{[4-(4-Chlorophenyl)-3-cyano-6-(2-naphthyl)-2-pyridinyl]oxy}-*N*'-[(4-hydroxyphenyl)methylidene] acetohydrazide (8b)

Yield 62%; mp 280–281°C (DMF). IR (KBr) ν 3200 (NH), 2217 (CN), 1672 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 5.12 (s, 2H, OCH_2), 7.75–8.55 (m, 13H, Ar-H), 8.60–8.89 (m, 4H, Ar-H, pyridine 5-H, benzylidine H), 10.12 (s, 1H, NH, D_2O exchangeable), 10.40 (s, 1H, OH, D_2O exchangeable). MS *m/z* 532 (M^+, 35%). Anal. Calcd for $C_{31}H_{21}ClN_4O_3$: C, 69.86; H, 3.97; Cl, 6.65; N, 10.51. Found: C, 69.91; H, 3.90; Cl, 6.68; N, 10.48.

***N*'-[(4-Chlorophenyl)methylidene]-2-{[3-cyano-6-(2-naphthyl)-4-(2-thienyl)-2-pyridinyl]oxy}acetohydrazide (8c)**

Yield 60%; mp 270–271°C (DMF). IR (KBr) ν 3208 (NH), 2215 (CN), 1671 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 5.05 (s, 2H, OCH_2), 7.37–8.40 (m, 12H, Ar-H), 8.50–8.80 (m, 4H, Ar-H, pyridine 5-H, benzylidine H), 9.60 (s, 1H, NH, D_2O exchangeable). MS *m/z* 522 (M^+, 25%), 327 (100), 368 (40). Anal. Calcd for $C_{29}H_{19}ClN_4O_2S$: C, 66.60; H, 3.66; Cl, 6.78; N, 10.71; S, 6.13. Found: C, 66.76; H, 3.59; Cl, 6.75; N, 10.68; S, 6.10.

2-{[3-Cyano-6-(2-naphthyl)-4-(2-thienyl)-2-pyridinyl]oxy}-*N*'-[(4-hydroxyphenyl)methylidene]acetohydrazide (8d)

Yield 60%; mp 300–301 °C (DMF). IR (KBr) ν 3186 (OH), 3054 (NH), 2216 (CN), 1669 (C=O) cm^{-1}. ^1H NMR (DMSO-d_6) δ 5.17 (s, 2H, OCH_2), 7.30–8.45 (m, 12H, Ar-H), 8.60–8.87 (m, 4H, Ar-H, pyridine 5-H, benzylidine H), 9.96 (s, 1H, NH, D_2O exchangeable), 10.33 (s, 1H, OH, D_2O exchangeable). MS *m/z* 504 (M^+, 32%), 368 (95), 327 (100), 340 (90). Anal. Calcd for $C_{29}H_{20}N_4O_3S$: C, 69.03; H, 4.00; N, 11.10; S, 6.35. Found: C, 68.99; H, 4.00; N, 11.08; S, 6.39.

*General procedure for the synthesis of compounds **9c**,**d***

A mixture of compound **8a** or **8d** (0.01 mol) and equimolar amount of the thioglycolic acid (0.01 mol) in

dry benzene (30 mL) was refluxed for 10 h. After evaporation of the solvent under reduced pressure, the obtained product was filtered off and recrystallized from the DMF to give compounds **9c**,**d**.

***N*-[2-(4-Chlorophenyl)-4-oxo-1,3-thiazolidin-3-yl]-2-{[3-cyano-6-(2-naphthyl)-4-(2-thienyl)-2-pyridinyl]oxy}acetamide (9c)**

Yield 60%; mp 320–321 °C (DMF). IR (KBr) ν 3208 (NH), 2215 (CN), 1665 (C=O), 1671 (C=O) cm^{-1}. ^1H NMR (DMSO-d_6) δ 4.30 (s, 1H, thiazolidine), 5.10 (d, 2H, CH_2-thiazolidine), 5.60 (s, 2H, CH_2), 7.20–7.43 (m, 3H, Ar-H, pyridine 5-H), 7.65–8.35 (m, 11H, Ar-H), 8.90 (s, 1H, Ar-H), 10.80 (s, 1H, NH, D_2O exchangeable). MS *m/z* 596 (M^+, 66%). Anal. Calcd for $C_{31}H_{21}ClN_4O_3S_2$: C, 62.36; H, 3.54; Cl, 5.94; N, 9.38; S, 10.74. Found: C, 62.29; H, 3.59; Cl, 5.98; N, 9.33; S, 10.71.

