Synthesis and Characterization of N-Substituted Tetrahydroisoquinoline Derivatives *via* a Pictet-Spengler Condensation

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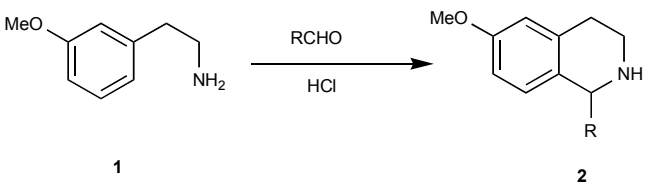
Abstract: Synthesis of N-substituted 1,2,3,4 –tetrahydroisoquinoline derivatives and bis-isoquinoline has been carried out *via* a Pictet-Spengler condensation. Tetrahydroisoquinolines were obtained from 2-(3',4'-dimethoxyphenyl) ethylamine in four steps. The entire synthesized compounds were characterized by IR, ^{1}H NMR and mass spectral data.

Keywords: Tetrahydroisoquinoline, Pictet-Spengler reaction, Imine, Trifluoroacetic acid.

INTRODUCTION

Tetrahydroisoquinoline (THIQ) alkaloids have attracted considerable interest over the years due to their potent biological activities. A wide range of N-substituted 1,2,3,4 -tetrahydroisoquinolines has been found to be a useful starting material for the construction of a variety of medically attractive intermediates [1, 2]. THIQ derivatives possess neuroprotective activity against neurological diseases such as epilepsy, ischemia, Parkinson's disease and multiple sclerosis [3-6]. The natural alkaloids containing THIQ unit are generally optically active compounds and possess antihypertensive, hemostatic, smooth or skeletal muscle relaxant, antispasmodic, antitussive, antimalarial, narcotic, analgesic or antipyretic activities [7-10]. Moreover, THIQ is a basic structural unit of many alkaloids isolated from natural sources which showed antitumor[11], antimicrobial[12] and other biological activities [13-17]. The Pictet-Spengler reaction and Bischler-Napieralski reaction are the key reactions for construction of the isoquinoline skeleton [18]. The Pictet-Spengler reaction is an acid-catalyzed intramolecular cyclization of the intermediate imine, which is formed by condensation of 2-arylethylamine with a carbonyl compound (Scheme **1**) [19-21].

Pictet-Spengler Reaction



1 **2**

Scheme 1:

Pictet-Spengler reaction was used in cyclocondensation of β-phenethylamine (**3**) with formaldehyde dimethyl acetal (**4**) in the presence of hydrochloric acid to give 1-methyl-1,2,3,4- tetrahydroisoquinoline (**5**) [22]. The reaction was later modified and subsequently intramolecular electrophilic substitution was proposed as depicted in (Scheme **2**) [23].

To improve the activity of THIQ based derivatives for various biological purposes such as antispasmodic, anticonvulsant efficacy, antimalarial, antimicrobial etc., we have introduced an extra heterocyclic ring in it. It is expected that such modification can improve the potential of resulted compounds. Therefore, we are reporting a four step synthetic strategy that gives N-substituted tetrahydro-isoquinoline derivatives. In this work we have also reported bis-isoquinoline synthesized by condensation of 2-(3',4'-dimethoxyphenyl)ethylamine and pthalal-dehyde.

RESULTS AND DISCUSSION

Scheme **3** shows the synthetic route of six new THIQ derivatives. We have also synthesized novel bis-THIQ (16) by adopting similar synthetic methodology (Scheme **4**).

First step of the synthesis is the condensation of 2-(3',4'-dimethoxyphenyl)ethylamine and substituted aldehydes in anhydrous toluene. It is followed by cyclization in presence of trifluoroacetic acid (TFA) to afford 1-(4-substitutedphenyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline. Further, product of the second step was treated with chloroacetyl chloride afforded the expected product in a good yield. The synthesis of proposed isoquinoline derivative has been completed by treating 2-chloro-1-(3,4-dihydro-6,7-dimethoxy-1-(4-substitutedphenyl)isoquinolin-2(1H)-yl)ethanone (12) with morpholine/N-methylpiperazine in presence of activated K_2CO_3.

