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Synthesis and Antibacterial Activity of 2-{2-[(4-chlorophenyl)sulfanyl]ethoxy}-3-methoxy-5-[6-(3,4,5-trimethoxyphenyl)-3-pyridazinyl]benzonitrile

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ABSTRACT

The present paper describes the synthesis of the title compound, which is a hybrid scaffold of our earlier reported work on 2,5-diaryltetrahydrofuran, utilizing an inexpensive commercially available vanillin as starting material, in over all eight steps. The newly synthesized title compound, displayed excellent to moderate activity towards the bacterial strains tested.

Keywords: Pyridazine, Synthesis, Stetter reaction, 1,4-Diketone, Benzyltrimethylammonium dichloroiodate, Vanillin.

INTRODUCTION

The pyridazine ring is often encountered as a structural component of compounds possessing biological activity: analgesic, inflammatory, antisecretory, antiulcer, antidepressants, anxiolytics, sedative-hypnotics, anticonvulsants, antiplatelet, antithrombotics, antitumor, cardiotonics, vasodilatators, antiarrhythmics, antidiabetic, antitubercular agents [1-7] and also as antibacterial [8], antihypertensive [9] or antihistaminic [10] activities have all been reported. This heterocycle is also useful for the preparation of other heterocycles [11], π-conjugated organic materials with desirable electronic properties [12] and self-assembled supramolecular architectures [13].These pharmacological and technological properties of pyridazines encourage the development of methods for their synthesis and functionalization [14]. They are also used as intermediates for drugs, agrochemicals and other anticipated properties [15-21]. The present paper describes the synthesis of 2-{2-[(4-chlorophenyl)sulfanyl]ethoxy}-3-methoxy-5-[6-(3,4,5-trimethoxyphenyl)-3- pyridazinyl]benzonitrile, from commercially available vanillin as starting material in a few high yielding steps utilizing milder reaction conditions (Scheme **1**). The title compound is a hybrid scaffold of our earlier reported work on 2, 5-diaryltetrahydrofuran [21-25]. The newly synthesized title compound was evaluated against two Gram positive and two Gram negative bacteria and also tested against two fungi species.

MATERIALS AND METHODS

Chemical and solvents used were purchased either from Fluka or Merck. All the reagents were of analytical grade. Thin-layer chromatography (TLC) was performed on E.Merck AL silica gel 60 F254 plates and visualized under UV

light. The IR spectra were recorded on a Perkin Elmer FT-IR spectrometer. The ^{1}H NMR spectra were recorded in $CDCl_3$ on a Varian EM-360 spectrometer (400MHz). The ^{13}C NMR spectra recorded in $CDCl_3$ on a Varian EM-360 spectrometer operating at 100MHz. All the chemical shifts were reported in δ (ppm) using TMS as an internal standard. The mass spectra were recorded on Agilent ion trap MS. All the reactions were carried out under argon atmosphere.

Experimental methods

3-Methoxy-4-hydroxy-5-iodo benzaldehyde **(2)**

A mixture of vanillin **1** (10 g, 65.72 mmol), benzyltrimethylammonium dichloroiodate ($BTMACl_2I$) (25 g, 71.83 mmol), and $CaCO_3$ (46.90 g, 469.0 mmol) in dichloro methane (160 mL) and MeOH (70 mL) was stirred for 5 hours at room temperature. After the completion of starting material checked by TLC, the mixture was filtered, and precipitate was washed with dichloromethane (2 x 25 mL). The combined organic solvent was successively washed with 0.5 N sodiumthiosulphate solution (200 mL) and brine (200 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum to dryness. The title products were purified by silica gel chromatography using hexanes-ethyl acetate (8:1-6:1) as eluent to afford 5-iodo-vanillin. Yellow solid, m.p. 183-184 ^oC, Yield: 17.53 g, 96%; IR (KBr): υ_{max} 3186, 2847,1666, 1459, 1259, 854, 670 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.98 (s, 3 H), 7.34 (s, 1 H), 7.81 (s, 1 H), 9.73 (s, 1 H),10.04 (s,1 H); ^{13}C NMR (100 MHz,$CDCl_3$): δ 55.84, 82.45, 109.34, 129.67, 134.93, 146.85, 152.12, 188.92. EI-MS: m/z (rel.abund.%) 278 (M+, 100).