2-{[3-Cyano-6-(2-naphthyl)-4-(2-thienyl)-2-pyridinyl]oxy}-*N*-[2-(4-hydroxyphenyl)-4-oxo-1,3-thiazolidin-3-yl]acetamide (9d)

Yield 65%; mp 300–301°C (DMF). IR (KBr) ν 3186 (OH), 3054 (NH), 2215 (CN), 1665 (C=O), 1671 (C=O) cm^{-1}. ^1H NMR (DMSO-d_6) δ 4.30 (s, 1H, thiazolidine), 5.10 (d, 2H, CH_2-thiazolidine), 5.60 (s, 2H, CH_2), 7.22–7.44 (m, 3H, Ar-H, pyridine 5-H), 7.65–8.35 (m, 11H, Ar-H), 8.91 (s, 1H, Ar-H), 10.80 (s, 1H, NH, D_2O exchangeable), 10.33 (s, 1H, OH, D_2O exchangeable). MS *m/z* 578 (M^+, 66%). Anal. Calcd for $C_{31}H_{22}N_4O_4S_2$: C, 64.35; H, 3.83; N, 9.68; S, 11.06. Found: C, 64.42; H, 3.88; N, 9.64; S, 11.00.

2-{[4-Acetyl-5-(4-chlorophenyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl]methoxy}-6-(2-naphthyl)-4-(2-thienyl)nicotinonitrile (10c)

A mixture of (0.005 mol) of compound **8c** and acetic anhydride (20 mL) was refluxed for 3 h. The excess acetic anhydride and acetic acid were removed in vacuo and the solid residue was filtered off, washed with water, dried and recrystallized from dioxane to give compound **10c.** Yield 40%; mp 201–202 °C (dioxane). IR (KBr) ν 2215 (CN), 1654 (C=O) cm^{-1}. ^1H NMR (DMSO-d_6) δ 2.15 (s, 3 H, CH_3), 5.12 (s, 2H, OCH_2), 5.08 (s, 1H, oxadiazole H), 7.75–8.53 (m, 15H, Ar-H). MS *m/z* 564 (M^+, 60%). Anal. Calcd for $C_{31}H_{21}ClN_4O_3S$: C, 65.90; H, 3.75; Cl, 6.27; N, 9.92; S, 5.67. Found: C, 66.00; H, 3.70; Cl, 7.30; N, 9.89; S, 6.62.

*General procedure for the synthesis of compounds **11a–c***

A mixture of compound **7a** (0.01 mol) and monosaccharides (D-glucose, D-galactose or arabinose (0.01 mol)) in ethanol (50 mL) and a catalytic amount of acetic acid was heated at 80 °C for 1 h. The precipitate formed was filtered off hot, washed with ethanol several times and dried to give compounds **11a–c**.

2-{[3-Cyano-6-(2-naphthyl)-4-(2-thienyl)-2-pyridinyl]oxy}-*N*'-(glucosylidene)acetohydrazide (11a)

