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Microwave-assisted synthesis and transformations of sterically hindered 3-(5-tetrazolyl)pyridines

Sergey M. Lukyanov,[a,*] Igor V. Bliznets,[b] Sergey V. Shorshnev,[a] Grigory G. Aleksandrov,[a] Aleksandr E. Stepanov[b] and Andrei A. Vasil'ev[c]

[a]*ChemBridge Corporation, Malaya Pirogovskaya 1, 119435 Moscow, Russian Federation*
[b]*M.V. Lomonosov Moscow State Academy of Fine Chemical Technology, Malaya Pirogovskaya 1, 119435 Moscow, Russian Federation*
[c]*N.D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, Leninsky pr. 47, 119991 Moscow, Russian Federation*

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Abstract—Sterically hindered 2,4-disubstituted 3-(5-tetrazolyl)pyridines were synthesized from corresponding nicotinonitriles using microwave technology. 2-Methylnicotinonitriles were converted into the 2-azidomethyl-3-cyanopyridines via 2-hydroxymethyl and 2-chloromethyl derivatives. Intramolecular [3+2] cycloaddition of an heteroaromatic cyano group to side azido group was carried out to form a novel heterocyclic system containing a (tetrazolo)azaisoindole unit. Condensation of the 2-methylnicotinonitriles and aldehydes gave rise to the corresponding 2-vinyl derivatives, which were then transformed into novel heterocyclic system (5,6-dihydrotetrazolo[5,1-*f*]-1,6-naphthyridine) by intramolecular N-alkylation reaction of tetrazole ring with olefinic fragment. The 3-(5-tetrazolyl)pyridines obtained were alkylated to give the various *N*- and *C*-benzyl derivatives as well as acylated to afford the 3-(1,3,4-oxadiazol-2-yl)pyridines in good yields. A majority of above-mentioned reactions was carried out under microwave irradiation.

1. Introduction

For a long time 3-(5-tetrazolyl)pyridine **1** and its derivatives have been of particular interest to the chemists because of the interesting pharmacological activity of these compounds[1–5] (Scheme 1). For example, some 3-(5-tetrazolyl)pyridines, substituted in the pyridine moiety, were described as potential lipolysis inhibitors similar to nicotinic acid, but of greater metabolic stability.[2,3,6] Indeed, tetrazole ring is well known as a bioisosteric substitute for the carboxylic group in many biologically active molecules,[7] since they both possess comparable acidity and size[2,3,8] (see also review[9]). On the other hand, related biphenyl derivatives **2** bearing a sterically hindered *ortho*-tetrazole group have been described recently as novel angiotensin II receptor antagonists.[10–12]

In this context, it would be interesting to synthesize a series of 3-(5-tetrazolyl)pyridines with substituents at both positions adjacent to the tetrazole unit such as 2-alkyl-4-aryl-3-(5-tetrazolyl)pyridines **3** as well as other similar compounds **4** where X is bulk aliphatic group, and Y is alkyl or (FG)–CH_2 (FG=functional group) (Scheme 1). These compounds **3**, **4** could be core structures for some combinatorial libraries based on the nicotinic acid derivatives such as nicotinonitriles.

We reported in our preliminary communication[13] that the corresponding nicotinonitriles **5a–c** (Scheme 2) prepared by the literature method[14] were used as starting materials for syntheses under three different conditions: (a) NaN_3, AcOH, *n*-BuOH;[1] (b) NaN_3, $ZnBr_2$, H_2O;[4,15] (c) Me_3SiN_3, Bu_2SnO, toluene.[11,16] However, only compound **3** (R=H) was obtained from nitrile **5a** in moderate yield using trimethylsilyl azide and dibutyltin oxide (conditions c, 100 °C, 72 h). All attempts to obtain the desired tetrazoles from nitriles **5b**,**c** were ineffective under above-named conditions. It should be noted that these results turned out not surprising for us since many reactions of nitrile group are very susceptible to sterical hindrances (e.g., Pinner reaction). Poor yields of tetrazoles from *ortho*-substituted benzonitriles were also reported.[10,11]

We have found[13] that the sterically hindered 3-(5-tetrazolyl)pyridines **3**, **4** can be successfully synthesized using microwave technology (MW) (see footnote below in Section 4.3.5.3). At that time a synthesis of tetrazoles from some simplest model nitriles under microwave irradiation was described in only one paper.[17] Another investigation on

Keywords: Nicotinic acid; Nicotinonitriles; Tetrazolyl derivatives; 1,3,4-Oxadiazoles; Intramolecular cycloaddition; Fused tetrazoles; Microwave irradiation.
* Corresponding author. Tel.: +7 95 775 06 54; fax: +7 95 956 49 48; e-mail: semiluk@chembridge.ru

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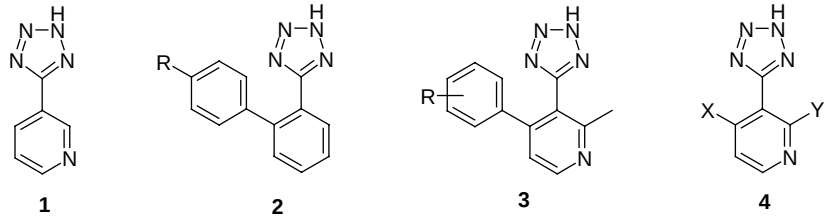
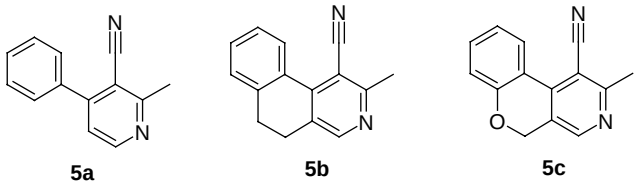


Scheme 1.

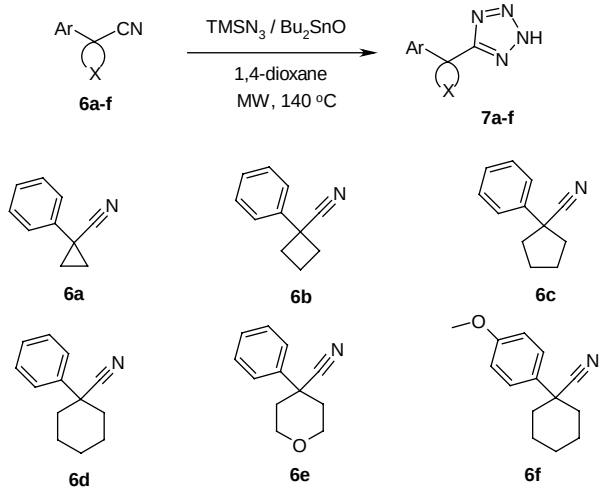


Scheme 2.

the same subject was reported[18] concurrently and independently of our preliminary communication.[13] Now, we describe in more detail not only the synthesis but also transformations of 2,4-disubstituted 3-(5-tetrazolyl)pyridines carried out under microwave irradiation.

2. Results and discussion

Initially, we investigated the reactions of nicotinonitriles **5a–c** as well as a series of model sterically hindered aliphatic nitriles **6a–f** (Scheme 3) under above-mentioned conditions (a–c) using Milestone Ethos SYNTH and CEM Discover microwave labstations. We quickly discovered that an application of NaN_3 was unsuitable for microwave-assisted reactions because of both toxic and explosion risk (conditions a, acid promoted HN_3 liberation) as well as a considerable hydrolysis of the starting nitriles to amides in the presence of water (conditions b). At the same time the reagent system $TMSN_3/Bu_2SnO$ (conditions c) was found to be best with respect to the reproducibility and ease of handling. It should be noted that 1,4-dioxane was used instead of toluene for this reagent system as the solvent more suitable for microwave conditions.



Scheme 3. Synthesis of model tetrazoles **7a–f**.

The optimal reaction conditions were initially determined using the model nitriles **6a–f**. We found that the yields of target products **7a–f** depended considerably on the ratio of reactants, and the optimal molar ratio being 'nitrile/Bu_2SnO/$TMSN_3$ = 1:0.3:4'. The results of the model experiments are presented in Table 1. It is seen that the yields of tetrazoles **7a–f** decreased gradually along with the growth of the carbocycle size. The unreacted nitriles **6a–f** can be isolated from the reaction mixtures; therefore, the yields coincided practically with the conversion of the starting reactants. The yields can be also improved upon by a prolongation of microwave irradiation as well as by an increasing of Bu_2SnO content (entries 5, 8).

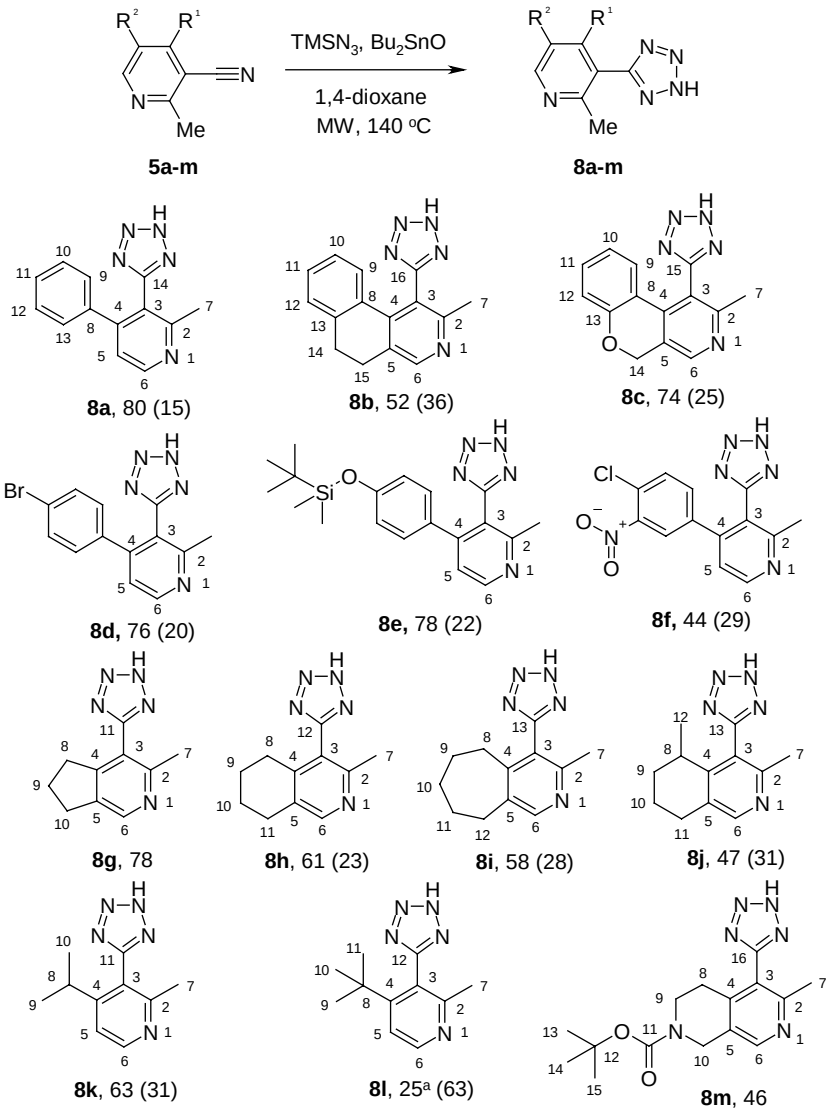
Table 1. Conditions and yields of model tetrazoles **7a–f**

Entry	**6**,**7**	Ar	X	Time (h)	Yield **7** (%)
1	**a**	Ph	$-(CH_2)_2-$	3	100
2	**b**	Ph	$-(CH_2)_3-$	3	90
3	**c**	Ph	$-(CH_2)_4-$	5	84
4	**d**	Ph	$-(CH_2)_5-$	7	38
5	**d**	Ph	$-(CH_2)_5-$	8	89[a]
6	**e**	Ph	$-(CH_2)_2O(CH_2)_2-$	5	83
7	**f**	*p*-$CH_3OC_6H_4$	$-(CH_2)_5-$	9	63
8	**f**	*p*-$CH_3OC_6H_4$	$-(CH_2)_5-$	8	85[a]

[a] Bu_2SnO (1 equiv) used.

These reaction conditions were applied in the preparation of the 2,4-disubstituted 3-(5-tetrazolyl)pyridines **8a–m** from the corresponding nicotinonitriles **5a–m** (Schemes 4 and 5). All the experiments were carried out at 140 °C for 8 h (but only for 4 h at 120 °C for **8m** because of partial thermal deprotection as well as at 110 °C for **8f** owing to resinification).

