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SYNTHESIS OF 3-(3-PIPERIDYL)-ISOQUINOLINE AND 3-(4-PIPERIDYL)-ISOQUINOLINE

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3-(3-Piperidyl)isoquinoline and 3-(4-piperidyl)isoquinoline have been synthesized from o-tolylaldehyde aldimines and the methylmethoxycarboxamides (Weinreb amides) of N-Boc-substituted nipecotic and isonipecotic acids.

Keywords: Weinreb amide, isoquinoline, 3-(3-piperidyl)isoquinoline, 3-(4-piperidyl)isoquinoline.

Despite the abundance of biologically active compounds containing an isoquinoline fragment the interest in a related structure has not diminished. At his time there has accumulated a rich volume of data concerning isoquinolines with different substituents in all positions [1]. At the same time, the development of methods leading to the preparation of 3-substituted isoquinolines has been given the least attention. This is possibly related to the large number of stages or to the low availability of starting reagents.

The Bischler-Napieralski and Pictet-Gams [1] methods have been used most often. The limitation of these routes is the mandatory presence of functional groups which activate the aromatic ring towards electrophilic substitution. More contemporary is a method based on the palladium catalyzed reaction of *o*-iodobenzaldehyde imines with different acetylenes which eventually leads to the formation of 3-substituted isoquinolines [2]. The particular value of this reaction is that, beside variation of the substituent in the 3 position, in certain conditions there may be introduced into the 4 position of the isoquinoline an iodine atom [3], aryl and allyl [4], and also acyl fragments [5]. This route is of great practical interest but the scope of readily available acetylenes is limited and the reaction course demands expensive catalysts. Another method based on the acylation of the methyl group of *o*-tolylaldehyde cyclohexylimine by Weinreb amides and subsequent cyclization in aqueous ammonia of the ketone formed to a 3-substituted isoquinoline [6] was the basis of the route we selected for the preparation of isoquinolines with a 3-piperidyl fragment in position 3. This type of compound is certainly of interest thanks to the combination of two known pharmacophoric heterocycles which, in turn, opens a route to novel, potentially biologically active compounds.

The N-Boc-substituted methylmethoxycarboxamides of 4- and 3-piperidinocarboxylic acids (**3** and **6** respectively) were used as the source of the piperidyl fragment. The synthesis of compound **3** was achieved by a

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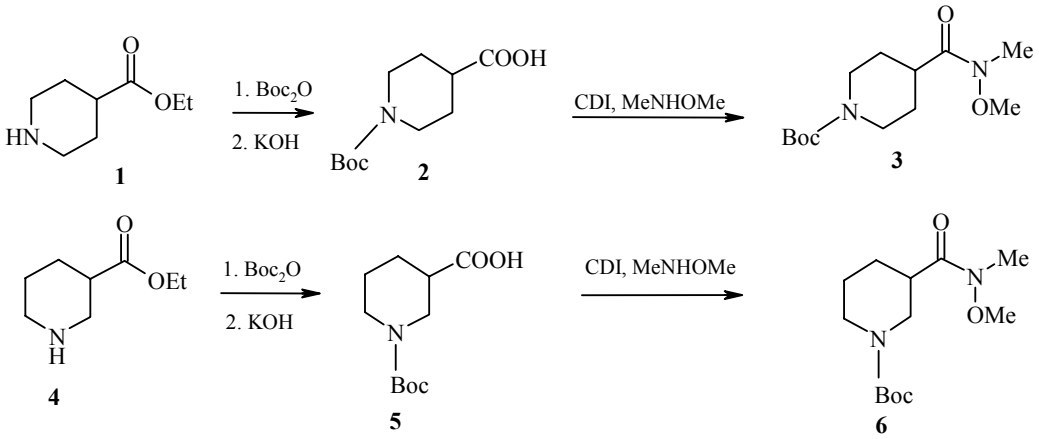
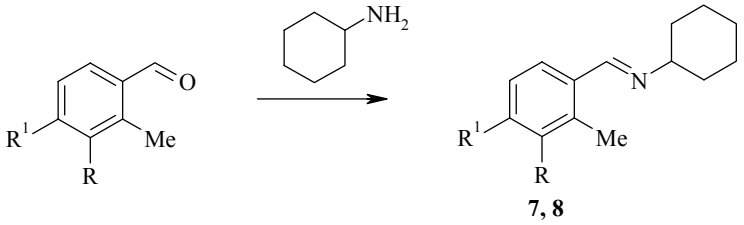
scheme including the introduction of a Boc-group into ethyl isonipecotate (**1**), hydrolysis of the ester, and subsequent acylation of N,O-dimethylhydroxylamine by N-Boc-isonipecotic acid (**2**). Amide **6** was prepared by a similar scheme from ethyl N-Boc-nipecotate with intermediate separation of N-Boc-nipecotic acid (**5**).