Yield 65%; mp 210–211 °C (EtOH). IR (KBr) ν 3442–3320 (broad OH, NH), 2215 (CN), 1676 (C=O) cm^{-1}. ^1H NMR (DMSO-d_6) δ 5.00 (s, 2H, OCH_2), 3.00–3.80 (m, 4H, protons of alditol congregated with the water signals), 3.50–3.90 (m, 2H, CH_2OH), 4.30–4.50 (m, 2H, 2 × OH, D_2O exchangeable), 5.30–5.80 (m, 3H, 3 × OH, D_2O exchangeable), 7.30 (s, 1H, pyridine 5-H), 7.64 (d, *J* = 5.4 Hz, 1H, thiophene H), 7.93–8.55 (m, 8H, Ar-H, HC=N), 8.88 (m, 1H, thiophene H), 9.10 (s, 1H, Ar-H), 10.00 (s, 1H, NH, D_2O exchangeable). MS *m/z* 562 (M^+, 31%). Anal. Calcd for $C_{28}H_{26}N_4O_7S$: C, 59.78; H, 4.66; N, 9.96; S, 5.70. Found: C, 59.70; H, 4.60; N, 10.02; S, 5.72.

2-{[3-Cyano-6-(2-naphthyl)-4-(2-thienyl)-2-pyridinyl]oxy}-*N*'-(galactoylidene)acetohydrazide (11b)

Yield 65%; mp 210–211 °C (EtOH). IR (KBr) ν 3400–3300 (broad OH, NH), 2215 (CN), 1680 (C=O) cm^{-1}. ^1H NMR (DMSO-d_6) δ 3.30–3.80 (m, 4H, protons of alditol congregated with the water signals), 4.20–4.60 (m, 5H, 5 × OH, D_2O exchangeable), 5.10 (s, 2H, CH_2), 5.60–5.80 (m, 2H, 6'-H, 6''-H), 7.30 (s, 1H, pyridine 5-H), 7.65 (d, *J* = 5.4 Hz, 1H, thiophene H), 7.92–8.55 (m, 9H, Ar-H, HC=N), 9.00 (s, 1H, Ar-H), 11.40 (s, 1H, NH, D_2O exchangeable). MS *m/z* 562 (M^+, 45%). Anal. Calcd for $C_{28}H_{26}N_4O_7S$: C, 59.78; H, 4.66; N, 9.96; S, 5.70. Found: C, 59.82; H, 4.58; N, 10.01; S, 5.60.

2-{[3-Cyano-6-(2-naphthyl)-4-(2-thienyl)-2-pyridinyl]oxy}-*N*'-(arabinosylidene)acetohydrazide (11c)

Yield 65%; mp 220–221 °C (EtOH). IR (KBr) ν 3400–3300 (broad OH, NH), 2215 (CN), 1676 (C=O). ^1H NMR (DMSO-d_6): δ 3.35–3.80 (m, 3H of alditol), 4.40–4.80 (m, 4H, 4 × OH, D_2O exchangeable), 5.20 (s, 2H, OCH_2), 5.41 (m, 2H, 5'-H-, 5''-H), 7.38 (s, 1H, pyridine 5-H), 7.65 (d, *J* = 5.4 Hz, 1H, thiophene H), 8.00–8.40 (m, 9H, Ar-H, HC=N), 8.82 (s, 1H, Ar-H), 11.60 (s, 1H, NH, D_2O exchangeable). MS *m/z* 532 (M^+, 44%). Anal. Calcd for $C_{27}H_{24}N_4O_6S$: C, 60.89; H, 4.54; N, 10.52; S, 6.02. Found: C, 60.88; H, 4.55; N, 10.48; S, 6.08.

*General procedure for the synthesis of compounds **12a**,**b***

A mixture of compound **7a** or **7b** (0.01 mol), phenyl isothiocyanate (0.01 mol) and a catalytic amount of triethyl amine in dry benzene (20 mL) was refluxed for 7 h. The reaction mixture was concentrated and the precipitate formed was filtered off and recrystallized from the DMF to give compounds **12a**,**b**.