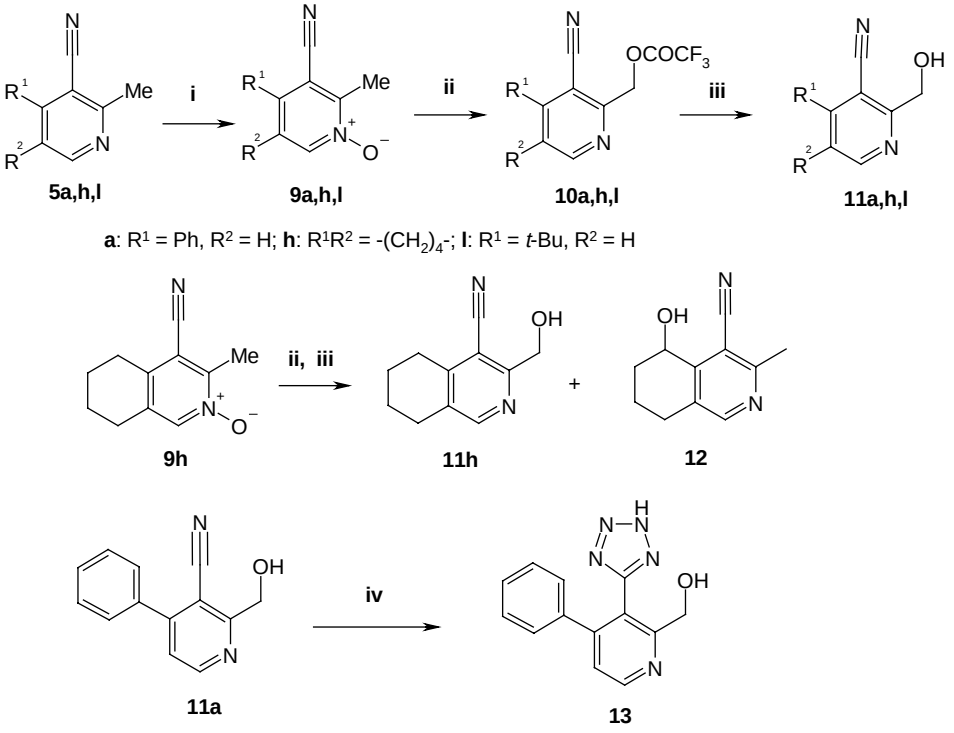
That the 3-(5-tetrazolyl)pyridines **8a–m** obtained may serve as core structures for combinatorial libraries, they should contain two or more functional groups as derivatization points. These groups can be positioned in 4-aryl substituent (e.g., structures **8d–f**) and/or in alkyl (cycloalkyl) group (e.g., structure **8m**). To achieve more diversity and enhance the synthetical potential of the system, it could be of interest to introduce an aliphatic functional group into the core structures. One of these possibilities was a functionalization of the 2-methyl group at pyridine nucleus. It seemed promising to transform the 2-methyl group prior to constructing a tetrazole ring. Therefore, we have chosen a pathway for the functionalization of nicotinonitriles **5**. As we reported in our preliminary communication[19] this functionalisation involved the well-known rearrangement[20] of pyridine *N*-oxides **9a**,**h**,**l** under acylation conditions as a key step. The use of hydrogen peroxide followed by trifluoroacetic anhydride gave rise to labile trifluoroacetates **10a**,**h**,**l** that were converted very



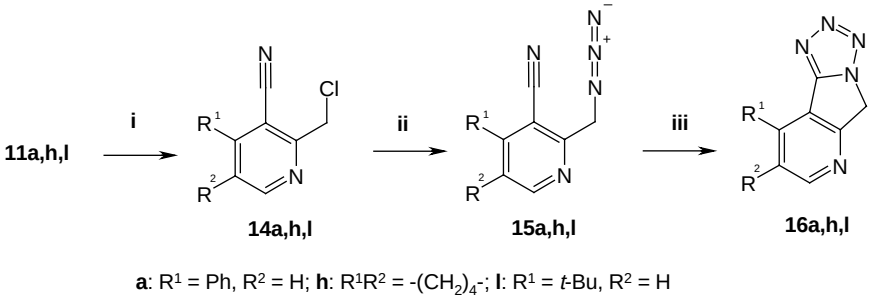
Scheme 4. 3-(5-Tetrazolyl)pyridines **8a**–**m**, yields (%) and recovered starting nitriles (%, in brackets). [a] 1 equiv of Bu_2SnO used.

smoothly into alcohols **11a**,**h**,**l** by treatment with methanol. It should be noted that two isomeric alcohols **11h** and **12** were obtained from the pyridine *N*-oxide **9h** in yields of 23 and 31%, respectively (Scheme 5). Such introduction of a hydroxy group into a 4-alkyl substituent at a pyridine ring has been reported previously.[21] At last, this pathway was successfully accomplished by straightforward conversion of the alcohol **11a** into 2-hydroxymethyl-3-(5-tetrazolyl)pyridine **13** under microwave irradiation (Scheme 5). It is of note that no protection of hydroxyl group was required for this transformation.

Further to this result we carried out an intramolecular reaction between aromatic cyano and side azido groups (Scheme 6). The corresponding 2-azidomethyl-3-cyanopyridines **15a**,**h**,**l** were prepared in two steps from the 2-hydroxymethyl derivatives **11a**,**h**,**l**. Treatment of alcohols **11a**,**h**,**l** with mesyl chloride gave rather the desired 2-chloromethylated intermediates **14a**,**h**,**l** than mesylates. Then 2-azidomethyl-3-cyanopyridines **15a**,**h**,**l** obtained from chlorides were cyclized on heating in the toluene solution at 130–140 °C. It is significant to note that a flexibility of the azidomethyl group is very important for this intramolecular cycloaddition. Therefore, only the azidomethylated intermediate **15h** obtained from compound **11h** underwent smooth cyclization to give the tetracyclic product **16h**. However, no reaction between the fixed cyano and azido groups in azidomethylated isomer prepared from the intermediate **12** occurred under various conditions (heating in sealed tube for several days in toluene at 160 °C or microwave irradiation for 4 h at 150 °C). This result is in accordance with literature data concerning a significance of positional relationship of a nitrile and an azido group for the thermal intramolecular [3+2] cycloaddition. It was reported that the tetrazoles formed under these conditions can be fused only to five- or six-membered ring systems but not to seven-membered cycles.[22] Very few examples of the similar intramolecular tetrazole formation were described in literature. In the most of cases aliphatic[23] and heteroatom-substituted nitriles (cyanates, thiocyanates, cyanamides)[15,22] were used in such cycloaddition while only one example with aromatic nitrile was reported.[24] To the best of our knowledge, such intramolecular cycloaddition in a heterocyclic series was unprecedented.



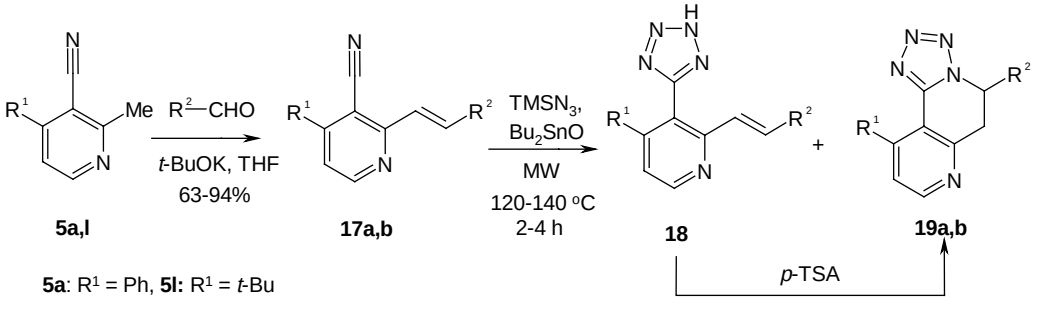
Scheme 5. Functionalization of methyl group in 2-methyl-3-cyanopyridines **5a**,**h**,**l**. Reagents and conditions: (i) H_2O_2, AcOH, 70 °C; (ii) $(CF_3CO)_2O$, CH_2Cl_2, 40 °C; (iii) MeOH, rt; (iv) Me_3SiN_3, Bu_2SnO, dioxane, MW, 140 °C.



Scheme 6. Reaction pathway to tricyclic tetrazolylpyridine system **16a**,**h**,**l**. Reagents and conditions: (i) MsCl, TEA, CH_2Cl_2, rt; (ii) NaN_3, DMSO, rt; (iii) PhMe, MW, 120–140 °C.

It should be noted that the compounds **16a**,**h**,**l** are the first representatives of novel heterocyclic (tetrazolo)azaisoindole system that were initially obtained in our laboratory by refluxing of intermediates **15a**,**h**,**l** in toluene for 90–120 h.[19] More recently we have found that this intramolecular [3+2] cycloaddition can be carried out under microwave irradiation, and the reaction occurred at the same temperature (130–140 °C) for 2–4 h to afford the products **16a**,**l** in yields 80–99%.

The reaction of nicotinonitriles **5** with aldehydes in the presence of potassium *tert*-butoxide was found as another possibility to functionalize the 2-methyl substituent (Scheme 7). The interaction resulted in 2-vinyl derivatives



Scheme 7. Reaction pathway to tricyclic tetrahydro(tetrazolo)naphthyridine system **19a**,**b**.

17a,**b** that were then subjected to tetrazole ring formation from 3-cyano group. The reaction of intermediate **17a** (R^1 = Ph, R^2 = *t*-Bu) under microwave irradiation (140 °C, 2 h) afforded a mixture of two products **18** and **19a** in yields 22 and 52%, respectively. The structure of the tricyclic product **19a** was unequivocally confirmed by X-ray crystallographic analysis (Fig. 1) and manifested an intramolecular N-alkylation of tetrazole moiety with olefinic fragment. There are some reports in literature about similar intermolecular N-alkylation in the presence of strong acids (to convert the olefins into carbocations).[25] Indeed, we succeeded to convert the 2-(3,3-dimethylbut-1-enyl)-3-(5-tetrazolyl)-4-phenylpyridine **18** into the product **19a** using *para*-toluenesulfonic acid. The analogous reaction of the isomeric 2-styryl derivative **17b** (R^1 = *t*-Bu, R^2 = Ph; MW, 140 °C, 4 h) gave the tricyclic product **19b** directly in yield 68%. Therefore, we are inclined to believe that we found a first example of an intramolecular N-alkylation of tetrazoles with olefins under neutral conditions. Further, the obtained 5,6-dihydrotetrazolo[5,1-*f*]-1,6-naphthyridines **19a**,**b** are the representatives of another novel heterocyclic system that could serve not only as a core structure for combinatorial libraries but also as an interesting subject for further investigation.

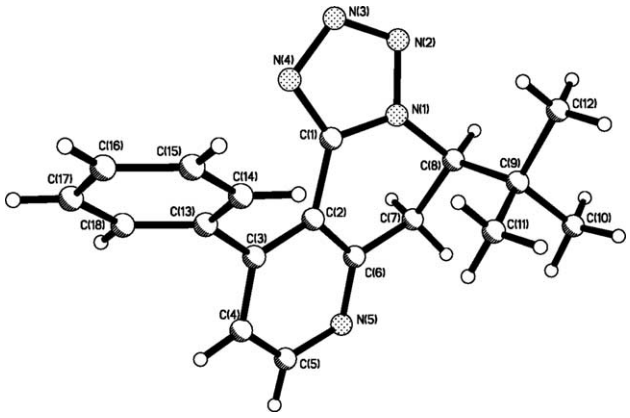


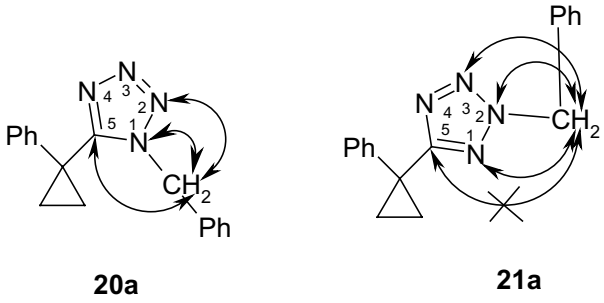
Figure 1. X-ray crystal structure of compound **19a**.

A diversity of above-mentioned potential combinatorial libraries can be extended also by a modification of the tetrazole fragment as such, for example, an alkylation in the presence of bases. This alkylation can yield both 1-alkyl and 2-alkyl substituted tetrazoles.[26] To determine a behavior of sterically hindered tetrazoles in this process, we carried out N-alkylation of the model tetrazoles **7a**–**e** using benzyl bromide as test alkylating reagent (Scheme 8). The yields of isomeric products **20**, **21** are presented in Table 2.

Table 2. Yields of alkylation products **20**, **21**

Entry	**7**, **20**, **21**	X	Yield **20** (%)	Yield **21** (%)
1	**a**	$-(CH_2)_2-$	37	47
2	**b**	$-(CH_2)_3-$	33	58
3	**c**	$-(CH_2)_4-$	23	72
4	**d**	$-(CH_2)_5-$	20	79
5	**e**	$-(CH_2)_2O(CH_2)_2-$	11	79

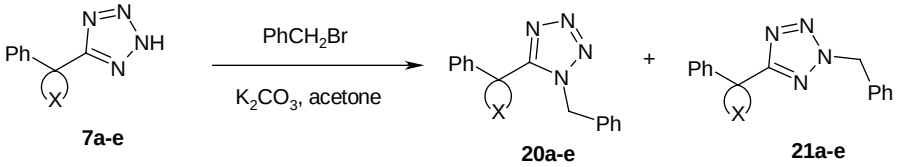
The structures of the isomers **20a** and **21a** were determined by the assignment of the ^1H and ^{13}C NMR spectra involving ^1H ^{13}C HSQC, HMBC and ^1H ^{15}N HMBC experiments. The position of benzyl group at N(1) atom in compound **20a** was established by the cross-peak in the proton-carbon 2D-HMBC spectrum between *N*-methylene protons and C(5) atom of tetrazole ring (Scheme 9). Such cross-peak resulted from a coupling ^3J of these atoms through three bonds. Besides, two cross-peaks were found in the proton-nitrogen 2D-HMBC spectrum resulted from the coupling constants ^2J and ^3J of *N*-methylene protons and the nitrogen nuclei N(1) and N(2) (Scheme 9).



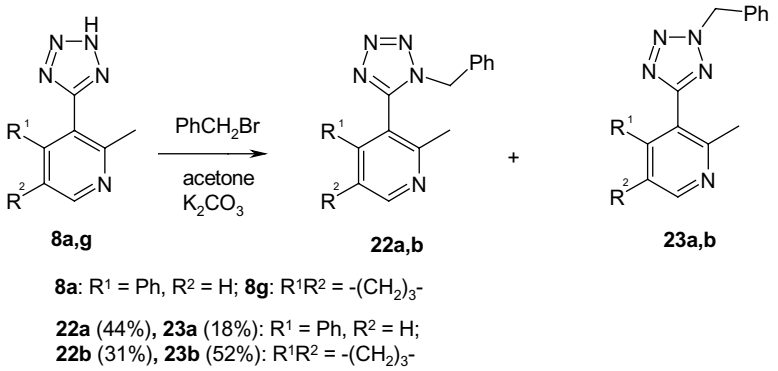
Scheme 9. The proton-carbon and proton-nitrogen couplings in structures **20a** and **21a**.