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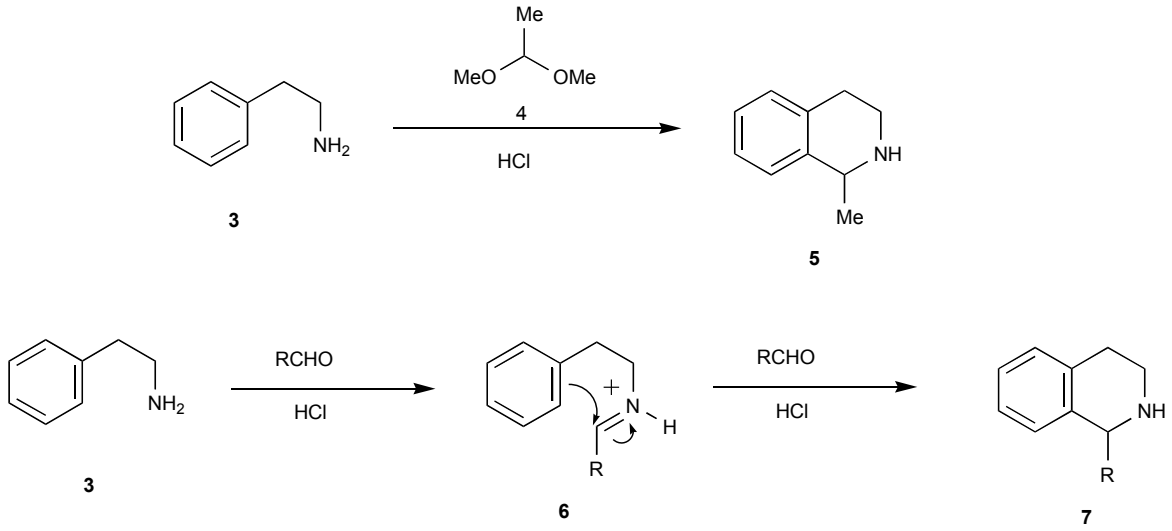
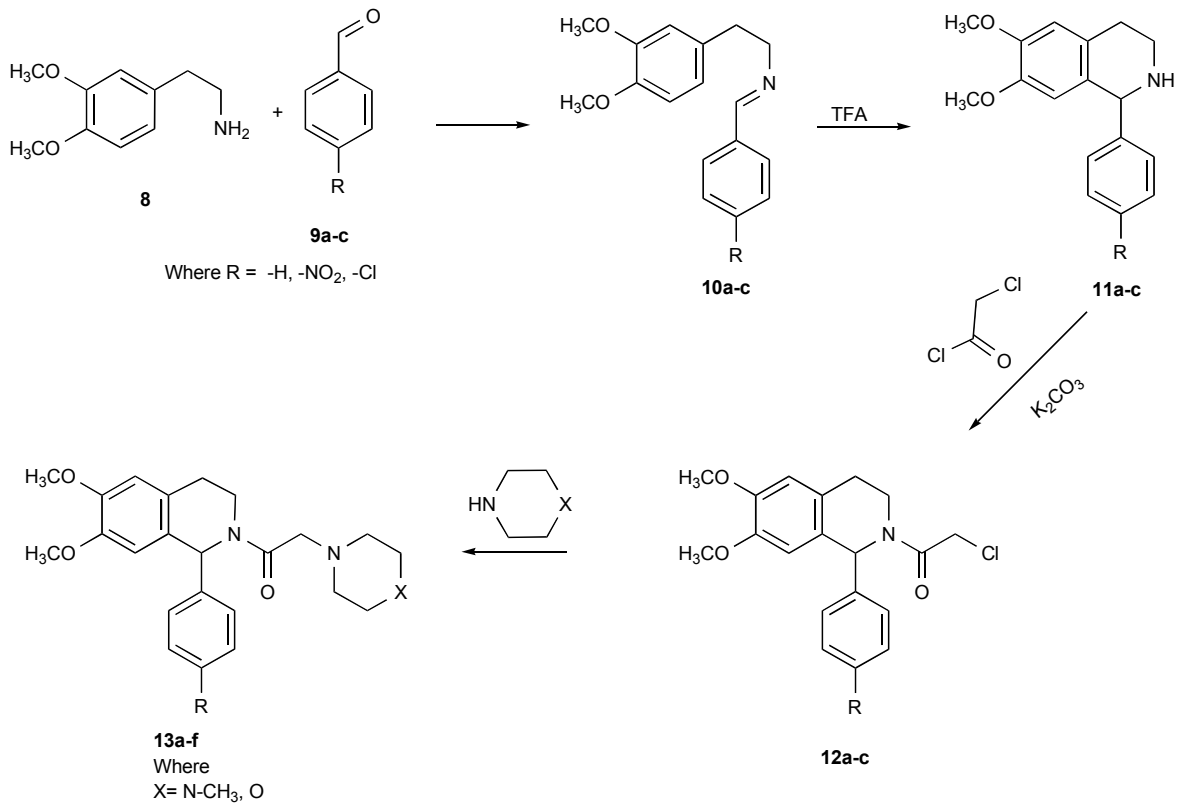