1 **2** **3** **4** **5** **6**

CDI – N,N'-carbonyldiimidazole

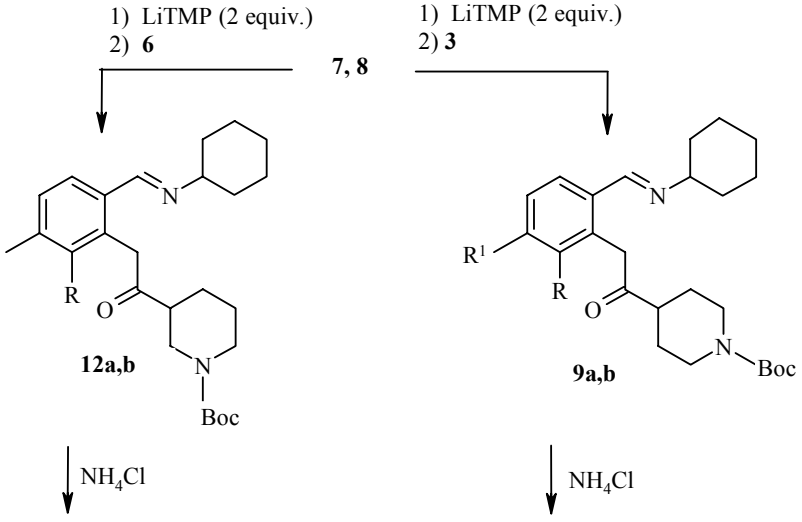
2-Methylbenzaldehyde and 4-methoxy-2,3-dimethylbenzaldehyde were used as precursors of the isoquinoline fragment. Schiff bases were prepared by a classical method.



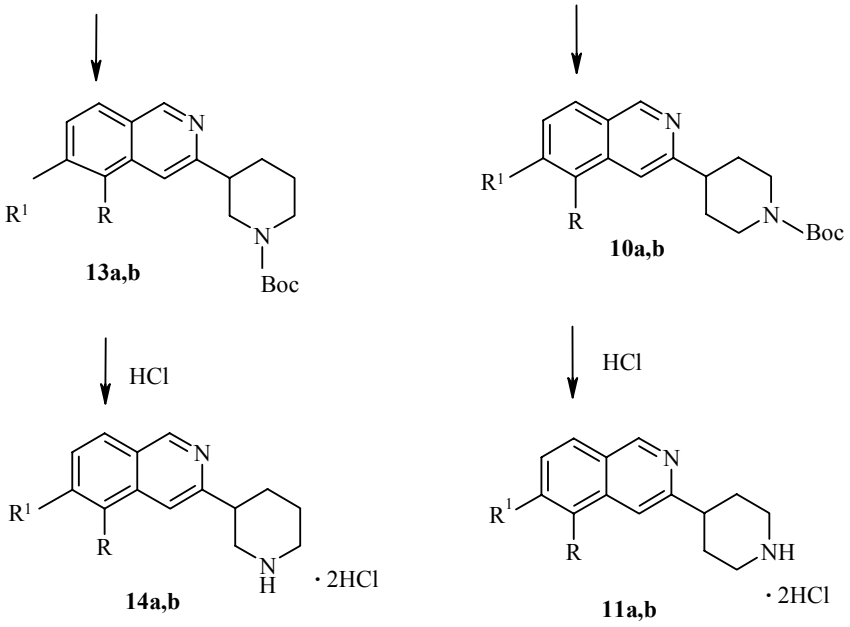
7, 8

7 R = R^1 = H; **8** R = Me, R^1 = OMe

Metallation of imines **7** and **8** was carried out under conditions close to those used in the study [6] adding compounds **7** and **8** to a solution of lithium tetramethylpiperide (LiTMP) in THF at low temperature and then treatment with the Weinreb amide.