As regards the compound **21a**, no cross-peak between *N*-methylene protons and C(5) atom of tetrazole ring through four bonds was observed in the ^1H ^{13}C 2D-HMBC spectrum. At the same time three cross-peaks were registered in the ^1H ^{15}N 2D-HMBC spectrum resulted from a coupling of *N*-methylene protons with three nitrogen nuclei N(1), N(2), and N(3) (Scheme 9). These facts indicate the position of benzyl group at N(2) atom of tetrazole moiety.

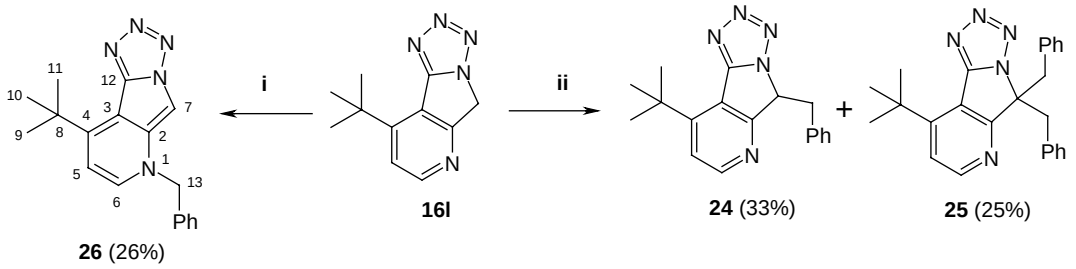
Besides, it should be noted that the signal of the *N*-methylene (i.e., benzylic) protons in ^1H NMR spectrum of compound **21a** was characterized by a low-field chemical shift (δ 5.83 ppm) in comparison with that for compound



Scheme 8. N-Alkylation of model tetrazoles **7a**–**e**.



Scheme 10. N-Alkylation of 3-(5-tetrazolyl)pyridines **8a**,**g**.



Scheme 11. Alkylation of tricyclic compound **16l**. Reagents and conditions: (i) $PhCH_2Br$, acetone, 65 °C, 80 h, then aqueous $NaHCO_3$; (ii) *t*-BuOK, THF, then $PhCH_2Br$.

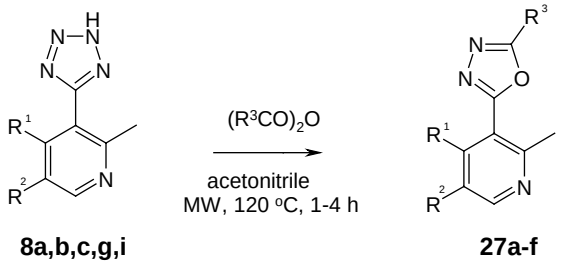
20a (δ 5.38 ppm). Therefore, we distinguished other pairs of isomers **20b**–**e** and **21b**–**e** using this feature of the corresponding ^{1}H NMR spectra.

It is obvious from Table 2 that the N-alkylation of tetrazoles occurred with good yields of products but a fraction of 2-alkylated derivatives **21a**–**e** increased as a carbocycle enlarged. An analogous N-alkylation of the 3-(5-tetrazolyl)pyridines **8a**,**g** gave rise also to mixtures of isomeric products **22a**,**b** and **23a**,**b** (Scheme 10). The structures of the isomers **22a** and **23a** were also determined by the assignment of the ^{1}H and ^{13}C NMR spectra involving ^{1}H ^{13}C HSQC, HMBC and ^{1}H ^{15}N HMBC experiments. The same proton-carbon and proton-nitrogen couplings were registered in the corresponding spectra. It is noteworthy that the signals of benzylic protons in ^{1}H NMR spectra of 2-benzylated isomers **23a**,**b** appeared again as the low-field singlets while the same protons in 1-benzylated compounds **22a**,**b** gave the pairs of high-field doublet signals.

The isomeric *N*-alkylated tetrazoles **20**, **21** as well as **22**, **23** can be effectively separated by column chromatography, with the 2-alkyl derivatives migrating quicker than their 1-isomers.

We have found that the tricyclic compound **16l** can be also subjected to alkylation (Scheme 11). A treatment with benzyl bromide in the presence of potassium *tert*-butoxide in THF resulted in a separable mixture of *C*-benzyl **24** and *C*,*C*-dibenzyl derivative **25**. Alternatively, refluxing of tricyclic compound **16l** with benzyl bromide in acetone followed by treatment with aqueous $NaHCO_3$ afforded a bright red N-alkylation product **26**. The structure **26** was established with the help of ^{1}H and ^{13}C NMR spectra involving HSQC and HMBC experiments.

Finally, tetrazoles can be recyclized into 1,3,4-oxadiazoles by action of acylating reagents.[27] We carried out an acylation of 3-(5-tetrazolyl)pyridines **8a**,**b**,**c**,**g**,**i** with a series of carboxylic anhydrides and obtained the corresponding 3-(1,3,4-oxadiazol-2-yl)pyridines **27a**–**f** in good to excellent yields (Scheme 12) (Table 3). It should be emphasized that this rearrangement under conventional conditions (refluxing in toluene) turned out extremely slow (more than 100 h) and resulted in complicated mixtures of products, and the target 3-(1,3,4-oxadiazol-2-yl)pyridines were isolated from these mixtures in poor yields. However, an application of microwave irradiation and acetonitrile as solvent allowed reduction of the reaction time up to 1–4 h and dramatically increase the yields. To our knowledge, it is a first example of such recyclization under microwave irradiation.



Scheme 12. Recyclization of 3-(5-tetrazolyl)pyridines **8** upon acylation.

Table 3. Yields of 3-(1,3,4-oxadiazol-2-yl)pyridines **27a–f**

8	27	R^1	R^2	R^3	Yield (%)
a	**a**	Ph	H	Me	95
a	**b**	Ph	H	CF_3	100
b	**c**	-*o*-C_6H_4–$(CH_2)_2$–		*t*-Bu	96
c	**d**	*o*-C_6H_4–OCH_2–		$MeO(CH_2)_2$	80
g	**e**	–$(CH_2)_3$–		*i*-Pr	99
i	**f**	–$(CH_2)_5$–		4-Cl–C_6H_4	68

3. Conclusion

In summary, we revealed some possibilities to convert a series of readily available sterically hindered nitriles into the corresponding tetrazole derivatives, including the fused polycyclic systems, using microwave technology. Besides, it was found that the 3-(5-tetrazolyl)pyridines can be derivatized by alkylation and acylation reactions to give a wide variety of nicotinic acid analogs that could constitute a basis for a potential combinatorial library. This library containing 222 compounds was tested by the computer software PASS (prediction of activity spectra for substances).[28] This program illustrates the predicted activity spectrum of a compound as probability of activity (P_a) and probability of inactivity (P_i). For example, it was predicted by the PASS that the tricyclic system **16** can possess an antineurotoxic activity for in all the tested examples with P_a more than 80% as well as all the 3-(5-tetrazolyl)pyridines **8** can be a 5-hydroxytriptamine release inhibitors with P_a more than 70%. Our further investigations will be directed to the synthesis of the compounds with the potential activity predicted, and then to a pharmacological evaluation of the latter.

4. Experimental

4.1. General

Milestone Ethos SYNTH (reactors MPR 600/12S and PRO-24) and CEM Discover microwave labstations (both operating at 2450 MHz under continuous internal temperature control) were used for the experimental and scale-up reactions. Melting points were determined by open glass capillary method and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker Avance DRX 400 (400 MHz) spectrometer equipped with a 5 mm inverse multinuclear gradient probehead in DMSO-d_6 or $CDCl_3$. ^{13}C NMR spectra were recorded on the same instrument at 100 MHz using DMSO-d_6 as solvent. The assignments of signals in ^{1}H and ^{13}C NMR spectra were performed using HSQC and HMBC experiments. Mass spectra were run by electron impact at 70 eV on a Kratos MS-30 spectrometer or by chemical ionization (LCMS) on an 1100 LCMSD (Agilent Technologies) instrument with ELSD (PL-ELS-1000) detector. IR spectra were measured on an EQUINOX 55 Bruker spectrometer. Elemental analyses were carried out in CARLO-ERBA 1106 and 1500 automatic elemental analyzers. Single-crystal X-ray diffraction data were measured using an Enraf-Nonius Cad-4 diffractometer (graphite-monochromated λMo Kα radiation, λ= 0.71073 Å) and processed using the SHELX97 package.[29] The reactions were monitored by TLC (aluminium sheets, silica gel 60 F_{254}, Merck). Merck Kieselgel 60 (230–400 mesh) was used for a column chromatography.

Materials. Starting nicotinonitriles **5** for 3-(5-tetrazolyl)-pyridines **8a–c**, **g–l** have already been described.[14] Nitriles **6a**,**b**,**d**,**f** are commercially available, and compounds **6c** and **6e** were prepared according to literature procedures.[30] 3-Methoxypropanoic, 2-methylpropanoic, and 4-chlorobenzoic anhydrides were synthesized using known procedures.[31]

4.2. General procedure for the preparation of model (1-aryl-cycloalkyl)tetrazoles 7a–f

Dibutyltin oxide (0.75 g, 3 mmol) and trimethylsilyl azide (4.61 g, 5.31 mL, 40 mmol) were added to a solution of nitrile **6** (10 mmol) in anhydrous 1,4-dioxane (10 mL). The reaction mixture was subjected to microwave irradiation in a tightly sealed Teflon vessel (70 mL) for 3–8 h at 140 °C with stirring then cooled to room temperature. The solvent was removed under reduced pressure (80 °C/20 Torr). The residue was dissolved in diethyl ether (30 mL). The product was extracted with 2 N aqueous solution of NaOH (3× 10 mL). The aqueous layer was acidified with 4 N HCl to pH 1 and treated with ethyl acetate (4×10 mL). The organic extract was washed with brine (20 mL), dried over $MgSO_4$, and evaporated under reduced pressure (60 °C/20 Torr) to give the target tetrazole **7a–f** that was recrystallized from ethyl acetate.

4.2.1. 5-(1-Phenylcyclopropyl)-2*H*-tetrazole (7a). Reaction time: 3 h. Yield 100%; colorless needles, mp 176–178 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 1.43–1.50 (m, 2H, CH_2), 1.50–1.57 (m, 2H, CH_2), 7.26–7.39 (m, 5H, Ph), 15.0–17.0 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6, δ ppm): 16.3 (CH_2), 20.4 (CH_2), 127.3, 128.7, 140.2 (Ph), 160.1 (br s, CN_4H). IR $_{max}$ (KBr) 3127, 2996, 2858, 2705, 2599, 2469, 1875, 1566, 1429, 1267, 1044, 935, 701. Analysis found: C, 64.25; H, 5.48; N, 30.05%. Calcd for $C_{10}H_{10}N_4$ (186.22): C, 64.50; H, 5.41; N, 30.09%.

4.2.2. 5-(1-Phenylcyclobutyl)-2*H*-tetrazole (7b). Reaction time: 3 h; yield 90%; white needles, mp 105–108 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 1.87–2.05 (m, 2H, CH_2), 2.69–2.80 (m, 2H, CH_2), 2.81–2.91 (m, 2H, CH_2), 7.20–7.39 (m, 5H, Ph), 15.3–17.0 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6, δ ppm): 16.6 (CH_2), 33.6 (CH_2), 43.6 (Ph*C*), 125.8, 126.8, 128.6, 144.8 (Ph), 162.3 (br s, CN_4H). IR ν_{max} (KBr) 3103, 2978, 2859, 2702, 2603, 2486, 1870, 1551, 1411, 1257, 1149, 1038, 745. Analysis found: C, 66.07; H, 6.01; N, 27.94%. Calcd for $C_{11}H_{12}N_4$ (200.25): C, 65.98; H, 6.04; N, 27.98%.

4.2.3. 5-(1-Phenylcyclopentyl)-2*H*-tetrazole (7c). Reaction time: 5 h; yield 84%; colorless needles, mp 151–153 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 1.47–1.61 (m, 2H, CH_2), 1.69–1.82 (m, 2H, CH_2), 2.14–2.26 (m, 2H, CH_2), 2.64–2.75 (m, 2H, CH_2), 7.18–7.35 (m, 5H, Ph), 15.5–16.6 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6, δ ppm): 22.8 (CH_2), 37.6 (CH_2), 49.6 (Ph*C*), 126.4, 126.8, 128.6, 144.2 (Ph), 161.4 (br s, CN_4H). IR ν_{max} (KBr) 3097, 2974, 2876, 2699, 2602, 2490, 1876, 1551, 1493, 1412, 1259, 1039, 749.

Analysis found: C, 67.24; H, 6.57; N, 26.09%. Calcd for $C_{12}H_{14}N_4$ (214.27): C, 67.27; H, 6.59; N, 26.15%.