Scheme 2:

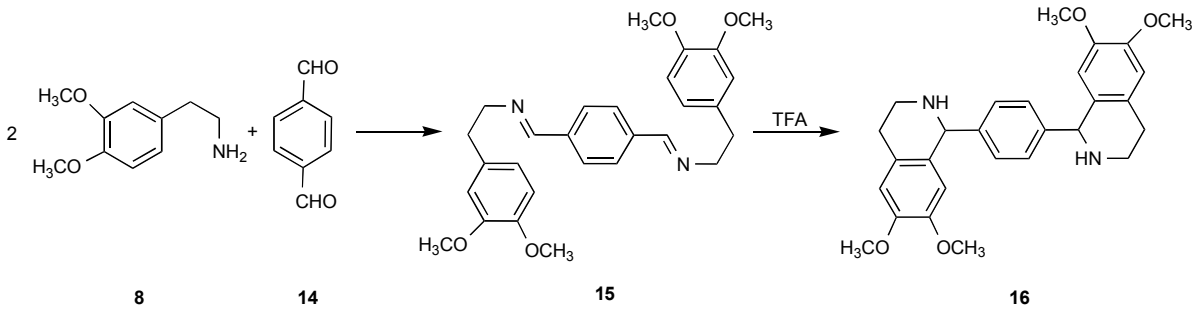


Scheme 3:

Bis-isoquinoline derivative, namely, 1,2,3,4-tetrahydro-1-(4-(1,2,3,4-tetrahydro-6,7-dimethoxy isoquinolin-1-yl)phenyl)-6,7-dimethoxyisoquinoline (16) has also been synthesized by the condensation of 2-(3',4'-dimethoxyphenyl)ethylamine (8) and pthaldehyde (14) followed by cyclization in presence of TFA. The introduction of morpholine/N-methylpiperazine ring in the THIQ derivatives may result improved biological activities.

EXPERIMENTAL

Reagents were purchased from SD Fine, Sisco Research Laboratory (SRL), Qualigens Limited. TLC was performed on Merck 60 F_{254} aluminium coated plates and the spots were visualized under UV light. ^1H NMR spectra were recorded on Bruker Avance 400 spectrometer in $CDCl_3$. Mass spectra were recorded on Thermo-Fischer DSQ II GCMS instrument. IR spectra



8 14 15 16

Scheme 4:

were recorded on a Shimadzu Prestige 21 spectrometer. Melting points were recorded in a Thiele's tube using paraffin oil and are uncorrected.

General Procedure for the Synthesis of N-(Substitutedbenzylidene)-2-(3,4-dimethoxyphenyl) ethanamine (10a-c)

A mixture of 2-(3',4'-dimethoxyphenyl)ethylamine (1.8g, 10mmol) and suitable aldehyde derivative (12mmol) in anhydrous toluene (50mL) was refluxed for 3h and then cooled and evaporated in vacuo. The oil residue was treated with diethyl ether to give a solid residue, which was crystallized from ethanol to afford the desired imine.

(E)-N-benzylidene-2-(3,4-dimethoxyphenyl) ethanamine (10a)

Yield 71.1 %, Pale Yellow crystals. Melting point 119-121 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.92-3.95 (t, 2H, $ArCH_2$), 3.79 (s, 3H, OMe), 3.82 (s, 3H, OMe), 3.80-3.83 (m, 2H, NCH_2), 6.58-6.67 (m, 3H, ArH), 7.42-7.46 (m, 3H, ArH), 7.63-7.66 (m, 2H, ArH), 8.16 (s, 1H, =CH). Mass (EI): m/z (%): M^+ 269 (10.0), 270 (18.47), 192 (100). IR (KBr, cm^{-1}): 1588.