12a,b **9a,b**



9–14 a R = R^1 = H; **b** R = Me, R^1 = OMe

As found experimentally, treatment of the reaction mixture with a saturated solution of ammonium chloride at the stage of preparation of ketones of type **9** and **12** leads to partial, or sometimes full, cyclization to form the isoquinolines **10** and **13** but further refluxing in aqueous ammonia did not increase the yield of the target cyclization product (Table 1).

The authors of the report [6] have shown the reaction needs, as a minimum, the addition of a further equivalent of the lithium base for satisfactory yields. We propose that the first equivalent is most likely consumed by deprotonation of the tertiary carbon atom of the cyclohexyl fragment (route A) or by formation of a benzyl anion which is accompanied by migration of the double bond (route B). The second equivalent is used for deprotonation of the methyl group.

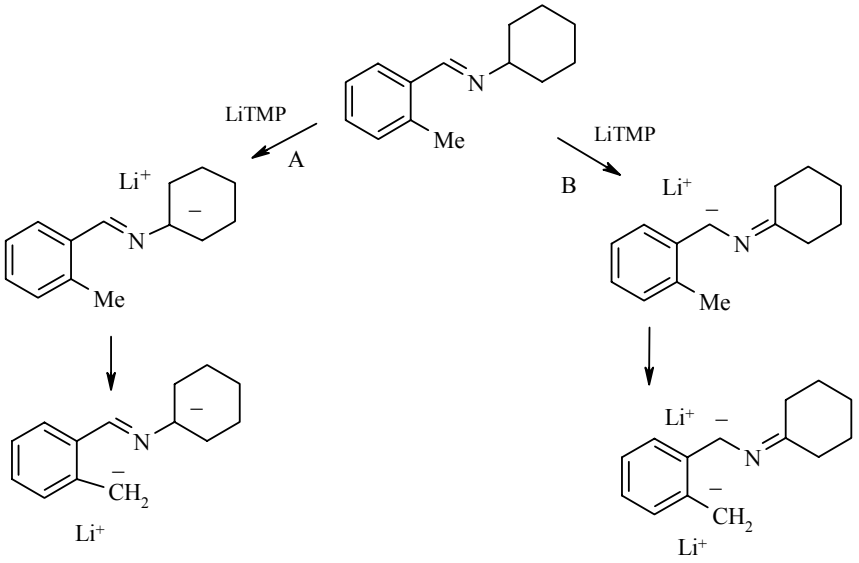


TABLE 1. Characteristics of the Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, %				*m/z* $[M+H]^+$	mp, °C	Yield, %
		C	H	Cl	N			
10a	$C_{19}H_{24}N_2O_2$	73.12 / 73.05	7.67 / 7.74	—	9.01 / 8.97	313	120-121	47
10b	$C_{21}H_{28}N_2O_3$	70.84 / 70.76	7.88 / 7.92	—	7.75 / 7.86	357	144-146	31
11a	$C_{14}H_{18}Cl_2N_2$	59.12 / 58.96	6.40 / 6.36	24.77 / 24.86	9.93 / 9.82	213	195-199	93
11b	$C_{16}H_{22}Cl_2N_2O$	58.45 / 58.36	6.71 / 6.73	21.61 / 21.53	8.60 / 8.51	257	237-241	96
13a	$C_{19}H_{24}N_2O_2$	73.11 / 73.05	7.69 / 7.74	—	9.03 / 8.97	313	105-107	48
13b	$C_{21}H_{28}N_2O_3$	70.84 / 70.76	7.85 / 7.92	—	7.88 / 7.86	357	152-155	38
14a	$C_{14}H_{18}Cl_2N_2$	59.05 / 58.96	6.31 / 6.36	24.80 / 24.86	9.88 / 9.82	213	220-222	96
14b	$C_{16}H_{22}Cl_2N_2O$	58.40 / 58.36	6.79 / 6.73	21.50 / 21.53	8.57 / 8.51	257	247-250	94
14c	$C_{24}H_{27}N_2O_3$	72.84 / 73.38	6.51 / 6.43	—	7.56 / 7.44	377	—	71
14d	$C_{21}H_{27}ClN_4O$	67.31 / 67.22	6.57 / 6.62	8.05 / 8.63	13.71 / 13.63	411 and 413	—	77
14e	$C_{22}H_{26}Cl_2N_2O$	64.81 / 65.19	6.58 / 6.46	18.10 / 17.99	7.12 / 6.91	333	117-121	55