3-Methoxy-4-(bromoethoxy)-5-iodo benzaldehyde **(3)**

To a stirred solution of K_2CO_3 (14.17 g, 102.0 mmol) in 2-MeTHF (125 mL) was added drop wise a solution of compound **2** (25 g, 85.0 mmol) in 2-MeTHF (50 mL) at room temperature. The reaction mixture was stirred for 30 min and then 1,2-dibromoethane (24.57 mL, 275.0 mmol) was added drop wise. After the addition, the reaction mixture was stirred at 80 °C for 4 hours. The reaction was quenched with water and extracted with isopropyl acetate. The organic layer was washed with water (2 x 100 mL) followed by brine solution (2 x 50 mL), dried over $MgSO_4$, filtered and evaporated in *vacuo* to yield **3.** Yellow solid; m.p.73-75 °C, Yield: 25.40 g, 81%; IR (KBr): υ_{max} 3448, 2965, 1675, 1476, 1447, 1280,1160, 1034 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.70 (t, 2 H, *J* = 6.0 Hz), 3.90 (s, 3 H), 4.40 (t, 2 H, *J* = 6.0 Hz), 7.41 (s, 1H), 7.82 (s, 1H), 9.8 (s,1H); ^{13}C NMR (100 MHz,$CDCl_3$): δ 29.96, 56.09, 72.49, 92.15, 111.16,133.15, 134.40, 152.54, 189.50. EI-MS: m/z (rel.abund.%) 384 (M+, 100).

3-Methoxy-4-(4-chlorophenyl thioethoxy)-5-iodo-benzaldehyde **(4)**

To a stirred solution of compound **3** (15 g, 37.0 mmol) in 2-MeTHF (75 mL) was added 4-chlorothiophenol (5.97 g, 41.0 mmol) and NaOMe (2.45 g, 45.0 mmol). The reaction mixture was stirred at room temperature for 12 h and then the solvent was removed. The residue was purified by flash column chromatography (silica gel, 3:1 hexane/ethyl acetate) to afford compound **4.** Pale yellow crystalline solid; m.p. 65 °C, Yield: 15.0 g, 88%; IR (neat): υ_{max} 3447, 2831, 1695, 1451, 1382, 1266, 1136, 1038, 976,814, 660 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.35 (t, 2 H, *J* = 6.2 Hz), 3.88 (s, 3 H), 4.22 (t, 2 H, *J* = 6.2 Hz), 7.31 (m, 4 H), 7.38 (s, 1H), 7.84 (s, 1H), 9.82 (s,1H). ^{13}C NMR (100MHz, $CDCl_3$): δ 33.45, 55.95, 71.14, 92.41, 110.97, 128.59 (3 C), 130.77 (3 C), 133.90, 134.45 (2 C), 152.53, 189.35;. EI-MS: m/z (rel.abund.%) 447 (M+, 100).

l-[4-(2-(4-chlorophenylthioethoxy)-3-iodo-5-methoxyphenyl] prop-2-en-1-ol **(5)**

To a stirred solution of compound **4** (15 g, 33.0 mmol) in 2-MeTHF (75 mL) was added vinylmagnesium bromide (5.97 g, 45.0 mmol) and the reaction mixture was stirred at room temperature for 5 hours. The reaction mixture was quenched with saturated aqueous NaCl solution and extracted with isopropyl acetate. The organic layer was washed with water (2 x 25 mL) and saturated NaCl, dried over $MgSO_4$, filtered and evaporated in *vacuo* to afford carbinol derivative **5** as a yellow viscous liquid**.** The crude compound was utilized as such in the next step without further purification.