(E)-N-(4-nitrobenzylidene)-2-(3,4-dimethoxyphenyl) ethanamine (10b)

Yield 74.3 %, Yellow crystals. Melting point 130 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.98-3.01 (t, 2H, $ArCH_2$), 3.82 (s, 3H, OMe), 3.85 (s, 3H, OMe), 3.89-3.93 (t, 2H, NCH_2), 6.73-6.81 (m, 3H, ArH), 7.85-7.87 (d, 2H, ArH), 8.19 (s, 1H, =CH), 8.25-8.27 (d, 2H, ArH). Mass (EI): m/z (%): M^+ 313 (100), 150 (58.47), 163 (18.42), 117 (28.92), 77 (15.21). IR (KBr, cm^{-1}): 1597.

(E)-N-(4-chlorobenzylidene)-2-(3,4-dimethoxyphenyl)ethanamine (10c)

Yield 77.1 %, Pale Yellow Crystals. Melting point 99-102 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$):δ 2.95-2.98 (t, 2H, $ArCH_2$), 3.81 (s, 3H, OMe), 3.82-3.85 (m, 2H, NCH_2), 3.86 (s, 3H, OMe), 6.74-6.81 (m, 3H, ArH), 7.38-7.40 (d, 2H, ArH), 7.63-7.66 (d, 2H, ArH), 8.09 (s, 1H, =CH). Mass (EI): m/z (%): M^+ 302.5(11.72), 150(100), 152.5(27.67), 124.5(24.92), 89(15.12). IR (KBr, cm^{-1}): 1571.

General Procedure for the Synthesis of 1-(4-Substitutedphenyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (11a-c)

TFA (10mL) was added to a solution of benziliden [2-(3,4-dimethoxyphenyl)ethyl]amine (3.2mmol), and the mixture was refluxed for 1.5h. The reaction was quenched by adding water, and the mixture was basified (pH 8-9) with sodium hydroxide to give the isoquinoline derivative as a solid. The crude product was collected by filtration and purified by crystallization with MeOH to afford compounds.

1,2,3,4-tetrahydro-6,7-dimethoxy-1-phenylisoquinoline (11a)

Yield 68.3%, White crystals. Melting point 110-111 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.95 (s, 1H, NH), 2.65-2.78 (m, 2H, $ArCH_2$), 2.86-3.10 (m, 2H, NCH_2), 3.69 (s, 3H, OMe), 3.77 (s, 3H, OMe), 5.20 (s, 1H, CH), 6.36 (s, 2H, ArH), 6.87 (s, 1H, ArH), 7.23-7.39 (d, 2H, ArH), 7.88-7.96 (d, 2H, ArH). Mass (EI): m/z (%): M^+ 269 (42.0), 268 (45), 192 (100). IR (KBr, cm^{-1}): 3434.

1,2,3,4-tetrahydro-6,7-dimethoxy-1-(4-nitrophenyl) isoquinoline (11b)

Yield 65.0%, White crystals. Melting point 144 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.99 (s, 1H, NH), 2.75-2.98 (m, 2H, $ArCH_2$), 3.04-3.20 (m, 2H, NCH_2), 3.65 (s, 3H, OMe), 3.89 (s, 3H, OMe), 5.16 (s, 1H, CH), 6.16 (s, 1H, ArH), 6.67 (s, 1H, ArH), 7.45-7.47 (d, 2H, ArH), 8.18-8.20 (d, 2H, ArH). Mass (EI): m/z (%): M^+ 314 (20.71), 312 (100), 192 (64.53). IR (KBr, cm^{-1}): 3436.

1-(4-chlorophenyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (11c)

Yield 70.1 %, White crystals. Melting point 106 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$ δ 2.19 (s, 1H, NH), 2.79-

3.24 (m, 4H, $ArCH_2CH_2$), 3.67 (s, 3H, OMe), 3.89 (s, 3H, OMe), 5.10 (s, 1H, CH), 6.21 (s, 1H, ArH), 6.70 (s, 1H, ArH), 7.18-7.25 (d, 2H, ArH), 7.29-7.33 (d, 2H, ArH). Mass (EI): m/z (%): M^+ 303.5 (44.79), 302.5 (73.95), 192 (100). IR (KBr, cm^{-1}): 3436.