2-({[4-(4-Chlorophenyl)-3-cyano-6-(2-naphthyl)-2-pyridinyl]oxy}acetyl)-*N*-phenylhydrazinecarbothioamide (12a)

Yield 55%; mp 230–231 °C (DMF). IR (KBr) ν 3428, 3270 (2NH), 2211 (CN), 1652 (C=O), 1428 (C=S) cm^{-1}. ^1H NMR (DMSO-d_6) δ 4.19 (s, 1H, NH, D_2O exchangeable), 5.76 (s, 2H, CH_2), 7.10 (s, 1H, pyridine 5-H),

7.22 (d, J = 5.4 Hz, 1H, Ar-H), 7.32 (d, J = 5.4 Hz, 1H, Ar-H), 7.55–8.22 (m, 13H, Ar-H), 8.80 (s, 1H, Ar-H), 12.83 (s, 2H, 2 × NH, D_2O exchangeable). MS *m/z* 563 (M^+, 56%). Anal. Calcd for $C_{31}H_{22}ClN_5O_2S$: C, 66.01; H, 3.93; Cl, 6.29; N, 12.42; S, 5.68. Found: C, 66.15; H, 3.97; Cl, 6.33; N, 12.35; S, 5.60.

2-({[3-Cyano-6-(2-naphthyl)-4-(2-thienyl)-2-pyridinyl]oxy}acetyl)-*N*-phenylhydrazinecarbothioamide (12b)

Yield 66%; mp 340–341 °C (DMF). IR (KBr) ν 3428, 3270 (2NH), 2211 (CN), 1652 (C=O), 1428 (C=S) cm^{-1}. ^1H NMR (DMSO-d_6) δ 4.19 (s, 1H, NH, D_2O exchangeable), 5.76 (s, 2H, CH_2), 7.10 (s, 1H, pyridine 5-H), 7.23 (d, J = 5.4 Hz, 1H, Ar-H), 7.35 (d, J = 5.4 Hz, 1H, Ar-H), 7.58–8.25 (m, 12H, Ar-H), 8.84 (s, 1H, Ar-H), 12.83 (s, 1H, NH, D_2O exchangeable). MS *m/z* 535 (M^+, 66%), 328 (100), 339 (25). Anal. Calcd for $C_{29}H_{21}N_5O_2S_2$: C, 65.03; H, 3.95; N, 13.07; S, 11.97. Found: C, 65.14; H, 3.88; N, 13.00; S, 11.99.

*General procedure for the synthesis of compounds **13a,b***

A mixture of compound **12a** or **12b** (0.01 mol) and chloroacetic acid (0.01 mol) in ethanol (30 mL) was refluxed for 7 h. The reaction mixture was concentrated and the precipitate formed was filtered off and recrystallized from the DMF to give compounds **13a**,**b**.

2-{[4-(4-Chlorophenyl)-3-cyano-6-(2-naphthyl)-2-pyridinyl]oxy}-*N*-[4-oxo-2-(phenylimino)-1,3-thiazolidin-3-yl]acetamide (13a)

Yield 66%; mp 250–251 °C (DMF). IR (KBr) ν 3300, 3200 (NH), 2220 (CN), 1720, 1685 (2C=O) cm^{-1}. ^1H NMR (DMSO-d_6) δ 2.57 (s, 2H, methylene H), 5.35 (s, 2H, OCH_2), 7.10 (s, 1H, pyridine 5-H), 7.20–8.26 (m, 15H, Ar-H), 8.88 (s, 1H, Ar-H), 10.80 (s, 1H, NH, D_2O exchangeable). MS *m/z* 603 (M^+, 66%), 328 (100), 339 (25). Anal. Calcd for $C_{33}H_{22}ClN_5O_3S$: C, 65.61; H, 3.67; Cl, 5.87; N, 11.59; S, 5.31. Found: C, 65.55; H, 3.60; Cl, 5.95; N, 11.62; S, 5.34.