TABLE 2. ^{1}H NMR Spectra of the Compounds Synthesized

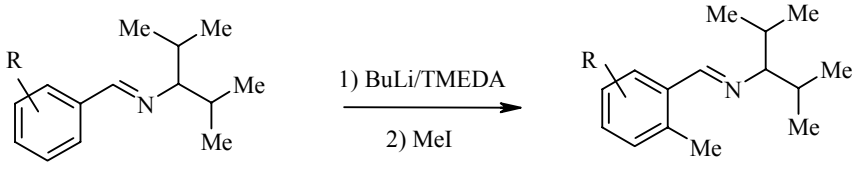
Compound	Chemical shifts, δ, ppm (*J*, Hz)*
1	2
3	1.49 (9H, s, *t*-Bu); 1.71 (4H, m, CH_2CHCH_2); 2.81 (3H, m, CH_2N+CH); 3.19 (3H, s, OCH_3); 3.71 (3H, s, NCH_3); 4.19 (2H, m, CH_2N)
6	1.41 (9H, s, *t*-Bu); 1.51 and 1.91 (2H, m, $CH_2CH_2CH_2CH$); 1.72 (2H, m, $CH_2CH_2CH_2CH$); 2.71 (1H, m, CH); 2.91 (2H, m, CH_2N); 3.15 (3H, s, OCH_3); 3.74 (3H, s, NCH_3); 4.09 and 4.19 (2H, m, CH_2N)
8	1.15–1.80 (10H, m, $(CH_2)_5$); 2.10 (3H, s, 3-CH_3); 2.35 (3H, s, 2-CH_3); 3.18 (1H, m, CH_2CHCH_2); 3.78 (3H, s, OCH_3); 6.84 (1H, d, *J* = 8.7, H-5); 7.59 (1H, d, *J* = 8.7, H-6); 8.58 (1H, s, HC=N)
10a	1.49 (9H, s, *t*-Bu); 1.68 (2H, m, $CHCH_2$); 1.95 (2H, m, $CHCH_2$); 2.89 (2H, m, CH_2N); 3.0 (1H, m, CH_2CHCH_2); 4.11 (2H, m, CH_2N); 7.58 (1H, t, *J* = 7.3, H-7); 7.65 (1H, s, H-4); 7.72 (1H, t, *J* = 7.8, H-6); 7.87 (1H, d, *J* = 8.2, H-5); 8.04 (1H, d, *J* = 7.8, H-8); 9.21 (1H, s, H-1)
10b	1.42 (9H, s, $C(CH_3)_3$); 1.70 (2H, m, CH_2CH), 1.86 (2H, m, CH_2CH); 2.39 (3H, s, 5-CH_3); 2.81 (2H, m, CH_2N); 2.96 (1H, m, CH_2CHCH_2); 3.91 (3H, s, 6-OCH_3); 4.10 (2H, m, CH_2N); 7.46 (1H, d, *J* = 8.5, H-7); 7.55 (1H, s, H-4); 7.93 (1H, d, *J* = 8.5, H-8); 9.09 (1H, s, H-1)
11a	2.11 (2H, m, $CHCH_2$); 2.25 (2H, m, $CHCH_2$); 3.09 (2H, m, CH_2N); 3.41 (3H, m, CH_2N and CH_2CHCH_2); 7.82 (1H, t, *J* = 7.8, H-7); 8.05 (1H, t, *J* = 7.8, H-6); 8.09 (1H, s, H-4); 8.15 (1H, d, *J* = 7.8, H-5); 8.35 (1H, d, *J* = 7.8, H-8); 9.11 (1H, br. s, NH); 9.31 (1H, br. s, HCl); 9.61 (1H, s, H-1)
11b	2.19 (2H, m, $CHCH_2$); 2.29 (2H, m, $CHCH_2$); 2.39 (3H, s, CH_3); 3.11 (2H, m, CH_2N); 3.44 (3H, m, CH_2CHCH_2+CH_2N); 4.11 (3H, s, OCH_3); 7.58 (1H, br. d, H-7); 7.91 (1H, br. d, H-8); 8.15 (1H, s, H-4); 9.41 (3H, br. s, H-1 + NH + HCl)
13a	1.41 (9H, s, *t*-Bu); 1.51–2.02 (4H, m, CH_2CH_2); 2.81–2.91 (2H, m, CH_2N); 3.09 (1H, m, CH_2CHCH_2); 3.95–4.21 (2H, m, CH_2N); 7.61 (1H, t, *J* = 7.8, H-7); 7.69 (1H, s, H-4); 7.75 (1H, t, *J* = 7.3, H-6); 7.91 (1H, d, *J* = 8.2, H-5); 8.05 (1H, d, *J* = 7.8, H-8); 9.26 (1H, s, H-1)