l-[3-Methoxy-4-(4-chlorophenylthioethoxy)-5-iodophenyl]-prop-2-en-l-one **(6)**

N-Bromosuccinimide (0.93 g, 5.24 mmol) and NH_4Cl (0.33g, 6.28 mmol) were added to a stirred solution of alcohol (2.5 g, 5.24 mmol) in acetonitrile: water (17.5/7.5 mL). The reaction mixture was heated to 80^{o}C for 2.5 hours. The reaction mixture was extracted with cyclopentyl methyl ether. The combined organic layer was washed with a saturated solution of $NaHCO_3$ and dried over $MgSO_4$. The solvent was evaporated under vacuum, and the residue thus obtained was purified by column chromatography on silica gel using isopropyl acetate/heptanes (1:4) as eluent. Evaporation of the solvent yielded the vinyl ketone **6**. Pale yellow crystalline solid, m.p. 89 °C, Yield: 1.52 g, 82%; IR (KBr): υ_{max} 3447, 2942, 1669, 1578, 1476, 1404,1272, 1155, 1092, 1022, 875 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$):

δ 3.32 (t, 2 H, *J* = 8.0 Hz), 3.9 (s, 3 H), 4.2 (t, 2 H, *J* = 8 Hz), 5.92 (dd, I H, *J* = 2.0 Hz, 8.0 Hz, CH=CH_2), 6.39 (dd, 1 H, *J* = 2.0 Hz, 16.0 Hz, CH=CH_2) , 7.11(dd, I H, *J* = 8.0 Hz, 16.0 Hz, CH=CH_2), 7.31 (m, 4 H), 7.47 (s, 1 H), 7.9 (s, 1H). ^{13}CNMR (100MHz, $CDCl_3$): δ 32.84, 42.33, 51.82, 56.20, 70.03, 93.10, 112.37, 128.01, 130.20, 130.73,133.70, 134.54, 151.30, 151.70, 194.50. EI-MS: m/z (rel.abund.%) 475 (M+, 100).

l-[3-Methoxy-4-(4-chlorophenylthioethoxy)-5-iodophenyl]-4-(3,4,5- trimethoxyphenyl)butane-l,4-dione **(8)**
A mixture of compound **6** (5.0 g, 10.5 mmol), 3,4,5-trimethoxybenzaldehyde **7** (2.4 g, 12.2 mmol), 3-benzyl-5-(2-hydroxyethyl)-4-methyl-thiazolium chloride (0.55 g, 2.1 mmol) and triethylamine (2.2 ml, 14 mmol) in cyclopentyl methyl ether was stirred at 70 °C for 6 hours. The reaction mixture was then acidified with 10% 10% HCl and extracted with dichloromethane. The organic layer was washed with 10% HCI, water and saturated NaCl solution. The organic layer was dried over $MgSO_4$ filtered and evaporated *in vacuo* to yield **8.** Yellow solid, m.p.115-117 °C, Yield: 6.2 g, 89%; IR (KBr): υ_{max} 3470, 2931,1651, 1458, 1403, 1272, 1125, 1093, 858 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 3.33 (t, 2 H, *J* = 7.3 Hz), 3.41 (m, 4 H), 3.84 (s, 3 H), 3.92 (s, 9 H), 4.26 (t, 2 H, *J* = 7.3 Hz), 7.26 (m, 4 H), 7.34 (s, 2 H), 7.52 (s, 1 H), 8.02 (s, 1 H). ^{13}C NMR (100 MHz,$CDCl_3$): δ 32.30,33.30, 55.89, 56.19, 60.77, 71.05, 92.17, 105.57, 111.70, 128.95, 130.72, 131.38, 131.70,132.20, 133.95, 134.27, 151.53, 151.87, 152.94, 196.25, 197.10.; EI-MS: m/z (rel.abund.%) 671 (M+, 100).