4.2.4. 5-(1-Phenylcyclohexyl)-2*H*-tetrazole (7d). Reaction time: 8 h; yield 38% (89% with 1 equiv of Bu_2SnO); white crystals, mp 156–157 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 1.20–1.40 (m, 3H, CH_2, 4-H), 1.49–1.58 (m, 1H, 4-H), 1.59–1.70 (m, 2H, CH_2), 2.01–2.13 (m, 2H, CH_2), 2.53–2.63 (m, 2H, CH_2), 7.17–7.24 (m, 3H, Ph), 7.27–7.35 (m, 2H, Ph), 15.5–16.5 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6, δ ppm): 22.5 (CH_2), 24.8 (CH_2), 35.4 (CH_2), 41.9 (Ph*C*), 125.7, 126.7, 128.6, 145.5 (Ph), 160.3 (br s, CN_4H). IR ν_{max} (KBr) 3094, 2944, 2857, 2738, 2600, 1812, 1544, 1496, 1448, 1257, 1155, 1040, 893, 747, 700. Analysis found: C, 68.54; H, 7.01; N, 24.68%. Calcd for $C_{13}H_{16}N_4$ (228.30): C, 68.39; H, 7.06; N, 24.54%.

4.2.5. 5-(4-Phenyltetrahydro-2*H*-pyran-4-yl)-2*H*-tetrazole (7e). Reaction time: 5 h; yield 83%; white crystals, mp 141–142 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 2.21–2.33 (m, 2H, CH_2), 2.58–2.68 (m, 2H, CH_2), 3.26–3.37 (m, 2H, CH_2), 3.79–3.88 (m, 2H, CH_2), 7.21–7.29 (m, 3H, Ph), 7.30–7.38 (m, 2H, Ph), 15.5–16.8 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6, δ ppm): 35.2 (CH_2), 39.7 (Ph*C*), 63.9 (OCH_2), 125.6, 127.1, 128.8, 144.5 (Ph), 160.3 (br s, CN_4H). IR ν_{max} (KBr) 3106, 2980, 2962, 2865, 2788, 2608, 1545, 1499, 1463, 1397, 1245, 1147, 1106, 1040, 1032, 838, 739, 691. Analysis found: C, 62.65; H, 6.18; N, 24.11%. Calcd for $C_{12}H_{14}N_4O$ (230.27): C, 62.59; H, 6.13; N, 24.33%.

4.2.6. 5-[1-(4-Methoxyphenyl)cyclohexyl]-2*H*-tetrazole (7f). Reaction time: 8 h; yield 63% (85% with 1 equiv of Bu_2SnO); white crystals, mp 188–190 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 1.18–1.39 (m, 3H, CH_2, 4-H), 1.47–1.56 (m, 1H, 4-H), 1.57–1.68 (m, 2H, CH_2), 1.97–2.10 (m, 2H, CH_2), 2.49–2.60 (m, 2H, CH_2), 3.70 (s, 3H, OCH_3), 6.86 (d, 2H$_{arom}$, J=9 Hz, 3′-H, 5′-H), 7.12 (d, 2H$_{arom}$, J=9 Hz, 2′-H, 6′-H), 15.5–16.5 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6, δ ppm): 22.5 (CH_2), 24.9 (CH_2), 35.5 (CH_2), 41.1 (Ph*C*), 55.1 (OCH_3), 113.9, 126.9, 137.4, 157.9 (Ph), 160.8 (br s, CN_4H). IR ν_{max} (KBr) 3100, 2959, 2858, 2606, 1517, 1302, 1265, 1038, 807. Analysis found: C, 65.15; H, 7.04; N, 21.55%. Calcd for $C_{14}H_{18}N_4O$ (258.33): C, 65.09; H, 7.02; N, 21.69%.

4.3. Preparation of the 3-(5-tetrazolyl)pyridines 8a–m

Starting nicotinonitriles **5d–f,m** for 3-(5-tetrazolyl)pyridines **8d–f,m** were prepared according to literature procedure.[14]

4.3.1. 4-(4-Bromophenyl)-2-methylnicotinonitrile (5d). Obtained from 4-bromoacetophenone; yield 79%; creamy crystals, mp 138–140 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 2.76 (s, 3H, Me), 7.50 (d, 1H, J=5.1 Hz, 5-H), 7.61 (d, 2H$_{arom}$, J=8.6 Hz, 2′-H, 6′-H, Ar), 7.79 (d, 2H$_{arom}$, J=8.6 Hz, 3′-H, 5′-H, Ar), 8.75 (d, 1H, J=5.1 Hz, 6-H). IR ν_{max} (film) 2216 (C≡N).

4.3.2. 4-(4-{[*tert*-Butyl(dimethyl)silyl]oxy}phenyl)-2-methylnicotinonitrile (5e). Obtained from 1-(4{[*tert*-butyl(dimethyl)silyl]oxy}phenyl)ethanone; yield 32%; amber crystals, mp 68–69 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 0.25 (s, 6H, $Si(CH_3)_2$), 0.98 (s, 9H, $SiC(CH_3)_3$), 2.74 (s, 3H, Me), 7.04 (d, 2H$_{arom}$, J=8.8 Hz, Ar), 7.46 (d, 1H, J=5.1 Hz, 5-H), 7.59 (d, 2H$_{arom}$, J=8.8 Hz, Ar), 8.68 (d, 1H, J=5.1 Hz, 6-H). IR ν_{max} (film) 2224 (C≡N).

4.3.3. 4-(4-Chloro-3-nitrophenyl)-2-methylnicotinonitrile (5f). Obtained from 1-(4-chloro-3-nitrophenyl)ethanone; yield 46%; dark yellow crystals, mp 188–190 °C (decomp.); ^{1}H NMR (DMSO-d_6, δ ppm): 2.77 (s, 3H, Me), 7.60 (d, 1H, J=5.1 Hz, 5-H), 8.00–8.04 (m, 2H$_{arom}$, Ar), 8.39–8.42 (m, 1H$_{arom}$, Ar), 8.81 (d, 1H, J=5.1 Hz, 6-H). IR ν_{max} (film) 2223 (C≡N).

4.3.4. *tert*-Butyl 5-cyano-6-methyl-3,4-dihydro-2,7-naphthyridine-2(1*H*)-carboxylate (5m). Obtained from *tert*-butyl 4-oxopiperidine-1-carboxylate; yield 66%; pale yellow crystals, mp 133–134 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 1.43 (s, 9H, *t*-Bu), 2.63 (s, 3H, Me), 2.88 (t, 2H, J=5.9 Hz, 5-CH_2), 3.62 (t, 2H, J=5.9 Hz, 6-CH_2), 4.55 (s, 2H, 8-CH_2), 8.54 (s, 1H, 1-H). ^{13}C NMR (DMSO-d_6, δ ppm): 23.1, 26.9, 28.0, 40.2, 42.3, 79.5, 108.2, 115.7, 127.8, 147.4, 150.2, 153.9, 158.7. IR ν_{max} (KBr) 2975, 2870, 2230 (C≡N), 1695 (C=O), 1470, 1420, 1250, 1170, 1120, 920, 765. Mass (*m/z*): 273 (2) $[M]^+$, 216 (16) $[M-C_4H_9]^+$, 200 (13) $[M-C_4H_9O]^+$, 172 (24) $[M-C_4H_9OCO]^+$, 144 (21), 56 (100) $[C_4H_8]^+$, 55 (37). Analysis found: C, 65.98; H, 6.94; N, 15.31%. Calcd for $C_{15}H_{19}N_3O_2$ (273.34): C, 65.91; H, 7.01; N, 15.37%.

4.3.5. General procedure for the preparation of 3-(5-tetrazolyl)pyridines 8a–m. Dibutyltin oxide (0.75 g, 3 mmol) and trimethylsilyl azide (4.61 g, 5.31 mL, 40 mmol) were added to a solution of nitrile **5** (10 mmol) in anhydrous 1,4-dioxane (10 mL). The reaction mixture was subjected to microwave irradiation in a tightly sealed Teflon vessel (70 mL) for 8 h at 140 °C with stirring then cooled to room temperature. The solvent was removed under reduced pressure (60 °C/15 Torr). The residue was dissolved in methanol (20 mL). Silica gel (5 g) was added to the solution, which was then evaporated to dryness. The solid residue was loaded on a top of a chromatography column packed with silica gel, and then eluted with chloroform and later with a gradient system with methanol in chloroform (0→30% v/v). The fractions obtained were concentrated under reduced pressure to give the target products, which were recrystallized from ethyl acetate.

Atom numbering for ^{1}H and ^{13}C NMR spectra below see in Scheme 4.

4.3.5.1. 2-Methyl-4-phenyl-3-(2*H*-tetrazol-5-yl)-pyridine, monohydrate (8a). Yield 80%; white crystals, mp 94–95 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 2.30 (s, 3H, Me), 7.06–7.13 (m, 2H, Ph), 7.28–7.35 (m, 3H, Ph), 7.44 (d, 1H, J=5.1 Hz, 5-H), 8.72 (d, 1H, J=5.1 Hz, 6-H). ^{13}C NMR (DMSO-d_6, δ ppm): 22.9 (CH_3), 119.0 (3-C), 122.2 (5-C), 128.3 (9-C, 13-C), 128.5 (10-C, 12-C), 128.6 (11-C), 137.1 (8-C), 149.9 (4-C), 151.0 (6-C), 152.8 (CN_4H), 157.6 (2-C). IR ν_{max} (film) 3070, 2460, 1940, 1595, 1440, 1240, 1160, 1100, 1060, 1010, 985, 855, 760, 710. Mass (*m/z*): 237 (29) $[M]^+$, 236 (76) $[M-H]^+$, 208 (38) $[M-HN_2]^+$, 194 (100) $[M-HN_3]^+$, 181 (64), 180 (45), 166 (32), 152 (35), 139 (31), 127 (33), 115 (20), 77 (41), 51 (38). Analysis

found: C, 61.11; H, 4.97; N, 27.46%. Calcd for $C_{13}H_{11}N_5$ + H_2O (255.29): C, 61.17; H, 5.13; N, 27.43%.

4.3.5.2. 2-Methyl-1-(2*H*-tetrazol-5-yl)-5,6-dihydrobenzo[*f*]isoquinoline (8b). Yield 52%; creamy crystals, mp 269–270 °C (decomp.); ^{1}H NMR (DMSO-d_6, δ ppm): 2.26 (s, 3H, Me), 2.82 (br s, 4H, CH_2–CH_2), 6.20–6.31 (m, 1H, Ph), 6.93–7.04 (m, 1H, Ph), 7.20–7.31 (m, 1H, Ph), 7.33–7.42 (m, 1H, Ph), 8.61 (s, 1H, 6-H). ^{13}C NMR (DMSO-d_6, δ ppm): 22.7 (CH_3), 25.3 (15-C), 28.4 (14-C), 116.0 (3-C), 126.2 (10-C), 126.6 (12-C), 128.6 (11-C), 129.5 (9-C), 130.5 (8-C), 131.4 (5-C), 140.4 (13-C), 141.9 (4-C), 149.7 (6-C), 153.8 (CN_4H), 156.4 (2-C). IR ν_{max} (film) 2940, 2360, 1960, 1590, 1430, 1390, 1230, 1195, 1105, 1095, 1005, 890, 850, 750. Mass (*m*/*z*): 263 (14) $[M]^+$, 234 (13) $[M-HN_2]^+$, 220 (100) $[M-HN_3]^+$, 207 (18), 190 (14), 165 (19), 77 (10). Analysis found: C, 68.49; H, 4.94; N, 26.61%. Calcd for $C_{15}H_{13}N_5$ (263.30): C, 68.43; H, 4.98; N, 26.60%.

4.3.5.3. 2-Methyl-1-(2*H*-tetrazol-5-yl)-5*H*-chromeno[3,4-*c*]pyridine (8c). The title compound was described[†] in preliminary communication.[13]

4.3.5.4. 4-(4-Bromophenyl)-2-methyl-3-(2*H*-tetrazol-5-yl)pyridine (8d). Yield 76%; pale grey crystals, mp 212–215 °C (decomp.); ^{1}H NMR (DMSO-d_6, δ ppm): 2.31 (s, 3H, Me), 7.01 (d, 2H, J=8.4 Hz, 2′-H, 6′-H, Ar), 7.45 (d, 1H, J=5.1 Hz, 5-H), 7.52 (d, 2H, J=8.3 Hz, 3′-H, 5′-H, Ar), 8.72 (d, 1H, J=5.1 Hz, 6-H), 15.5–17.3 (br s, 1H, NH). Analysis found: C, 49.19; H, 3.11; Br, 25.25; N, 22.11%. Calcd for $C_{13}H_{10}BrN_5$ (316.16): C, 49.39; H, 3.19; Br, 25.27; N, 22.15%.

4.3.5.5. 4-(4-{[*tert*-Butyl(dimethyl)silyl]oxy}phenyl)-2-methyl-3-(2*H*-tetrazol-5-yl)pyridine (8e). $CHCl_3$/THF system was used for purification; yield 78%; pale yellow crystals, mp 207–210 °C (decomp.); ^{1}H NMR (DMSO-d_6, δ ppm): 0.16 (s, 6H, $Si(CH_3)_2$), 0.92 (s, 9H, $SiC(CH_3)_3$), 2.28 (s, 3H, Me), 6.77 (d, 2H, J=8.8 Hz, 3′-H, 5′-H, Ar), 6.97 (d, 2H, J=8.8 Hz, 2′-H, 6′-H, Ar), 7.42 (d, 1H, J=5.1 Hz, 5-H), 8.67 (d, 1H, J=5.1 Hz, 6-H). Analysis found: C, 62.42; H, 7.01; N, 18.69%. Calcd for $C_{19}H_{25}N_5OSi$ (367.53): C, 62.09; H, 6.86; N, 19.06%.

4.3.5.6. 4-(4-Chloro-3-nitrophenyl)-2-methyl-3-(2*H*-tetrazol-5-yl)pyridine (8f). Yield 44%; pale yellow crystals, mp 107–110 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 2.36 (s, 3H, Me), 7.31 (dd, 1H, J=8.4, 2.2 Hz, 6′-H, Ar), 7.53 (d, 1H, J=5.1 Hz, 5-H), 7.71 (d, 1H, J=8.4 Hz, 5′-H, Ar), 7.86 (d, 1H, J=2.2 Hz, 2′-H, Ar), 8.76 (d, 1H, J=5.1 Hz, 6-H). Analysis found: C, 49.49; H, 3.02; N, 26.93%. Calcd for $C_{13}H_9ClN_6O_2$ (316.71): C, 49.30; H, 2.86; N, 26.54%.