TABLE 2 (continued)

1	2
13b	1.40 (9H, s, *t*-Bu); 1.57–1.89 (4H, m, C$\underline{H}_2$C$\underline{H}_2$); 2.33 (3H, s, 5-CH_3); 2.83 (2H, m, CH_2N); 3.09 (1H, m, $CH_2C\underline{H}CH_2$); 3.81 (3H, s, 6-OCH_3); 3.95 (1H, m, CH_2N); 4.20 (1H, m, CH_2N); 7.39 (1H, d, *J* = 8.5, H-7); 7.50 (1H, s, H-4); 8.01 (1H, d, *J* = 8.5, H-8); 9.11 (1H, s, H-1)
14a	1.91–2.19 (4H, m, CHC$\underline{H}_2$C$\underline{H}_2$N); 2.91 (1H, m, $CH_2C\underline{H}CH_2$); 3.31 (2H, m, CH_2N); 3.61 (2H, m, CH_2N); 7.81 (1H, t, *J* = 7.3, H-7); 7.96 (1H, t, *J* = 7.3, H-6); 8.09 (1H, d, *J* = 8.5, H-5); 8.11 (1H, s, H-4); 8.34 (1H, d, *J* = 8.2, H-8); 9.41 (1H, br. s, NH); 9.61 (1H, br. s, HCl); 9.63 (1H, s, H-1)
14b	1.95–2.11 (4H, m, C$\underline{H}_2$C$\underline{H}_2$); 2.45 (3H, s, CH_3); 2.91 (1H, m, $CH_2C\underline{H}CH_2$); 3.31–3.62 (4H, m, 2CH_2N); 4.09 (3H, s, OCH_3); 7.80 (1H, d, *J* = 8.9, H-7); 8.08 (1H, s, H-4); 8.38 (1H, d, *J* = 9.1, H-8); 9.43 (1H, br. s, NH); 9.51 (1H, s, H-1); 9.72 (1H, br. s, HCl)
14c	1.67–2.12 (4H, m, CHC$\underline{H}_2$C$\underline{H}_2$); 3.01 (1H, m, $CH_2C\underline{H}CH_2$); 3.39 and 3.57 (2H, both m, CH_2N); 3.73 (6H, br. s, 2CH_3O); 4.56 and 3.71 (2H, both m, CH_2N); 6.53 (2H, m, H-5 Ar and H-6 Ar); 7.09 (1H, br. s, H-3 Ar); 7.51-8.09 (5H, m, H-4,5,6,7 and H-8 isoquinoline); 9.16 and 9.25 (1H, both br. s, H-1 isoquinoline)
14d	1.37 (3H, d, *J* = 6.2, CH_3); 1.80-2.16 (7H, m, CHC$\underline{H}_2$C$\underline{H}_2$, CH_3 pyrazole); 2.21 (3H, s, CH_3 pyrazole); 2.52-2.70 (1H, m, C(O)CH); 3.10-3.40 (5H, m, $CH_2C\underline{H}CH_2$, CH_2N and C(O)CHC$\underline{H}_2$N); 3.57-3.63 (2H, m, CH_2N); 7.90 (1H, br. s, H-7 isoquinoline); 8.08-8.30 (3H, m, H-4,5,6 isoquinoline); 8.45 (1H, d, *J* = 8.2, H-8 isoquinoline); 9.31 (1H, s, H-1 isoquinoline)
14e	1.70–2.20 (4H, m, CHC$\underline{H}_2$C$\underline{H}_2$); 2.97 (1H, m, $CH_2C\underline{H}CH_2$); 3.20-3.49 (2H, m, CH_2N); 3.65–3.72 (2H, m, CH_2N); 3.81 (3H, s, OCH_3); 4.30 (2H, s, Ar$\underline{CH}_2$); 7.05 (2H, br. d, H-3,6 Ar); 7.41 (1H, s, H-4 isoquinoline); 7.55-8.10 (4H, m, H-4,5 Ar, H-6,7 isoquinoline); 8.17 (2H, br. d, H-5,8 isoquinoline); 9.41 (1H, s, H-1 isoquinoline); 10.95 (1H, br. s, HCl)