General Procedure for the Synthesis of 2-chloro-1-(3,4-dihydro-6,7-dimethoxy-1-(4-substitutedphenyl) isoquinolin-2(1H)-yl)ethanone (12a-c)

To a solution of 1-phenyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines (1.5mmol) and triethylamine (2.19mmol) in dry dichloromethane (5ml), chloroacetyl-chloride (1.7mmol)) was added slowly. During addition the reaction mixture was kept in ice. On addition the mixture was stirred at room temperature for 4 h. After the completion of the reaction, evaporated off the solvent, diluted the residue with water and extracted with ethylacetate. The collective organic portion was washed with brine and dried over Na_2SO_4. It was finally concentrated and chromatographed on silica gel using ethylacetate-petroleum ether as eluent.

2-chloro-1-(3,4-dihydro-6,7-dimethoxy-1-phenyliso-quinolin-2(1H)-yl)ethanone (12a)

Yield 54.5 %, White powder. Melting point 219-220 ^oC. ^1H NMR (400 MHz, $CDCl_3$): δ 2.86-2.98 (m, 2H, $ArCH_2$), 3.40-3.47 (m, 2H, NCH_2), 3.72 (s, 3H, OMe), 3.31 (s, 3H, OMe), 4.22 (s, 2H, $COCH_2Cl$), 6.42 (s, 1H, CH), 6.66 (s, 1H ,ArH), 6.73 (s, 1H, ArH), 7.38-7.41 (d, 2H, ArH), 8.10-8.13 (d, 2H, ArH). Mass (EI): m/z (%): M^+ 345.5 (12.11), 310.0 (100). IR (KBr, cm^{-1}): 1646.

2-chloro-1-(3,4-dihydro-6,7-dimethoxy-1-(4-nitro-phenyl)isoquinolin-2(1H)-yl)ethanone (12b)

Yield 58.1 %, White powder. Melting point 172 ^oC. ^1H NMR (400 MHz, $CDCl_3$): δ 2.80-3.16 (m, 2H, $ArCH_2$), 3.38-3.46 (m, 2H, NCH_2), 3.70 (s, 3H, OMe), 3.91 (s, 3H, OMe), 4.17 (s, 2H, $COCH_2Cl$), 6.47 (s, 1H, CH), 6.71 (s, 1H ,ArH), 6.83 (s, 1H, ArH), 7.43-7.45 (d, 2H, ArH), 8.13-8.15 (d, 2H, ArH). Mass (EI): m/z (%): M^+ 390.5 (68.91), 354.5 (100), 268.5 (18.06), 76 (14.42). IR (KBr, cm^{-1}): 1637.

2-chloro-1-(1-(4-chlorophenyl)-3,4-dihydro-6,7-di-methoxyisoquinolin-2(1H)-yl)ethanone (12c)

Yield 55.9 %, White powder. Melting point 148 ^oC. ^1H NMR (400 MHz, $CDCl_3$): δ 2.76-2.96 (m, 2H, $ArCH_2$), 3.42-3.56 (m, 2H, NCH_2), 3.71 (s, 3H, OMe), 3.87 (s, 3H, OMe), 4.23 (s, 2H, $COCH_2Cl$), 6.66 (s, 1H, CH), 6.78 (s, 1H, ArH), 6.91 (s, 1H, ArH), 7.52-7.58 (d, 2H, ArH), 8.23-8.26 (d, 2H, ArH). Mass (EI): m/z (%): M^+ 380 (5.0), 344.5 (76.35), 343 (100), 302.5 (6.14). IR (KBr, cm^{-1}): 1651.

Procedure for the Synthesis of 1-(3,4-dihydro-6,7-dimethoxy-1-(4-nitrophenyl)isoquinolin-2(1H)-yl)-2-(4-methylpiperazin-1-yl)ethanone (13a)

A solution of N- methyl piperizine (0.063g, 0.63mmol) in DMF (1.5ml) was added slowly to a solution of 12a (0.21g, 0.6mmol) and activated K_2CO_3 (0.25g, 1.83mmol) in DMF (2ml). The mixture was stirred for 3h at 60 °C. After the completion of reaction, diluted the reaction mixture with water and extracted with ethylacetate. The collective organic portion was washed with brine and dried over Na_2SO_4. It was finally concentrated and chromatographed on silica gel using ethylacetate-petroleum ether as eluent to obtain desired compound in as a gummy material. Com-pounds 13b-f also prepared by similar experimental conditions.