2-{[3-Cyano-6-(2-naphthyl)-4-(2-thienyl)-2-pyridinyl]oxy}-*N*-[4-oxo-2-(phenylimino)-1,3-thiazolidin-3-yl]acetamide (13b)

Yield 66%; mp 270–271 °C (DMF). IR (KBr) ν 3300, 3200 (NH), 2220 (CN), 1720, 1685 (2C=O) cm^{-1}. ^1H NMR (DMSO-d_6) δ 2.63 (s, 2H, methylene H), 5.35 (s, 2H, OCH_2), 7.20 (s, 1H, pyridine 5-H), 7.25–8.36 (m, 14H, Ar-H), 8.80 (s, 1H, Ar-H), 10.81 (s, 1H, NH, D_2O exchangeable). MS *m/z* 575 (M^+, 46%), 328 (100), 339 (25). Anal. Calcd for $C_{31}H_{21}N_5O_3S_2$: C, 64.68; H, 3.68; N, 12.17; S, 11.14. Found: C, 64.74; H, 3.70; N, 12.12; S, 11.10.

2-[2-(3,5-Dimethyl-1*H*-pyrazol-1-yl)-2-oxoethoxy]-6-(2-naphthyl)-4-(2-thienyl)nicotinonitrile (14b)

A mixture of compound **7b** (0.01 mol) and acetyl acetone (0.03 mol) in absolute ethanol (20 mL) was refluxed for 12 h. The reaction mixture was concentrated and the precipitate formed was filtered off and recrystallized from the DMF to give compound **14b**. Yield 66%; mp 190–191 °C (DMF). IR (KBr) ν 3431 (OH), 2213 (CN), 1665 (C=O) cm^{-1}. ^1H NMR (DMSO-d_6) δ 1.74 (s, 3H, CH_3), 2.09 (s, 3H, CH_3), 6.57 (s, 1H, OH, D_2O exchangeable), 7.36 (s, 1H, pyridine 5-H), 7.55 (s, 1H, pyrazole H), 7.64–8.33 (m, 10H, Ar-H, C=CH-O), 8.75 (s, 1H, Ar-H). MS *m/z* 464 (M^+, 46%). Anal. Calcd for $C_{27}H_{20}N_4O_2S$: C, 69.81; H, 4.34; N, 12.06; S, 6.89. Found: C, 69.80; H, 4.21; N, 12.00; S, 6.83.

*General procedure for the synthesis of compounds **15a–d***

A solution of compound **7a** or **7b** (0.01 mol) in acetic acid and/or formic acid (20 mL) was refluxed for 7 h. The precipitate formed was filtered off and recrystallized from the DMF to give compounds **15a**–**d**.

4-(4-Chlorophenyl)-6-(2-naphthyl)-2-(1,3,4-oxadiazolidin-2-ylmethoxy)nicotinonitrile (15a)

Yield 66%; mp 260–261 °C (DMF). IR (KBr) ν 3167 (NH), 2216 (CN) cm^{-1}. ^1H NMR (DMSO-d_6) δ 5.06 (s, 1H, CH), 5.23 (s, 2H, CH_2), 5.43 (s, 2H, CH_2), 7.21 (s, 1H, pyridine 5-H), 7.57–8.88 (m, 11H, Ar-H), 10.20 (s, 1H, NH, D_2O exchangeable), 10.57 (s, 1H, NH, D_2O exchangeable). MS *m/z* 442 (M^+, 85%). Anal. Calcd for $C_{25}H_{19}ClN_4O_2$: C, 67.80; H, 4.32; Cl, 8.00; N, 12.65. Found: C, 67.74; H, 4.29; Cl, 8.05; N, 12.71.

4-(4-Chlorophenyl)-2-[(5-methyl-1,3,4-oxadiazolidin-2-yl)methoxy]-6-(2-naphthyl)nicotinonitrile (15b)

Yield 69%; mp 290–291 °C (DMF). IR (KBr) ν 3181 (NH), 2217 (CN) cm^{-1}. ^1H NMR (DMSO-d_6) δ 1.90 (s, 3H, CH_3), 5.05 (s, 1H, CH), 5.15 (s, 1H, CH), 5.23 (s, 2H, CH_2), 7.23 (s, 1H, pyridine 5-H), 7.37–8.89 (m, 11H, Ar-H), 9.97 (s, 1H, NH, D_2O exchangeable), 10.35 (s, 1H, NH, D_2O exchangeable). MS *m/z* 456 (M^+, 72%). Anal. Calcd for $C_{26}H_{21}ClN_4O_2$: C, 68.34; H, 4.63; Cl, 7.76; N, 12.26. Found: C, 68.42; H, 4.58; Cl, 7.80; N, 12.20.