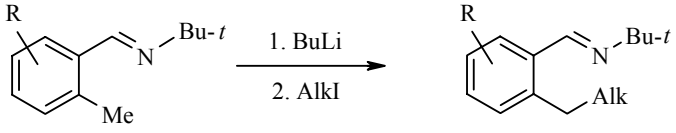
* ^{1}H NMR spectra recorded in $CDCl_3$ (compounds **3** and **6**) or in DMSO-d_6 (remaining compounds).

According to the results of the two experiments under similar conditions but with different amounts of base (1 and 2 equivalents) there is formed in the first case a small yield of the isoquinoline (~ 6%) and in the second an acceptable yield (59%). It should be noted that different data is given in publications by other authors. Thus according to [7], the Schiff base from benzaldehyde and the sterically hindered 3-amino- 2,4-dimethylpentane is readily metallated at position 2 of the aromatic ring and does not need this excess of base.

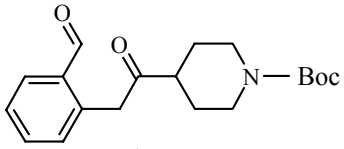


TMEDA – tetramethylenediamine

Other authors [8] have revealed the possibility of using a Schiff base from *tert*-butylamine which does not have the structural possibility of deprotonation under the action of base. However, the yield of the alkylation product is very low.



The formation of a tolyl anion is accompanied by the appearance of a deep violet color but treatment with the Weinreb agents **3, 6** causes almost complete decolorization. For analysis of the products of the acylation stage the reaction mass was treated not with NH_4Cl solution but with water. Chromato-mass spectrometric analysis (in the example of compound **9a**) showed that the acylation product of the *o*-tolyl-aldehyde **15** predominates in solution.



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None the less, in the studies [7, 8] there appear data supporting the formation of ketones with retention of the cyclohexyl fragment. Moreover, the authors point to the necessity of treating with a solution of ammonium chloride with subsequent refluxing of such a ketone in aqueous ammonia to reach completion of the reaction, i.e. formation of the isoquinoline fragment.

In our work we have shown that the formation of isoquinolines **11** and **14** needs only short treatment with NH_4Cl solution. This fact testifies to the formation of keto aldehyde **15**.

The ^{1}H NMR spectra of the N-Boc-substituted 3-piperidylisoquinolines **10** and **13** (Table 2) show signals for the piperidyl fragment at 1.5-4.0 ppm and a narrow singlet at 9.2 ppm corresponding to the 1-proton of the isoquinoline. The nine protons of the *tert*-butoxycarbonyl group appear as a narrow singlet at 1.4-1.5 ppm.

The amines **11a,b** ad **14a,b** satisfy all of the demands of the Lipinski rule [9], appearing as potentially biologically active compound. The selection criteria for the Lipinski rule are molecule weight (< 500), calculated solubility, control value ClogP (<5), as well as the number of donor and acceptor hydrogen bonds which should not be greater than 5 and 10 respectively.

Screening of the inhibitory activity towards protein kinases for the obtained amine derivatives **11a,b** and **14a,b**, obtained by reductive amination, and those derivatives obtained by acylation with carboxylic acids and sulfochlorides revealed significant activity in compounds **14c-e** (see Table 3).