4.3.5.7. 3-Methyl-4-(2*H*-tetrazol-5-yl)-6,7-dihydro-5*H*-cyclopenta[*c*]pyridine (8g). Yield 78%; pale brown crystals, mp 225–227 °C (decomp.); ^{1}H NMR (DMSO-d_6, δ ppm): 1.97–2.08 (m, 2H, 9-CH_2), 2.44 (s, 3H, Me), 2.84 (t, 2H, J=7.6 Hz, 8-CH_2), 2.95 (t, 2H, J=7.5 Hz, 10-CH_2), 8.48 (s, 1H, 6-H). ^{13}C NMR (DMSO-d_6, δ ppm): 22.3 (CH_3), 24.6 (9-CH_2), 29.8 (8-CH_2), 32.2 (10-CH_2), 118.2 (3-C), 138.3 (5-C), 144.8 (6-C), 153.4 (2-C), 153.5 (CN_4H), 155.1 (4-C). Mass (*m*/*z*): 201 (37) $[M]^+$, 173 (48) $[M-N_2]^+$, 172 (44) $[M-HN_2]^+$, 158 (62) $[M-HN_3]^+$, 157 (63) $[M-HN_3-H]^+$, 128 (58), 116 (22), 103 (18), 89 (15), 53 (37), 51 (46), 50 (100), 43 (48). Analysis found: C, 59.61; H, 5.68; N, 34.68%. Calcd for $C_{10}H_{11}N_5$ (201.23): C, 59.69; H, 5.51; N, 34.80%.

4.3.5.8. 3-Methyl-4-(2*H*-tetrazol-5-yl)-5,6,7,8-tetrahydroisoquinoline (8h). Yield 61%; pale yellow crystals, mp 220–222 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 1.59–1.75 (m, 4H, 9-CH_2, 10-CH_2), 2.15 (s, 3H, CH_3), 2.26–2.34 (m, 2H, 8-CH_2), 2.71–2.78 (m, 2H, 11-CH_2), 8.45 (s, 1H, 6-H). ^{13}C NMR (DMSO-d_6, δ ppm): 21.6 (10-CH_2), 21.7 (9-CH_2), 22.2 (CH_3), 25.6 (8-CH_2), 26.3 (11-CH_2), 120.2 (3-C), 130.6 (5-C), 146.0 (4-C), 150.9 (6-C), 152.5 (CN_4H), 153.4 (2-C). Mass (*m*/*z*): 215 (65) $[M]^+$, 187 (52) $[M-N_2]^+$, 186 (42) $[M-HN_2]^+$, 172 (100) $[M-HN_3]^+$, 171 (94) $[M-HN_3-H]^+$, 159 (71), 158 (34), 157 (47), 144 (73), 131 (17), 115 (30), 104 (24), 91 (41), 77 (62), 65 (38), 63 (54), 59 (51), 51 (58). Analysis found: C, 61.37; H, 6.09; N, 32.54%. Calcd for $C_{11}H_{13}N_5$ (215.26): C, 61.38; H, 6.09; N, 32.53%.

4.3.5.9. 3-Methyl-4-(2*H*-tetrazol-5-yl)-6,7,8,9-tetrahydro-5*H*-cyclohepta[*c*]pyridine (8i). Yield 58%; brown crystals, mp 224–226 °C (decomp.); ^{1}H NMR (DMSO-d_6, δ ppm): 1.35–1.45 (m, 2H, 9-CH_2), 1.53–1.62 (m, 2H, 11-CH_2), 1.69–1.79 (m, 2H, 10-CH_2), 2.05 (s, 3H, CH_3), 2.27–2.35 (m, 2H, 8-CH_2), 2.75–2.82 (m, 2H, 12-CH_2), 8.26 (s, 1H, 6-H). ^{13}C NMR (DMSO-d_6, δ ppm): 22.7 (CH_3), 26.5 (9-CH_2), 27.7 (11-CH_2), 31.0 (10-CH_2), 31.6 (8-CH_2), 31.8 (12-CH_2), 122.6 (3-C), 136.0 (5-C), 148.6 (6-C), 151.6 (4-C), 154.7 (2-C), 154.8 (CN_4H). Mass (*m*/*z*): 229 (41) $[M]^+$, 200 (28) $[M-HN_2]^+$, 186 (100) $[M-HN_3]^+$, 172 (79), 159 (33), 145 (37), 144 (75), 132 (18), 115 (20), 101 (15), 91 (38), 77 (32), 59 (41), 57 (38), 43 (31). Analysis found: C, 62.88; H, 6.56; N, 30.45%. Calcd for $C_{12}H_{15}N_5$ (229.29): C, 62.86; H, 6.59; N, 30.54%.

4.3.5.10. 3,5-Dimethyl-4-(2*H*-tetrazol-5-yl)-5,6,7,8-tetrahydroisoquinoline (8j). Yield 47%; white powder, mp 172–174 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 0.77 (d, 3H, J=7.3 Hz, 12-CH_3), 1.55–1.85 (m, 4H, 9-CH_2, 10-CH_2), 2.10 (s, 3H, 7-CH_3), 2.63–2.89 (m, 3H, 8-H, 11-CH_2), 8.36 (s, 1H, 6-H). ^{13}C NMR (DMSO-d_6, δ ppm): 16.6 (10-CH_2), 21.2 (12-CH_3), 22.2 (7-CH_3), 25.4 (11-CH_2), 28.7 (9-CH_2), 28.8 (8-CH), 119.9 (3-C), 129.7 (5-C), 150.9 (4-C), 151.3 (6-C), 152.7 (CN_4H), 153.8 (2-C). Mass (*m*/*z*): 229 (39) $[M]^+$, 200 (12) $[M-HN_2]^+$, 186 (100) $[M-HN_3]^+$, 185 (38) $[M-HN_3-H]^+$, 172 (38), 156 (24), 144 (34), 130 (16), 114 (16), 102 (16), 91 (25), 76 (21), 59 (84), 57 (64), 43 (42), 42 (35). Analysis found: C, 62.99; H, 6.53; N, 30.46%. Calcd for $C_{12}H_{15}N_5$ (229.29): C, 62.86; H, 6.59; N, 30.54%.

4.3.5.11. 4-Isopropyl-2-methyl-3-(2*H*-tetrazol-5-yl)pyridine (8k). Yield 63%; light brown crystals, mp 160–163 °C (decomp.); ^{1}H NMR (DMSO-d_6, δ ppm): 1.08 (d, 6H, J=6.8 Hz, 9-CH_3, 10-CH_3), 2.15 (s, 3H, 7-CH_3), 2.38 (m, 1H, J=6.8 Hz, 8-CH), 7.40 (d, 1H, J=5.2 Hz,

[†] The authors apologise for inaccuracy in structure **6c** in the communication[13] where oxygen atom was depicted as connected with pyridine ring. This oxygen atom has to be connected with phenyl ring; the correct structure is **8c** in this paper (Scheme 4).

5-H), 8.57 (d, 1H, $J=5.2$ Hz, 6-H). ^{13}C NMR (DMSO-d_6, δ ppm): 22.7 (9-CH_3, 10-CH_3), 22.8 (7-CH_3), 30.2 (8-CH), 118.5 (5-C), 119.7 (3-C), 150.8 (6-C), 152.6 (CN_4H), 156.7 (2-C), 157.6 (4-C). Mass (*m*/*z*): 203 (34) $[M]^+$, 174 (17) $[M-HN_2]^+$, 160 (100) $[M-HN_3]^+$, 159 (51) $[M-HN_3-H]^+$, 145 (78), 131 (29), 118 (34), 91 (32), 77 (53), 65 (56), 63 (31), 59 (50), 57 (35), 51 (58). Analysis found: C, 59.11; H, 6.41; N, 34.41%. Calcd for $C_{10}H_{13}N_5$ (203.25): C, 59.10; H, 6.45; N, 34.46%.

4.3.5.12. 4-*tert*-Butyl-2-methyl-3-(2*H*-tetrazol-5-yl)pyridine (8l). Yield 25%; pale yellow crystals, mp 165–167 °C (decomp.); ^{1}H NMR (DMSO-d_6, δ ppm): 1.05 (s, 9H, *t*-Bu), 1.98 (s, 3H, CH_3), 7.47 (d, 1H, $J=5.4$ Hz, 5-H), 8.55 (d, 1H, $J=5.4$ Hz, 6-H). ^{13}C NMR (DMSO-d_6, δ ppm): 22.8 (7-CH_3), 30.6 (9-CH_3, 10-CH_3, 11-CH_3), 36.1 (8-C), 119.3 (3-C), 119.6 (5-C), 150.8 (6-C), 154.2 (CN_4H), 157.8 (2-C), 159.0 (4-C). Mass (*m*/*z*): 217 (43) $[M]^+$, 202 (14) $[M-NH]^+$, 189 (17) $[M-N_2]^+$, 174 (55) $[M-HN_3]^+$, 160 (61) $[M-t\text{-Bu}]^+$, 159 (100), 145 (43), 132 (29), 118 (14), 91 (21), 77 (36), 57 (31). Analysis found: C, 61.19; H, 7.03; N, 32.58%. Calcd for $C_{11}H_{15}N_5$ (217.28): C, 60.81; H, 6.96; N, 32.23%.

4.3.5.13. *tert*-Butyl-6-methyl-5-(2*H*-tetrazol-5-yl)-3,4-dihydro-2,7-naphthyridine-2(1*H*)-carboxylate (8m). Reaction time 4 h at 120 °C; yield 46%; pale yellow crystals, mp 187–190 °C (decomp.); ^{1}H NMR (DMSO-d_6, δ ppm): 1.42 (s, 9H, *t*-Bu), 2.24 (s, 3H, Me), 2.45 (t, 2H, $J=5.7$ Hz, 8-CH_2), 3.49 (t, 2H, $J=5.7$ Hz, 9-CH_2), 4.60 (s, 2H, 10-CH_2), 8.49 (s, 1H, 6-H). ^{13}C NMR (DMSO-d_6, δ ppm): 22.5 (7-CH_3), 26.1 (13-CH_3, 14-CH_3, 15-CH_3), 28.1 (8-C), 40.7 (10-C), 42.7 (9-C), 79.4 (12-C), 120.0 (3-C), 127.7 (5-C), 143.9 (4-C), 148.7 (6-C), 152.3 (CN_4H), 153.9 (11-C), 154.6 (2-C). IR ν_{max} (film) 2970, 2925, 2340, 1920, 1680 (C=O), 1600, 1455, 1420, 1285, 1250, 1165, 1105, 1045, 980, 910, 780. Mass (*m*/*z*): 316 (2) $[M]^+$, 259 (24) $[M-C_4H_9]^+$, 243 (10) $[M-C_4H_9O]^+$, 216 (24) $[M-C_4H_9-HN_3]^+$, 200 (12), 187 (27), 172 (45), 142 (28), 55 (100). Analysis found: C, 56.98; H, 6.41; N, 26.51%. Calcd for $C_{15}H_{20}N_6O_2$ (316.37): C, 56.95; H, 6.37; N, 26.56%.

4.4. Preparation of the 5*H*-tetrazolo[1′,5′:1,5]-pyrrolo[3,4-*b*]pyridines 15a,h,l

4.4.1. Functionalization of 2-methyl group. General procedure for a conversion **5a**,**h**,**l**→**9a**,**h**,**l**→**10a**,**h**,**l**→**11a**,**h**,**l** was described in preliminary communication (for compound **5a**).[19]

4.4.1.1. 3-Methyl-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile 2-oxide (9h). Yield 94%; pale yellow crystals, mp 135–138 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 2.62–2.96 (m, 4H, 6-CH_2, 7-CH_2), 2.49 (s, 3H, CH_3), 2.62–2.69 (m, 2H, 5-CH_2), 2.74–2.80 (m, 2H, 8-CH_2), 8.35 (s, 1H, 1-H). IR ν_{max} (film) 2229 (C≡N).

4.4.1.2. 4-*tert*-Butyl-2-methylnicotinonitrile 1-oxide (9l). Yield 50%; pale yellow crystals, mp 147–149 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 1.44 (s, 9H, $(CH_3)_3$), 2.58 (s, 3H, CH_3), 7.39 (d, 1H, $J=7.1$ Hz, 5-H), 8.44 (d, 1H, $J=7.1$ Hz, 6-H). IR ν_{max} (film) 2227 (C≡N).

4.4.1.3. 3-(Hydroxymethyl)-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile (11h). Yield 23%; pale yellow crystals, mp 69–72 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 1.71–1.84 (m, 4H, 6-CH_2, 7-CH_2), 2.72–2.77 (m, 2H, 5-CH_2), 2.83–2.88 (m, 2H, 8-CH_2), 4.61 (d, 2H, $J=5.8$ Hz, CH_2OH), 5.50 (t, 1H, $J=5.8$ Hz, OH), 8.46 (s, 1H, 1-H). IR ν_{max} (film) 3217 (OH), 2224 (C≡N).

4.4.1.4. 5-Hydroxy-3-methyl-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile (12). Yield 31%; pale yellow crystals, mp 138–140 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 1.65–1.93 (m, 4H, CH_2), 2.53–2.62 (m, 1H, CH_2), 2.63 (s, 3H, CH_3), 2.72–2.83 (m, 1H, CH_2), 4.72–4.77 (m, 1H, CHOH), 5.56 (d, 1H, $J=5.9$ Hz, OH), 8.46 (s, 1H, 1-H). IR ν_{max} (film) 3187 (OH), 2228 (C≡N).