6-(2-Naphthyl)-2-(1,3,4-oxadiazolidin-2-ylmethoxy)-4-(2-thienyl)nicotinonitrile (15c)

Yield 66%; mp 240–241°C (DMF). IR (KBr) ν 3177 (NH), 2215 (CN) cm^{-1}. ^1H NMR (DMSO-d_6) δ 5.05 (s, 1H, CH), 5.24 (s, 2H, CH_2), 5.18 (s, 2H, CH_2), 7.24 (s, 1H, pyridine 5-H), 7.38–8.88 (m, 10H, Ar-H), 10.20 (s, 1H, NH, D_2O exchangeable), 10.56 (s, 1H, NH, D_2O exchangeable). MS *m/z* 414 (M^+, 85%), 340 (55), 325 (50). Anal. Calcd for $C_{23}H_{18}N_4O_2S$: C, 66.65; H, 4.38; N, 13.52; S, 7.73. Found: C, 66.90; H, 4.16; N, 13.49; S, 7.68.

2-[(5-Methyl-1,3,4-oxadiazolidin-2-yl)methoxy]-6-(2-naphthyl)-4-(2-thienyl)nicotinonitrile (15d)

Yield 69%; mp 280–281 °C (DMF). IR (KBr) ν 3190 (NH), 2215 (CN) cm^{-1}. ^1H NMR (DMSO-d_6) δ 1.88 (s, 3H, CH_3), 5.05 (s, 1H, CH), 5.15 (s, 1H, CH), 5.18 (s, 2H, CH_2), 7.21 (s, 1H, pyridine 5-H), 7.38–8.90 (m, 10H, Ar-H), 9.95 (s, 1H, NH, D_2O exchangeable), 10.32 (s, 1H, NH, D_2O exchangeable). MS *m/z* 428 (M^+, 62%). Anal. Calcd for $C_{24}H_{20}N_4O_2S$: C, 67.27; H, 4.70; N, 13.07; S, 7.47. Found: C, 67.22; H, 4.73; N, 12.95; S, 7.39.

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Povzetek

Sintetizirali smo nove diaril-3-ciano-1*H*-piridinonske derivate **2a**–**c**. Pri reakciji s fosforjevim oksikloridom so iz njih nastali klorovi derivati **3b**,**c**. Piridinski derivat **2a** smo uporabili za pripravo tienopiridinskega derivata **4a**. Spojini **2b**,**c** smo glikozidirali z 2,3,4,6-tetra-*O*-acetil-α-glukopiranozil bromidom (α-ABG) pri čemer so nastali ustrezni nukleozidi **5b**,**c**. Iz spojin **2a**,**b** sta z etil kloroacetatom nastala *O*-etil glikolatna derivata **6a**,**b**. Spojini **6a**,**b** sta ob obdelavi s hidrazin hidratom dali hidrazinska derivata **7a**,**b** ki sta z ustreznim aldehidom kondenzirala do arilmetilenskih hidrazonov **8a**–**d**. Ti so s tioglikolno kislino v acetanhidridu ciklizirali v spojine **9c**,**d** in **10c**. Z reakcijo hidrazida **7b** z nekaterimi monosaharidi so nastali hidrazonski derivati **11a**–**c**. Raziskali smo tudi obna{anje spojin **7a**,**b** ob prisotnosti fenil izotiocianata ter tako pripravili spojini **12a**,**b**, ki sta s kloroocetno kislino kondenzirali v spojini **13a**,**b**. Spojino **14b** smo pripravili z reakcijo z acetilacetonom. Spojini **7a**,**b** sta reagirali z alifatskima kislinama (mravljična in ocetna kislina) do spojin **15a**–**d**. Nekateri novi produkti so pokazali močno aktivnost proti rakastim celicam in mikrobom.