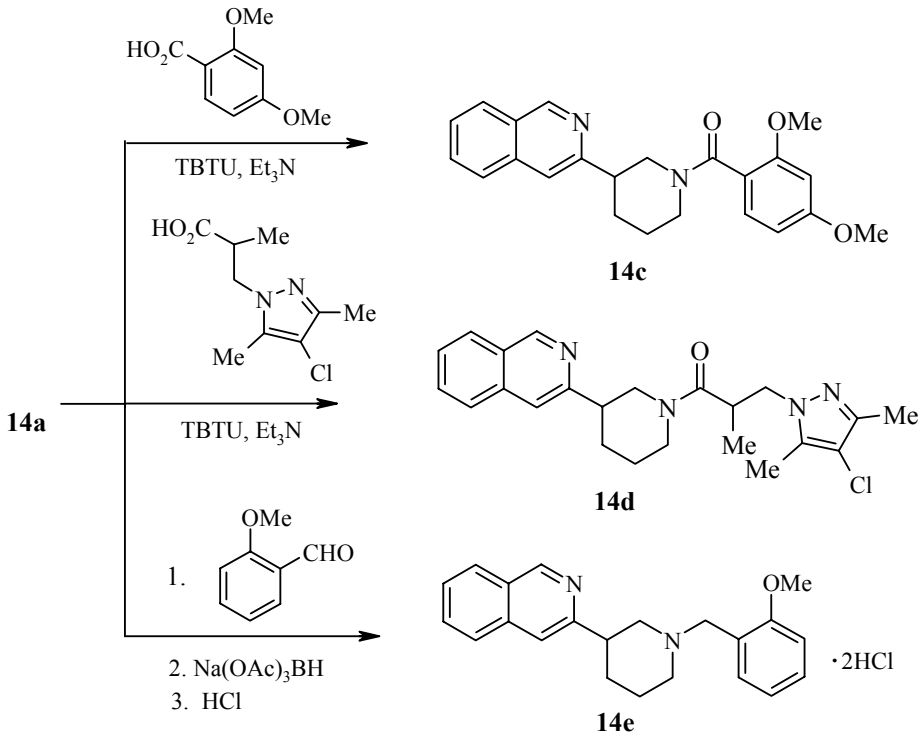
Hence we have synthesized the novel isoquinolines 3-(3-piperidyl)isoquinoline and 3-(4-piperidyl)isoquinoline. Use of this method leads to the production of isoquinolines with different amino acid residues at position 3. The introduction and subsequent modification of the piperidyl fragment leads to the preparation of substances inhibiting protein kinases.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Mercury 400 (400 MHz) instrument using TMS as internal standard. Melting points were measured on a Gallenkamp apparatus. The course of the reactions was monitored by TLC on Silica gel/TLC card plates (Fluka) with different eluents. Chromato mass spectra were obtained on a

TABLE 3. Bioscreening Results

Compound	Type of inhibited kinase	IC_{50}, μmol
14c	Bruton's Tyrosine Kinase [10]	0.5
	Glycogen synthase Kinase 3b [11]	10.0
14d	BTK	0.9
14e	GSK 3b	9.0
	Lymphocyte Kinase [12]	3.5



TBTU – 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate

Thermo Finnigan Surveyor MSQ chemical ionization instrument for a solution (15 eV) with a YMC Hydrosphere C18 column (12 nm, S-3 μm, 33×3 mm) using gradient elution (acetonitrile – 0.1% aqueous formic acid, eluent flow rate 1.3 ml/min).

N-Boc-isonipecotic Acid Methoxymethylamide (3). A solution of di-*tert*-butylpyrocarbonate (480 g, 2.2 mol) in dichloromethane (400 ml) was added dropwise to a solution of the ethyl ester **1** (317 g, 2.0 mol) in dichloromethane (500 ml) at 0ºC. The reaction mixture was stirred for 1 h. At the end of the reaction the solvent was evaporated and the ethyl N-Boc- isonipecotate obtained was dissolved in a mixture of ethanol (100 ml) and water (600 ml). KOH (150 g, 2.7 mol) was added portionwise at room temperature, the product was stirred at room temperature for 6-7 h, and 5% hydrochloric acid was added to neutrality at the end of the reaction. The precipitated acid **2** was filtered off, washed with water, and dried *in vacuo* to give product (420 g, 91% based on ester **1**). N,N-Carbonyl-diimidazole (171 g, 1.06 mol) was added portionwise with stirring to a suspension of acid **2** (220 g, 0.96 mol) in acetonitrile (800 ml). After 30 min, N,O-dimethylhydroxylamine hydrochloride (87 g, 1.25 mol) followed by a solution of triethylamine (130 g, 1.3 mol) in acetonitrile (150 ml) were added. The product was held for 5-7 h and the triethylamine hydrochloride was filtered off and washed with cold ethyl acetate. The mother liquor was evaporated by 2/3 from the starting volume, diluted with ethyl acetate (200 ml), and washed with 5% $NaHCO_3$. The organic layer was separated, dried over Na_2SO_4, evaporated, and purified by flash chromatography to give an oil which was triturated with hexane. The precipitate was filtered, washed with hexane, and dried to give N-Boc-isonipecotic acid methylmethoxycarboxamide (**3**) (233 g, 81%).