4.4.1.5. 4-*tert*-Butyl-2-(hydroxymethyl)nicotinonitrile (11l). yield 86%; pale yellow crystals, mp 66–68 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 1.47 (s, 9H, $(CH_3)_3$), 4.71 (d, 2H, $J=5.6$ Hz, CH_2), 5.46 (t, 1H, $J=5.6$ Hz, OH), 7.49 (d, 1H, $J=5.4$ Hz, 5-H), 8.69 (d, 1H, $J=5.4$ Hz, 6-H). IR ν_{max} (film) 3226 (OH), 2221 (C≡N).

4.4.1.6. [4-Phenyl-3-(2*H*-tetrazol-5-yl)pyridine-2-yl]methanol (13). Dibutyltin oxide (0.046 g, 0.18 mmol) and trimethylsilyl azide (0.33 mL, 2.5 mmol) were added to a solution of nitrile **11a** (0.20 g, 0.95 mmol) in anhydrous 1,4-dioxane (5 mL). The reaction mixture was subjected to microwave irradiation in a tightly sealed glass vessel for 2 h at 120 °C with stirring then cooled to room temperature. The solvent was removed under reduced pressure (80 °C/20 Torr). The residue was treated with methanol (5 mL), and the mixture was evaporated to dryness. The residue was mixed with acetonitrile (10 mL). The precipitate was filtered off and recrystallized from methanol to give the titled product **13** (0.13 g, 51%) as white powder, mp 240–242 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 3.01–3.60 (br s, 1H, OH), 4.44 (s, 2H, CH_2), 7.05–7.12 (m, 2H, Ph), 7.28–7.36 (m, 3H, Ph), 7.53 (d, 1H, $J=5.1$ Hz, 5-H), 8.78 (d, 1H, $J=5.1$ Hz, 6-H). Analysis found: C, 60.80; H, 4.50; N, 27.35%. Calcd for $C_{13}H_{11}N_5O+0.2H_2O$ (256.87): C, 60.79; H, 4.47; N, 27.26%.

4.4.1.7. 3-(Chloromethyl)-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile (14h). Yield 55%; pale yellow glassy mass; ^{1}H NMR (DMSO-d_6, δ ppm): 1.71–1.85 (m, 4H, 2CH_2), 2.74–2.80 (m, 2H, CH_2), 2.85–2.92 (m, 2H, CH_2), 4.84 (s, 2H, CH_2Cl), 8.53 (s, 1H, 6-H).

4.4.1.8. 4-*tert*-Butyl-2-(chloromethyl)nicotinonitrile (14l). Yield 100%; pale yellow glassy mass; ^{1}H NMR (DMSO-d_6, δ ppm): 1.48 (s, 9H, $(CH_3)_3$), 5.74 (s, 2H, CH_2), 7.64 (d, 1H, $J=5.5$ Hz, 5-H), 8.79 (d, 1H, $J=5.5$ Hz, 6-H).

4.4.1.9. 3-(Azidomethyl)-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile (15h). Yield 91%; pale yellow crystals, mp 88–90 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 1.71–1.85 (m, 4H, 2CH_2), 2.74–2.80 (m, 2H, CH_2), 2.85–2.91 (m, 2H, CH_2), 4.63 (s, 2H, CH_2N_3), 8.55 (s, 1H, 6-H). IR ν_{max} (film) 2102 (N_3), 2224 (C≡N).

4.4.1.10. 2-(Azidomethyl)-4-*tert*-butylnicotinonitrile (15l). Yield 65%; pale yellow crystals, mp 65–67 °C; ^{1}H

NMR (DMSO-d_6, δ ppm): 1.47 (s, 9H, $(CH_3)_3$), 4.74 (s, 2H, CH_2), 7.57 (d, 1H, $J=5.5$ Hz, 5-H), 8.77 (d, 1H, $J=5.5$ Hz, 6-H). IR ν_{max} (film) 2111 (N_3), 2220 (C≡N).

4.4.2. Intramolecular [3+2] cycloaddition. All the compounds **16a**,**h**,**l** were described in preliminary communication.[19]

4.5. Preparation of the 5,6-dihydrotetrazolo[5,1-*f*]-1,6-naphthyridines 19a,b

4.5.1. 2-[(1*E*)-3,3-Dimethylbut-1-en-1-yl]-4-phenylnicotinonitrile (17a). Potassium *tert*-butoxide (0.34 g, 3 mmol) was added to a solution of 2-methyl-4-phenylnicotinonitrile (0.5 g, 2.57 mmol) in anhydrous THF (5 mL). Trimethylacetic aldehyde (0.29 mL, 2.7 mmol) was added dropwise to this bright red reaction mixture that was then stirred at room temperature for 2 h. The mixture was diluted with water (5 mL) and treated with ethyl acetate (4× 10 mL). The extract was dried over $MgSO_4$ and concentrated under reduced pressure (60 °C/10 Torr). The residue was chromatographed (silica gel, hexane/ethyl acetate 4:1) to give the product **17a** (0.63 g, 94%) as white powder, mp 173–175 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 1.16 (s, 9H, $(CH_3)_3$), 6.79 (d, 1H, $J=15.4$ Hz, CH=CH), 7.27 (d, 1H, $J=15.4$ Hz, CH=CH), 7.49 (d, 1H, $J=5.1$ Hz, 5-H), 7.54–7.61 (m, 3H, Ph), 7.62–7.69 (m, 2H, Ph), 8.79 (d, 1H, $J=$ 5.1 Hz, 6-H). Analysis found: C, 82.29; H, 6.97; N, 10.59%. Calcd for $C_{18}H_{18}N_2$ (262.36): C, 82.41; H, 6.92; N, 10.68%.

4.5.2. 4-*tert*-Butyl-2-[(*E*)-2-phenylvinyl]nicotinonitrile (17b). Potassium *tert*-butoxide (0.77 g, 6.88 mmol) was added to a solution of 4-*tert*-butyl-2-methylnicotinonitrile (1.0 g, 6.25 mmol) in anhydrous THF (10 mL) at 0 °C. The bright red reaction mixture was stirred at 0 °C for 15 min, and benzaldehyde (0.67 mL, 6.6 mmol) was added dropwise. The mixture was stirred at 0 °C for 10 min then at room temperature for 1 h. The mixture was diluted with water (10 mL) and treated with diethyl ether (4×20 mL). The extract was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed (silica gel, chloroform) to give the product **17b** (1.03 g, 63%) as white crystals, mp 130–131 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 1.47 (s, 9H, $(CH_3)_3$), 7.36–7.49 (m, 3H, Ph), 7.41 (d, 1H, $J=5.1$ Hz, 5-H), 7.58 (d, 1H, $J=15.5$ Hz, CH=CH), 7.66–7.72 (m, 2H, Ph), 7.97 (d, 1H, $J=15.5$ Hz, CH=CH), 8.73 (d, 1H, $J=5.1$ Hz, 6-H). Analysis found: C, 82.56; H, 7.12; N, 10.49%. Calcd for $C_{18}H_{18}N_2$ (262.36): C, 82.41; H, 6.92; N, 10.68%.

4.5.3. 5-*tert*-Butyl-10-phenyl-5,6-dihydrotetrazolo[5,1-*f*]-1,6-naphthyridine (19a). Dibutyltin oxide (0.068 g, 0.25 mmol) and trimethylsilyl azide (0.4 mL, 3 mmol) were added to a solution of nitrile **17a** (0.20 g, 0.76 mmol) in anhydrous 1,4-dioxane (2 mL). The reaction mixture was subjected to microwave irradiation in a tightly sealed glass vessel for 2 h at 140 °C with stirring then cooled to room temperature. The solvent was removed to dryness. The residue was treated with methanol (5 mL), and the mixture was evaporated to dryness. The residue was chromatographed (silica gel, hexane then hexane/ethyl acetate in gradient 2:1–1:100) to give the titled product **19a** (0.12 g, 52%) as white crystals, mp 174–176 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 0.90 (s, 9H, $(CH_3)_3$), 3.51 (dd, 1H, $J=17.4$, 1.7 Hz, CH_2), 3.80 (dd, 1H, $J=17.4$, 8.1 Hz, CH_2), 4.93 (dd, 1H, $J=8.1$, 1.7 Hz, CH), 7.32–7.40 (m, 3H, Ph), 7.44–7.51 (m, 2H, Ph), 7.48 (d, 1H, $J=5.2$ Hz, 5-H), 8.67 (d, 1H, $J=5.2$ Hz, 6-H). Analysis found: C, 70.68; H, 6.14; N, 22.79%. Calcd for $C_{18}H_{19}N_5$ (305.39): C, 70.80; H, 6.27; N, 22.93%. Crystallographic data for compound **19a**: $C_{18}H_{19}N_5$, monoclinic, space group $P2(1)/n$, $a=$ 9.1730(18), $b=9.4000(19)$, $c=18.803(4)$ Å, $\alpha=90°$, $\beta=$ 93.32(3)°, $\gamma=90°$, volume 1618.6(6) Å^3, $T=293(2)$ K, $Z=4$, $D_c=1.253$ Mg/m^3, $\mu=0.078$ mm^{-1}, $\theta_{max}=25.23°$, 3101 reflections measured and 2885 unique ($R_{int}=0.0401$) reflections, full matrix least-squares refinement on F^2, R_1 (obsd)=0.0474, and wR_2 (all data)=0.1333. Crystallographic data (excluding structure factors) for the structure in this paper in the form of a CIF have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 276729. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

4.5.4. 2-[(1*E*)-3,3-Dimethylbut-1-en-1-yl]4-phenyl-3-(2*H*-tetrazol-5-yl)pyridine (18). The title compound was also isolated from the reaction mixture (0.05 g, 22%) as white powder, mp 165–167 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 0.96 (s, 9H, $(CH_3)_3$), 5.88 (d, 1H, $J=15.5$ Hz, CH=CH), 6.97 (d, 1H, $J=15.5$ Hz, CH=CH), 7.06–7.12 (m, 2H, Ph), 7.22–7.28 (m, 3H, Ph), 7.34 (d, 1H, $J=5.0$ Hz, 5-H), 8.67 (d, 1H, $J=5.0$ Hz, 6-H). Analysis found: C, 70.84; H, 6.27; N, 22.78%. Calcd for $C_{18}H_{19}N_5$ (305.39): C, 70.80; H, 6.27; N, 22.93%.

4.5.5. 10-*tert*-Butyl-5-phenyl-5,6-dihydrotetrazolo[5,1-*f*]-1,6-naphthyridine (19b). Dibutyltin oxide (0.23 g, 0.9 mmol) and trimethylsilyl azide (0.4 mL, 3 mmol) were added to a solution of nitrile **17b** (0.20 g, 0.76 mmol) in anhydrous 1,4-dioxane (2 mL). The reaction mixture was subjected to microwave irradiation in a tightly sealed glass vessel for 4 h at 140 °C with stirring then cooled to room temperature. The solvent was removed to dryness. The residue was treated with methanol (5 mL), and the mixture was evaporated to dryness. The residue was chromatographed (silica gel, hexane/ethyl acetate 2:1) to give the titled product **19b** (0.16 g, 68%) as pale yellow crystals, mp 175–177 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 1.56 (s, 9H, $(CH_3)_3$), 3.73 (dd, 1H, $J=16.4$, 5.6 Hz, CH_2), 3.93 (dd, 1H, $J=16.4$, 5.6 Hz, CH_2), 4.93 (t, 1H, $J=5.6$ Hz, CH), 7.07–7.12 (m, 2H, Ph), 7.27–7.37 (m, 3H, Ph), 7.53 (d, 1H, $J=$ 5.5 Hz, 5-H), 8.53 (d, 1H, $J=5.5$ Hz, 6-H). Analysis found: C, 70.84; H, 6.31; N, 22.94%. Calcd for $C_{18}H_{19}N_5$ (305.39): C, 70.80; H, 6.27; N, 22.93%.

4.6. General procedure for alkylation of model tetrazoles 7a–f

Freshly calcined K_2CO_3 (0.15 g, 1.08 mmol) was added to a solution of the tetrazole (1.08 mmol) in acetone (2 mL). The mixture was refluxed under stirring for 2 h, and then benzyl bromide (0.13 mL, 1.13 mmol) was added to the reaction mixture. The latter was refluxed for 6 h then cooled to room temperature, diluted with acetone (10 mL) and filtered. The filtrate was evaporated to dryness. The residue was

chromatographed (silica gel, hexane/ethyl acetate in gradient 4:1 to 3:1) to give the isomeric products.

4.6.1. 1-Benzyl-5-(1-phenylcyclopropyl)-1*H*-tetrazole (20a). Yield 37%; pale yellow oil; ^{1}H NMR (DMSO-d_6, δ ppm): 1.42–1.48 (m, 2H, CH_2), 1.48–1.53 (m, 2H, CH_2), 5.38 (s, 2H, $PhCH_2$), 6.92–6.97 (m, 2H, Ph), 7.05–7.10 (m, 2H, Ph), 7.20–7.33 (m, 6H, Ph). ^{13}C NMR (DMSO-d_6, δ ppm): 15.1 (CH_2), 18.6 (Ph*C*), 50.3 (Ph*C*H_2), 126.7, 127.0, 127.8, 128.2, 128.6, 128.8, 133.8, 139.3 (Ph), 157.2 (CN_4H). IR ν_{max} (film) 3444, 3061, 3031, 1602, 1523, 1451, 1333, 1175, 1030, 931, 725, 700. Analysis found: C, 73.75; H, 5.69; N, 20.11%. Calcd for $C_{17}H_{16}N_4$ (276.34): C, 73.89; H, 5.84; N, 20.27%.