1-(3,4-dihydro-6,7-dimethoxy-1-phenylisoquinolin-2(1H)-yl)-2-(4-methylpiperazin-1-yl)ethanone (13a)

Yield 53.2 %, Gummy material. ^1H NMR (400 MHz, $CDCl_3$): δ 2.24 (s, 3H, NCH_3), 2.36-2.43 (m, 8H, piperazine), 2.76-2.82 (m, 2H, $ArCH_2$), 3.12 (S, 2H, $COCH_2N$) 3.42-3.50 (m, 2H, NCH_2), 3.69 (s, 3H, OMe), 3.75 (s, 3H, OMe), 6.28 (s, 1H, CH), 6.56 (s, 1H ,ArH), 6.77 (s, 1H, ArH), 7.46-7.54 (m, 5H, ArH). Mass (EI): m/z (%): M^+ 409 (8.43), 267 (4.00), 113 (100). IR (KBr, cm^{-1}): 1637.

1-(3,4-dihydro-6,7-dimethoxy-1-phenylisoquinolin-2(1H)-yl)-2-morpholinoethanone (13b)

Yield 51.6 %, Gummy material. ^1H NMR (400 MHz, $CDCl_3$): δ 2.40-2.48 (m, 4H, $N(CH_2)_2$), 2.71-2.78 (m, 4H, $O(CH_2)_2$), 2.78-2.84 (m, 2H, $ArCH_2$), 3.28 (S, 2H, $COCH_2N$), 3.44-3.54 (m, 2H, NCH_2), 3.71 (s, 3H, OMe), 3.79 (s, 3H, OMe), 6.24 (s, 1H, CH), 6.66 (s, 1H ,ArH), 6.69 (s, 1H, ArH), 7.38-7.52 (m, 5H, ArH). Mass (EI): m/z (%): M^+ 396 (10.13), 267 (6.00), 100 (100). IR (KBr, cm^{-1}): 1633.

1-(3,4-dihydro-6,7-dimethoxy-1-(4-nitrophenyl)iso-quinolin-2(1H)-yl)-2-(4-methylpiperazin-1-yl)ethanone (13c)

Yield 55.0 %, Gummy material. ^1H NMR (400 MHz, $CDCl_3$): δ 2.21 (s, 3H, NCH_3), 2.40-2.54 (m, 8H, piperazine), 2.82-2.94 (m, 2H, $ArCH_2$), 3.19 (S, 2H, $COCH_2N$) 3.38-3.49 (m, 2H, NCH_2), 3.74 (s, 3H, OMe), 3.84 (s, 3H, OMe), 6.54 (s, 1H, CH), 6.73 (s, 1H ,ArH), 6.84 (s, 1H, ArH), 7.40-7.46 (d, 2H, ArH), 8.14-8.19 (d, 2H, ArH). Mass (EI): m/z (%): M^+ 454 (10.13), 313 (4.72), 267 (4.00), 113 (100). IR (KBr, cm^{-1}): 1641.

1-(3,4-dihydro-6,7-dimethoxy-1-(4-nitrophenyl)iso-quinolin-2(1H)-yl)-2-morpholinoethanone (13d)

Yield 55.0 %, Gummy material. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.44-2.52 (m, 4H, $N(CH_2)_2$), 2.77-2.83 (m, 4H, $O(CH_2)_2$), 2.75-2.80 (m, 2H, $ArCH_2$), 3.33 (S, 2H, $COCH_2N$), 3.54-3.64 (m, 2H, NCH_2), 3.74 (s, 3H, OMe), 3.80 (s, 3H, OMe), 6.20 (s, 1H, CH), 6.56 (s, 1H ,ArH), 6.67 (s, 1H, ArH), 7.30-7.66 (m, 4H, ArH). Mass (EI): m/z (%): M^+ 441 (5.00), 309 (20.83), 100 (100). IR (KBr, cm^{-1}): 1636.