N-Boc-nipecotic Acid Methoxymethylamide (6). By a similar method from the ethyl nipecotate **4** (150 g, 0.95 mol) to give the N-Boc-nipecotic acid (**5**) (202 g, 93% based on ester **4**). This material (201 g, 0.88 mol) gave amide **6** (177 g, 74%).

2,3-Dimethyl-4-benzaldehyde Cyclohexylimine (8). A solution of 4-methoxy-2,3-dimethylbenzaldehyde (27.6 g, 0.17 mol), cyclohexylamine (16.7 g, 0.17 mol), and *p*-toluenesulfonic acid (0.01 g) was refluxed in benzene (300 ml) using a Dean-Stark apparatus. Solvent was evaporated and the oil obtained was triturated with hexane to give compound **8** (38.1 g, 92%).

***o*-Tolylaldehyde Cyclohexylimine (7)** was prepared similarly from *o*-tolylaldehyde (67.3 g, 0.56 mol). Yield of compound **7** 104.7 g (93%); bp 120-125ºC (1 mm Hg [6]).

N-Boc-3-(4-piperidyl)isoquinoline (10a). BuLi (150 ml, 0.37 mol, 2.5 molar in hexane) was added to a solution of 2,2,6,6-tetramethylpiperidine (52.3 g, 0.37 mol) in THF (750 ml) at -45ºC under an argon atmosphere. The mixture was held for 20-30 min at -40ºC and then from -17 to -20ºC. A solution of compound **7** (35.5 g, 0.18 mol) in THF was added dropwise. The solution obtained was dark-crimson in color and was stirred in an argon stream for 20-30 min at -20ºC. A solution of amide **3** (58 g, 0.21 mol) in THF was added in one portion, stirred for 30 min, and treated with a saturated solution of NH_4Cl (100 ml). Solvent was evaporated, extracted with ethyl acetate, and the organic layer was separated and evaporated. The oil obtained was treated with 20% aqueous ammonia (100 ml), several drops of acetic acid were added, and the product was stirred for 1 h at 80ºC. It was then cooled and extracted with ethyl acetate. The organic layer was washed twice with water (2×100 ml) to weakly basic reaction, dried over Na_2SO_4, and evaporated. Column chromatographic purification gave the N-Boc-isoquinoline **10a** (26.1 g, 47%).

Isoquinolines 10b, 13a,b (Tables 1 and 2) were prepared similarly.

3-(4-Piperidyl)isoquinoline Hydrochloride (11a). Dioxane saturated with hydrogen chloride (20 ml) was added to a refluxing solution of compound **10a** (3.5 g, 11 mmol) in 2-propanol (40 ml). At the end of the reaction the precipitate was filtered off, washed with 2-propanol, and dried to give compound **11a** (2.9 g, 93%).

Piperidylisoquinoline Hydrochlorides 11b, 14a,b (Tables 1 and 2) were prepared similarly.

3-(3-Piperidyl)isoquinoline Amides 14c,d (General Method). Triethylamine (0.25 ml, 2.5 mmol) was added to a suspension of amine **14a** (0.28 g, 1 mmol), 2,4-dimethoxybenzoic acid (or 3-(4-chloro-3,5-dimethylpyrazol-1-yl)-2-methylpropionic acid) (1 mmol), and 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyl-uronium tetrafluoroborate (0.32 g, 1 mmol) in acetonitrile (15 ml). The solution was stirred for 2 h, treated with saturated potassium carbonate solution (15 ml), and extracted with ethyl acetate. The organic layer was separated and evaporated and the residue was column chromatographed.

N-(2-Methoxybenzyl)-3-(3-piperidyl)isoquinoline (14e). Triethylamine (0.15 g, 1.5 mmol) was added to a suspension of amine **14a** (0.28 g, 1 mmol) and 2-methoxybenzaldehyde (0.13 g, 1 mmol) in acetonitrile (15 ml). After 10-15 min, sodium triacetoxyborohydride (0.42 g, 2 mmol) was added and the product was stirred for 1 day, and treated with saturated potassium carbonate solution (15 ml). The product was extracted with ethyl acetate and the organic layer was separated and evaporated. The amine **14e** was purified on a chromatographic column and treated with dioxane (2-3 ml) saturated with hydrogen chloride to give the amine hydrochloride **14e** (0.22 g, 55%).

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