4.6.2. 2-Benzyl-5-(1-phenylcyclopropyl)-2*H*-tetrazole (21a). Yield 47%; pale yellow oil; ^{1}H NMR (DMSO-d_6, δ ppm): 1.37–1.41 (m, 2H, CH_2), 1.47–1.52 (m, 2H, CH_2), 5.83 (s, 2H, $PhCH_2$), 7.22–7.41 (m, 10H, Ph). ^{13}C NMR (DMSO-d_6, δ ppm): 16.2 (CH_2), 22.1 (Ph*C*), 55.8 (Ph*C*H_2), 126.8, 128.1, 128.3, 128.8, 129.1, 134.2, 140.9 (Ph), 169.9 (CN_4H). IR ν_{max} (film) 3421, 3060, 3031, 1602, 1503, 1454, 1335, 1212, 1057, 1026, 935, 755, 723, 698. Analysis found: C, 73.85; H, 5.97; N, 20.28%. Calcd for $C_{17}H_{16}N_4$ (276.34): C, 73.89; H, 5.84; N, 20.27%.

4.6.3. 1-Benzyl-5-(1-phenylcyclobutyl)-1*H*-tetrazole (20b). Yield 33%; white crystals, mp 108–110 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 1.88–2.06 (m, 2H, CH_2), 2.66–2.77 (m, 2H, CH_2), 2.82–2.93 (m, 2H, CH_2), 5.16 (s, 2H, $PhCH_2$), 6.72–6.77 (m, 2H, Ph), 7.16–7.39 (m, 8H, Ph). IR ν_{max} (film) 3420, 3031, 2993, 2947, 2866, 1699, 1493, 1445, 1410, 1306, 1230, 1107, 829, 723, 699. Analysis found: C, 74.18; H, 6.15; N, 18.98%. Calcd for $C_{18}H_{18}N_4$ (290.37): C, 74.46; H, 6.25; N, 19.29%.

4.6.4. 2-Benzyl-5-(1-phenylcyclobutyl)-2*H*-tetrazole (21b). Yield 58%; white crystals, mp 104–106 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 1.86–2.04 (m, 2H, CH_2), 2.65–2.76 (m, 2H, CH_2), 2.79–2.88 (m, 2H, CH_2), 5.87 (s, 2H, $PhCH_2$), 7.16–7.22 (m, 1H, Ph), 7.24–7.41 (m, 9H, Ph). IR ν_{max} (film) 3445, 3022, 2978, 2939, 2863, 1599, 1550, 1486, 1445, 1320, 1196, 1147, 1077, 1020, 745, 722, 696. Analysis found: C, 74.48; H, 6.31; N, 19.17%. Calcd for $C_{18}H_{18}N_4$ (290.37): C, 74.46; H, 6.25; N, 19.29%.

4.6.5. 1-Benzyl-5-(1-phenylcyclopentyl)-1*H*-tetrazole (20c). Yield 23%; white crystals, mp 85–87 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 1.62–1.78 (m, 4H, CH_2), 2.25–2.35 (m, 2H, CH_2), 2.41–2.53 (m, 2H, CH_2), 5.14 (s, 2H, $PhCH_2$), 6.70–6.77 (m, 2H, Ph), 7.17–7.30 (m, 6H, Ph), 7.30–7.40 (m, 2H, Ph). IR ν_{max} (film) 3059, 2967, 2873, 1493, 1445, 1409, 1240, 1090, 1030, 748, 726, 703. Analysis found: C, 75.01; H, 6.54; N, 18.48%. Calcd for $C_{19}H_{20}N_4$ (304.40): C, 74.97; H, 6.62; N, 18.41%.

4.6.6. 2-Benzyl-5-(1-phenylcyclopentyl)-2*H*-tetrazole (21c). Yield 72%; white crystals, mp 109–110 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 1.44–1.57 (m, 2H, CH_2), 1.67–1.81 (m, 2H, CH_2), 2.09–2.21 (m, 2H, CH_2), 2.65–2.76 (m, 2H, CH_2), 5.87 (s, 2H, $PhCH_2$), 7.14–7.20 (m, 1H, Ph), 7.23–7.33 (m, 6H, Ph), 7.33–7.41 (m, 3H, Ph). IR ν_{max} (film) 3058, 3021, 2961, 2915, 2873, 1598, 1484, 1459, 1382, 1349, 1319, 1189, 1070, 1028, 745, 725, 696. Analysis found: C, 74.89; H, 6.45; N, 18.50%. Calcd for $C_{19}H_{20}N_4$ (304.40): C, 74.97; H, 6.62; N, 18.41%.

4.6.7. 1-Benzyl-5-(1-phenylcyclohexyl)-1*H*-tetrazole (20d). Yield 20%; white crystals, mp 102–103 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 1.27–1.40 (m, 1H, 4-H), 1.41–1.60 (m, 5H, CH_2, 4-H), 1.97–2.10 (m, 2H, CH_2), 2.41–2.50 (m, 2H, CH_2), 5.10 (s, 2H, $PhCH_2$), 6.72–6.78 (m, 2H, Ph), 7.17–7.21 (m, 2H, Ph), 7.21–7.31 (m, 4H, Ph), 7.31–7.39 (m, 2H, Ph). IR ν_{max} (film) 3063, 3010, 2947, 2926, 2862, 1596, 1492, 1443, 1399, 1278, 1235, 1112, 895, 743, 723, 700. Analysis found: C, 75.51; H, 7.07; N, 17.68%. Calcd for $C_{20}H_{22}N_4$ (318.43): C, 75.44; H, 6.96; N, 17.59%.

4.6.8. 2-Benzyl-5-(1-phenylcyclohexyl)-2*H*-tetrazole (21d). Yield 79%; white crystals, mp 92–93 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 1.17–1.39 (m, 3H, CH_2, 4-H), 1.46–1.56 (m, 1H, 4-H), 1.56–1.66 (m, 2H, CH_2), 1.96–2.09 (m, 2H, CH_2), 2.54–2.65 (m, 2H, CH_2), 5.91 (s, 2H, $PhCH_2$), 7.13–7.19 (m, 1H, Ph), 7.20–7.31 (m, 6H, Ph), 7.31–7.42 (m, 3H, Ph). IR ν_{max} (film) 3060, 2940, 2861, 1580, 1495, 1452, 1346, 1318, 1185, 1133, 1067, 1026, 895, 743, 724, 692. Analysis found: C, 75.57; H, 6.91; N, 17.69%. Calcd for $C_{20}H_{22}N_4$ (318.43): C, 75.44; H, 6.96; N, 17.59%.

4.6.9. 1-Benzyl-5-(4-phenyltetrahydro-2*H*-pyran-4-yl)-1*H*-tetrazole (20e). Yield 11%; white crystals, mp 113–115 °C; ^{1}H NMR ($CDCl_3$, δ ppm): 2.19–2.30 (m, 2H, CH_2), 2.37–2.45 (m, 2H, CH_2), 3.66–3.81 (m, 4H, CH_2OCH_2), 4.95 (s, 2H, $PhCH_2$), 6.79–6.85 (m, 2H, Ph), 7.12–7.18 (m, 2H, Ph), 7.22–7.28 (m, 3H, Ph), 7.28–7.40 (m, 3H, Ph). IR ν_{max} (film) 3032, 2956, 2889, 2866, 1597, 1493, 1447, 1412, 1296, 1242, 1201, 1135, 1098, 1025, 922, 749, 721, 697. Analysis found: C, 71.37; H, 6.22; N, 17.29%. Calcd for $C_{19}H_{20}N_4O$ (320.40): C, 71.23; H, 6.29; N, 17.49%.

4.6.10. 2-Benzyl-5-(4-phenyltetrahydro-2*H*-pyran-4-yl)-2*H*-tetrazole (21e). Yield 79%; white crystals, mp 92–94 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 2.17–2.27 (m, 2H, CH_2), 2.59–2.67 (m, 2H, CH_2), 3.23–3.29 (m, 2H, CH_2), 3.77–3.85 (m, 2H, CH_2), 5.92 (s, 2H, $PhCH_2$), 7.17–7.23 (m, 1H, Ph), 7.25–7.31 (m, 6H, Ph), 7.31–7.41 (m, 3H, Ph). IR ν_{max} (film) 3064, 3035, 2958, 2923, 2845, 2769, 1597, 1462, 1389, 1352, 1246, 1142, 1102, 1037, 933, 742, 721, 692. Analysis found: C, 71.20; H, 6.38; N, 17.52%. Calcd for $C_{19}H_{20}N_4O$ (320.40): C, 71.23; H, 6.29; N, 17.49%.

4.7. General procedure for alkylation of 3-(5-tetrazolyl)pyridines 8a,g

Freshly calcined K_2CO_3 (0.23 g, 1.68 mmol) was added to a solution of the 3-(5-tetrazolyl)pyridine (0.84 mmol) in acetone (2 mL). The mixture was heated in sealed tube at 70 °C under stirring for 2 h, and then benzyl bromide (0.10 mL, 0.84 mmol) was added to the reaction mixture. The latter was refluxed for 4 h then cooled to room temperature, diluted with acetone (10 mL) and filtered. The filtrate was evaporated to dryness. The residue was chromatographed (silica gel, hexane/ethyl acetate in gradient 3:1–1:1) to give the isomeric products.

4.7.1. 3-(1-Benzyl-1*H*-tetrazol-5-yl)-2-methyl-4-phenylpyridine (22a). Yield 44%; white crystals, mp 155–157 °C; ^{1}H NMR ($CDCl_3$, δ ppm): 2.98 (s, 3H, Me), 4.42 (d, 1H, J=14.8 Hz, $PhCH_2$), 5.12 (d, 1H, J=14.8 Hz, $PhCH_2$), 6.27–6.77 (m, 2H, Ph), 7.14–7.20 (m, 4H, Ph), 7.21–7.25 (m, 1H, Ph), 7.29–7.39 (m, 3H, Ph), 7.34 (d, 1H, J=5.5 Hz, 5-H), 8.71 (d, 1H, J=5.5 Hz, 6-H). ^{13}C NMR ($CDCl_3$, δ ppm): 22.7 (CH_3), 51.1 (Ph*C*H_2), 118.0, 121.5, 127.8, 128.3, 128.9, 129.0, 129.1, 132.5, 136.5, 150.0, 151.5, 152.1 (Ph), 159.2 (CN_4H). Analysis found: C, 73.38; H, 5.19; N, 21.43%. Calcd for $C_{20}H_{17}N_5$ (327.39): C, 73.37; H, 5.23; N, 21.39%.

4.7.2. 3-(2-Benzyl-2*H*-tetrazol-5-yl)-2-methyl-4-phenylpyridine (23a). Yield 18%; light brown oil; ^{1}H NMR ($CDCl_3$, δ ppm): 2.45 (s, 3H, Me), 5.72 (s, 2H, $PhCH_2$), 7.01–7.06 (m, 2H, Ph), 7.10–7.16 (m, 4H, Ph), 7.18–7.22 (m, 1H, Ph), 7.24 (d, 1H, J=5.1 Hz, 5-H), 7.29–7.37 (m, 3H, Ph), 8.64 (d, 1H, J=5.1 Hz, 6-H). ^{13}C NMR ($CDCl_3$, δ ppm): 23.3 (CH_3), 56.7 (Ph*C*H_2), 122.0, 122.1, 127.8, 128.0, 128.1, 128.5, 129.8, 130.0, 133.3, 138.1, 149.6, 151.2 (Ph), 158.5 (CN_4H), 163.1 (Ph). Analysis found: C, 73.02; H, 5.08; N, 21.28%. Calcd for $C_{20}H_{17}N_5$ (327.39): C, 73.37; H, 5.23; N, 21.39%.

4.7.3. 4-(1-Benzyl-1*H*-tetrazol-5-yl)-3-methyl-6,7-dihydro-5*H*-cyclopenta[*c*]pyridine (22b). Yield 31%; grey crystals, mp 102–104 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 1.79–2.10 (m, 3H, CH_2), 1.99 (s, 3H, Me), 2.36–2.46 (m, 1H, CH_2), 2.83–2.97 (m, 2H, CH_2), 5.48 (d, 1H, J=15.2 Hz, $PhCH_2$), 5.57 (d, 1H, J=15.2 Hz, $PhCH_2$), 6.96–7.02 (m, 2H, Ph), 7.24–7.33 (m, 3H, Ph), 8.50 (s, 1H, 6-H). IR ν_{max} (film) 3034, 2962, 2864, 1578, 1495, 1452, 1404, 1240, 1115, 988, 937, 727, 702. Analysis found: C, 70.19; H, 5.88; N, 23.93%. Calcd for $C_{17}H_{17}N_5$ (291.36): C, 70.08; H, 5.88; N, 24.04%.

4.7.4. 4-(2-Benzyl-2*H*-tetrazol-5-yl)-3-methyl-6,7-dihydro-5*H*-cyclopenta[*c*]pyridine (23b). Yield 52%; brown oil; ^{1}H NMR (DMSO-d_6, δ ppm): 1.97–2.06 (m, 2H, CH_2), 2.54 (s, 3H, Me), 2.89–2.96 (m, 4H, CH_2), 6.04 (s, 2H, $PhCH_2$), 7.34–7.44 (m, 5H, Ph), 8.42 (s, 1H, 6-H). IR ν_{max} (film) 3420, 3033, 2957, 1720, 1581, 1498, 1456, 1437, 1152, 1030, 939, 723, 692. Analysis found: C, 69.83; H, 6.03; N, 23.74%. Calcd for $C_{17}H_{17}N_5$ (291.36): C, 70.08; H, 5.88; N, 24.04%.