1-(1-(4-chlorophenyl)-3,4-dihydro-6,7-dimethoxyiso-quinolin-2(1H)-yl)-2-(4-methylpiperazin-1-yl)ethanone (13e)

Yield 58.9 %, Gummy material. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.26 (s, 3H, NCH_3), 2.48-2.58 (m, 8H, piperazine), 2.78-2.86 (m, 2H, $ArCH_2$), 3.28 (s, 2H, $COCH_2N$), 3.42-3.50 (m, 2H, NCH_2), 3.71 (s, 3H, OMe), 3.78 (s, 3H, OMe), 6.48 (s, 1H, CH), 6.66 (s, 1H ,ArH), 6.78 (s, 1H, ArH), 7.22-7.40 (m, 4H, ArH). Mass (EI): m/z (%): M^+ 443 (50), 342 (70), 302 (30), 113 (95), 70 (100). IR (KBr, cm^{-1}): 1636.

1-(1-(4-chlorophenyl)-3,4-dihydro-6,7-dimethoxyiso-quinolin-2(1H)-yl)-2-morpholinoethanone (13f)

Yield 50.0 %, Gummy material. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.32-2.42 (m, 4H, $N(CH_2)_2$), 2.68-2.74 (m, 4H, $O(CH_2)_2$), 2.70-2.76 (m, 2H, $ArCH_2$), 3.26 (S, 2H, $COCH_2N$), 3.62-3.66 (m, 2H, NCH_2), 3.73 (s, 3H, OMe), 3.78 (s, 3H, OMe), 6.18 (s, 1H, CH), 6.54 (s, 1H ,ArH), 6.64 (s, 1H, ArH), 7.34-7.64 (m, 4H, ArH). Mass (EI): m/z (%): M^+ 430.5 (7.37), 301.5 (5.47), 100 (100). IR (KBr, cm^{-1}): 1642.

Synthesis of N-(4-((E)-(3,4-dimethoxyphenethyl-imino)methyl)benzylidene)-2-(3,4-dimethoxyphenyl) ethanamine (15)

A mixture of 2-(3',4'-dimethoxyphenyl)ethylamine (1.8g, 10mmol) and pthaldehyde (6.9mmol) in anhydrous toluene (50mL) was refluxed for 3h and then cooled and evaporated in vacuo. The oil residue was treated with diethyl ether to give a solid residue, which was crystallized from ethanol to afford the desired diimine.

Yield 55.9 %, White crystals. Melting point 113 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.98-3.02(t, 2H X 2, $ArCH_2$), 3.85-3.90(m, 2H X 2, NCH_2), 3.82, 3.87(s,(3H X 2) X 2, OCH_3), 6.75-6.82 (m, 3H X 2, ArH), 7.7(s, 2H X 2, ArH), 8.14(s, 1H X 2, =CH). Mass (EI): m/z(%): M^+ 460(3), 256(23.74), 185(15), 128(26.58), 55(100). IR (KBr, cm^{-1}): 1641.

Synthesis of 1,2,3,4-tetrahydro-1-(4-(1,2,3,4-tetra-hydro-6,7-dimethoxyiso quinolin-1-yl)phenyl)-6,7-dimethoxyisoquinoline (16)

Trifluoroacetic acid (10mL) was added to a solution of compound 15(2.1mmol), and the mixture was refluxed for 1.5h. The reaction was quenched by adding water, and the mixture was basified (pH 8-9) with sodium hydroxide to give the isoquinoline derivative as a solid. The crude product was collected by filtration and purified by crystallization with MeOH to afford compound.

Yield 46.9 %, White crystals. Melting point 224 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.76 (s,1H X 2, NH), 2.75-3.23 (m, 4H X 2, NCH_2CH_2), 3.64, 3.90 (s, 6H X 2, OCH_3), 5.06 (s, 1H X 2, CH), 6.25 (s, 1H X 2, ArH), 6.64 (s, 1H X 2, ArH), 7.19-7.28 (d, 2H X 2, ArH). Mass (EI): m/z (%): M^+ 460 (3), 256 (21.07), 128 (28.03), 57 (100). IR (KBr, cm^{-1}): 3374.

CONCLUSION

A new approach for the preparation of N-substituted THIQ derivatives has been reported. THIQ derivatives (13a-f) are synthesized by four step synthetic strategy *via* a Pictet-Spengler condensation. A new bis-isoquinoline derivative, namely, 1,2,3,4-tetrahydro-1-(4-(1,2,3,4-tetrahydro-6,7-dimethoxyisoquinolin-1-yl)phenyl)-6,7-dimethoxyisoquinoline (16) has also been synthesized. The products and intermediates are characterized by IR, ^{1}H NMR and mass spectroscopy. The spectra of the synthesized compounds are matching with the desired products.

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