4.8. Alkylation of the 5*H*-tetrazolo[1′,5′:1,5]pyrrolo[3,4-*b*]pyridine 16l

4.8.1. 5-Benzyl-9-*tert*-butyl-5*H*-tetrazolo[1′,5′:1,5]-pyrrolo[3,4-*b*]pyridine (24). Potassium *tert*-butoxide (0.112 g, 1.0 mmol) was added to a solution of compound **16l** (0.20 g, 1.0 mmol) in anhydrous THF (2 mL) at −10 °C. The ice-cold mixture was stirred for 30 min, and benzyl bromide (0.12 mL, 1.0 mmol) was added to the mixture under stirring. The mixture was then stirred at −10 °C for 3 h and treated with water (2 mL). The product was extracted with ethyl acetate (3×4 mL), the extract was dried over $MgSO_4$ and evaporated. The residue was chromatographed (silica gel, hexane/ethyl acetate 3:1) to give the titled product **24** (0.1 g, 33%) as pale yellow solid, mp 113–114 °C; ^{1}H NMR ($CDCl_3$, δ ppm): 1.43 (s, 9H, *t*-Bu), 3.65 (dd, 1H, J=14.2, 4.5 Hz, CH_2), 3.87 (dd, 1H, J=14.2, 4.5 Hz, CHH_2), 5.72 (t, 1H, J=4.5 Hz, CH), 6.61–6.65 (m, 2H, Ph), 6.93–7.05 (m, 3H, Ph), 7.36 (d, 1H, J=5.4 Hz, 5-H), 8.64 (d, 1H, J=5.4 Hz, 6-H). Analysis found: C, 75.61; H, 6.28; N, 17.70%. Calcd for $C_{18}H_{19}N_5$ (305.39): C, 70.80; H, 6.27; N, 23.00%.

4.8.2. 5,5-Dibenzyl-9-*tert*-butyl-5*H*-tetrazolo[1′,5′:1,5]-pyrrolo[3,4-*b*]pyridine (25). The title compound was also isolated (0.1 g, 25%) as white crystals, mp 195–197 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 1.12 (s, 9H, *t*-Bu), 3.85 (dd, 4H, J=17.1, 13.8 Hz, $2CH_2$), 6.43–6.48 (m, 4H, Ph), 6.86–6.98 (m, 6H, Ph), 7.38 (d, 1H, J=5.4 Hz, 5-H), 8.81 (d, 1H, J=5.4 Hz, 6-H). Analysis found: C, 75.70; H, 6.59; N, 17.70%. Calcd for $C_{25}H_{25}N_5$ (395.51): C, 75.92; H, 6.37; N, 17.71%.

4.8.3. 6-Benzyl-9-*tert*-butyl-6*H*-tetrazolo[1′,5′:1,5]-pyrrolo[3,4-*b*]pyridine (26). Benzyl bromide (0.024 mL, 0.2 mmol) was added to a solution of compound **16l** (0.04 g, 0.2 mmol) in anhydrous acetone (1 mL). The mixture was heated in sealed tube at 65 °C for 80 h then cooled and diluted with anhydrous ether (1 mL). The precipitate formed was filtered off, washed with cold ether (2 mL) and dried to give an intermediate pyridinium bromide (0.02 g, 29%) as white crystals, mp 175–180 °C (decomp.); ^{1}H NMR (DMSO-d_6, δ ppm): 1.62 (s, 9H, *t*-Bu), 6.01 (s, 2H, CH_2), 6.25 (s, 2H, CH_2), 7.30–7.62 (m, 5H, Ph), 8.29 (d, 1H, J=6.7 Hz, 5-H), 9.20 (d, 1H, J=6.7 Hz, 6-H). The salt obtained was treated with saturated aqueous solution of $NaHCO_3$ (1 mL), and the product was extracted with ethyl acetate (4×1 mL). The extract was evaporated to give the title product (**26**) (0.015 g, 26% for two steps) as deep red crystals, mp 170–175 °C (decomp.); ^{1}H NMR ($CDCl_3$, δ ppm): 1.72 (s, 9H, *t*-Bu), 5.28 (s, 2H, CH_2), 6.69 (d, 1H, J=6.8 Hz, 5-H), 7.27–7.31 (m, 2H, Ph), 7.32 (s, 1H, 7-CH), 7.38–7.45 (m, 3H, Ph), 7.64 (d, 1H, J=6.8 Hz, 6-H). ^{13}C NMR ($CDCl_3$, δ ppm): 28.6 (9-C, 10-C, 11-C), 36.6 (8-C), 58.5 (13-C), 84.8 (7-C), 103.9 (5-C), 104.3 (3-C), 127.9 (Ph), 129.2 (Ph), 129.5 (Ph), 132.4 (Ph), 134.1 (4-C), 137.1 (6-C), 161.3 (2-C), 174.0 (12-C) (atom numbering see Scheme 11). Analysis found: C, 70.42; H, 6.78; N, 22.59%. Calcd for $C_{18}H_{19}N_5$ +0.1 mol Et_2O (312.79): C, 70.65; H, 6.44; N, 22.39%.

4.9. Preparation of 3-(1,3,4-oxadiazol-2-yl)pyridines 27a–f

4.9.1. 2-Methyl-3-(5-methyl-1,3,4-oxadiazol-2-yl)-4-phenylpyridine (27a). Acetic anhydride (0.12 mL, 1.26 mmol) was added to a solution of compound **8a** (0.2 g, 0.84 mmol) in anhydrous acetonitrile (2 mL). The solution was subjected to microwave irradiation in sealed reactor at 120 °C for 1 h. The reaction mixture was evaporated to dryness, the residue was chromatographed (silica gel, hexane/ethyl acetate in gradient 2:1–1:1) to give the target product **27a** (0.2 g, 95%) as white crystals, mp 104–105 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 2.41 (s, 3H, CH_3), 2.48 (s, 3H, CH_3), 7.16–7.23 (m, 2H, Ph), 7.35–7.42 (m, 3H, Ph), 7.45 (d, 1H, J=5.1 Hz, 5-H), 8.72 (d, 1H, J=5.1 Hz, 6-H). Analysis found: C, 71.76; H, 5.15; N, 16.69%. Calcd for $C_{15}H_{13}N_3O$ (251.29): C, 71.70; H, 5.21; N, 16.72%.

4.9.2. 2-Methyl-4-phenyl-3-[5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl]pyridine (27b). Trifluoroacetic anhydride (0.23 mL, 1.68 mmol) was added to a solution of compound **8a** (0.2 g, 0.84 mmol) in anhydrous acetonitrile (2 mL). The mixture was stirred at room temperature for 2 h and then concentrated under reduced pressure to dryness. The residue was treated with saturated aqueous solution of $NaHCO_3$ (3 mL), the mixture was extracted with ethyl acetate (4× 5 mL). The extract was dried over $MgSO_4$ and evaporated. The residue was chromatographed (silica gel, hexane/ethyl acetate in gradient 2:1–1:1) to give the target product **27b** (0.32 g, 100%) as white solid, mp 109–110 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 2.65 (s, 3H, CH_3), 7.15–7.22 (m, 2H, Ph), 7.37–7.45 (m, 3H, Ph), 7.52 (d, 1H, J=5.1 Hz, 5-H), 8.80 (d, 1H, J=5.1 Hz, 6-H). Analysis found: C, 58.98; H, 3.24; F, 18.53; N, 13.71%. Calcd for $C_{15}H_{10}F_3N_3O$ (305.26): C, 59.02; H, 3.30; F, 18.67; N, 13.77%.

4.9.3. 1-(5-*tert*-Butyl-1,3,4-oxadiazol-2-yl)-2-methyl-5,6-dihydrobenzo[*f*]isoquinoline (27c). 2,2-Dimethylpropanoic anhydride (0.16 g, 0.84 mmol) was added to a suspension of compound **8b** (0.2 g, 0.76 mmol) in anhydrous acetonitrile (2 mL). The mixture was subjected to microwave irradiation in sealed reactor at 120 °C for 2 h. Additional 2,2-dimethylpropanoic anhydride (0.16 g, 0.84 mmol) was added to the mixture that then irradiated at the same temperature for 2 h again. The reaction mixture was poured into saturated aqueous solution of $NaHCO_3$ (5 mL), and the mixture was extracted with ethyl acetate (4×5 mL). The extract was washed with brine (10 mL), dried over $MgSO_4$ and evaporated to dryness. The residue was chromatographed (silica gel, hexane/ethyl acetate in gradient 2:1–1:1) to give the target product **27c** (0.23 g, 96%) as light creamy crystals, mp 110–111 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 1.31 (s, 9H, $(CH_3)_3$), 2.45 (s, 3H, CH_3), 2.77–2.88 (m, 4H, CH_2), 6.46 (m, 1H, Ph), 7.12 (m, 1H, Ph), 7.31 (m, 1H, Ph), 7.39 (m, 1H, Ph), 8.63 (s, 1H, 6-H). Analysis found: C, 75.11; H, 6.64; N, 13.14%. Calcd for $C_{20}H_{21}N_3O$ (319.41): C, 75.21; H, 6.63; N, 13.16%.

4.9.4. 1-[5-(2-Methoxyethyl)-1,3,4-oxadiazol-2-yl]-2-methyl-5*H*-chromeno[3,4-*c*]pyridine (27d). 3-Methoxypropanoic anhydride (0.16 g, 0.84 mmol) was added to a suspension of compound **8c** (0.2 g, 0.75 mmol) in anhydrous acetonitrile (2 mL). The mixture was subjected to microwave irradiation in sealed reactor at 120 °C for 2 h. Additional 3-methoxypropanoic anhydride (0.08 g, 0.42 mmol) was added to the mixture that then irradiated at the same temperature for 1 h again. The reaction mixture was poured into saturated aqueous solution of $NaHCO_3$ (5 mL), and the mixture was extracted with ethyl acetate (4×5 mL). The extract was washed with brine (10 mL), dried over $MgSO_4$ and evaporated to dryness. The residue was chromatographed (silica gel, hexane/ethyl acetate in gradient 2:1–1:100) to give the target product **27d** (0.2 g, 80%) as light yellow crystals, mp 89–91 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 2.38 (s, 3H, CH_3), 3.22 (t, 2H, J= 6.2 Hz, CH_2CH_2O), 3.25 (s, 3H, CH_3O), 3.69 (t, 2H, J= 6.2 Hz, CH_2–CH_2O), 5.17 (s, 2H, CH_2O, dihydropyrane ring), 6.45 (m, 1H, Ph), 6.90 (m, 1H, Ph), 7.11 (m, 1H, Ph), 7.38 (m, 1H, Ph), 8.67 (s, 1H, 6-H). Analysis found: C, 66.75; H, 5.13; N, 12.83%. Calcd for $C_{18}H_{17}N_3O_3$ (323.35): C, 66.86; H, 5.30; N, 13.00%.

4.9.5. 4-(5-Isopropyl-1,3,4-oxadiazol-2-yl)-3-methyl-6,7-dihydro-5*H*-cyclopenta[*c*]pyridine (27e). 2-Methylpropanoic anhydride (0.25 mL, 1.5 mmol) was added to a solution of compound **8g** (0.20 g, 1.0 mmol) in anhydrous acetonitrile (2 mL). The mixture was subjected to microwave irradiation in sealed reactor at 120 °C for 2 h. The reaction mixture was evaporated to dryness, and the residue was chromatographed (silica gel, hexane/ethyl acetate in gradient 7:3–1:100) to give the target product **27e** (0.24 g, 99%) as dark brown oil; ^{1}H NMR ($CDCl_3$, δ ppm): 1.46 (d, 6H, J=7.1 Hz, $CH(CH_3)_2$), 2.16 (m, 2H, J=7.6 Hz, CH_2), 2.80 (s, 3H, Me), 3.00 (t, 2H, J=7.6 Hz, CH_2), 3.18 (t, 2H, J=7.6 Hz, CH_2), 3.30 (m, 1H, J=7.1 Hz, $CH(CH_3)_2$), 8.45 (s, 1H, 6-H). Analysis found: C, 69.04; H, 6.95; N, 17.27%. Calcd for $C_{14}H_{17}N_3O$ (243.31): C, 69.11; H, 7.04; N, 17.27%.

4.9.6. 4-[5-(4-Chlorophenyl)-1,3,4-oxadiazol-2-yl]-3-methyl-6,7,8,9-tetrahydro-5*H*-cyclohepta[*c*]pyridine (27f). 4-Chlorobenzoic anhydride (0.31 g, 1.05 mmol) was added to a suspension of compound **8i** (0.2 g, 0.87 mmol) in anhydrous acetonitrile (2 mL). The mixture was subjected to microwave irradiation in sealed reactor at 120 °C for 3 h. The reaction mixture was evaporated to dryness, and the residue was treated with saturated aqueous solution of $NaHCO_3$ (5 mL). The mixture was extracted with ethyl acetate (4×5 mL). The extract was dried over $MgSO_4$ and evaporated to dryness. The residue was chromatographed (silica gel, hexane/ethyl acetate in gradient 2:1–1:100) to give the target product **27f** (0.2 g, 68%) as light yellow crystals, mp 105–107 °C; ^{1}H NMR ($CDCl_3$, δ ppm): 1.60 (m, 4H, $(CH_2)_2$), 1.82–1.91 (m, 2H, CH_2), 2.49 (s, 3H, Me), 2.64–2.70 (m, 2H, CH_2), 2.83–2.90 (m, 2H, CH_2), 7.52 (d, 2H, J=8.6 Hz, Ph), 8.04 (d, 2H, J=8.6 Hz, Ph), 8.38 (s, 1H, 6-H). Analysis found: C, 67.18; H, 5.37; Cl, 10.46; N, 12.24%. Calcd for $C_{19}H_{18}ClN_3O$ (339.83): C, 67.16; H, 5.34; Cl, 10.43; N, 12.37%.

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