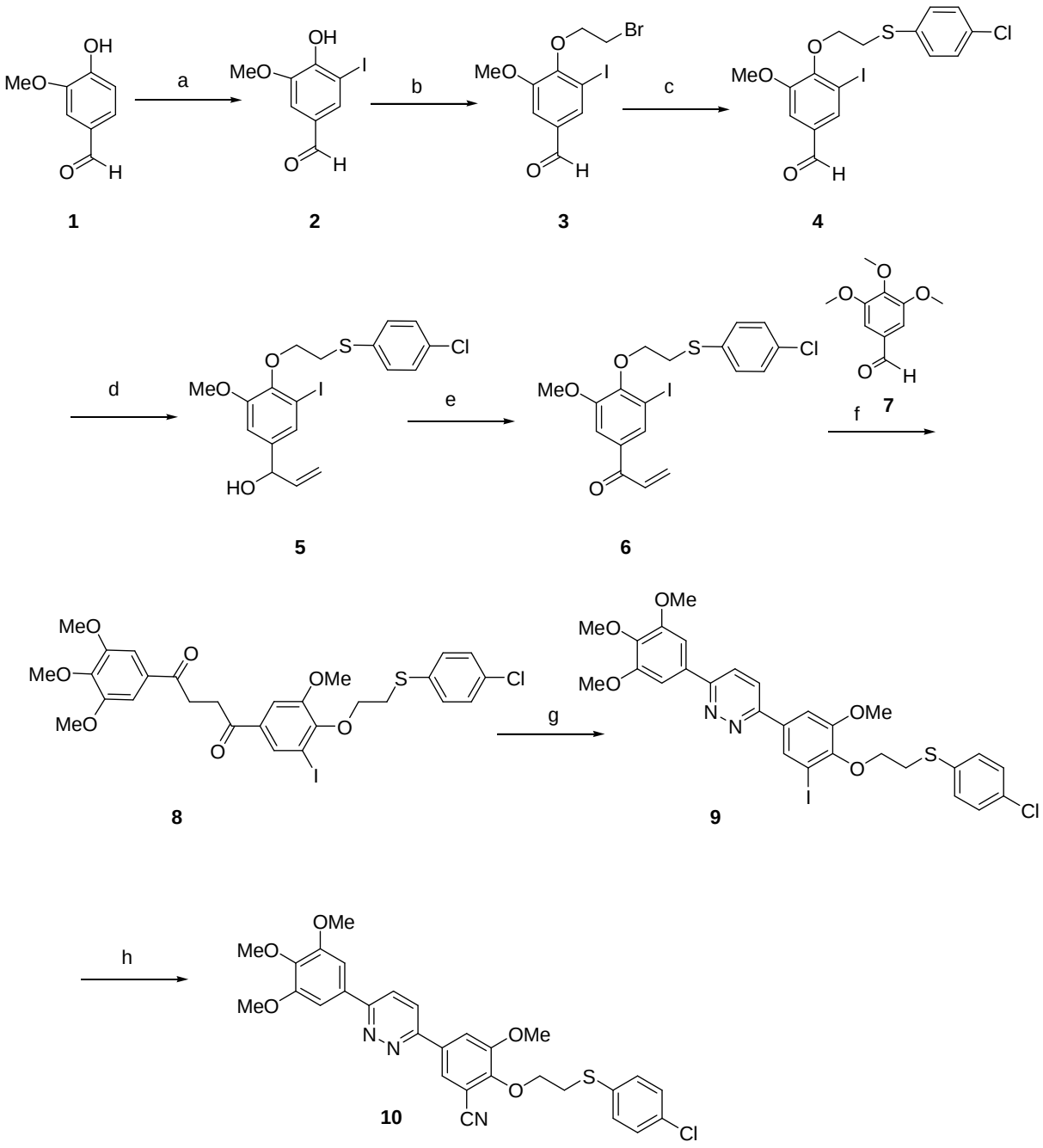
[3-(4-(2-(4-chlorophenylthio)ethoxy)-3-iodo-5-methoxyphenyl]-6-(3,4,5-trimethoxyphenyl)pyridazine **(9)**
To a stirred solution of compound **8** (5 g, 7.45 mmol) in EtOH (75 mL) was added hydrazine hydrate (1.66 g, 52.15 mmol) and the reaction mixture was stirred at reflux temperature for 3 h. The reaction was quenched with water and extracted with isopropyl acetate. The organic layer was washed with water and saturated NaCl, dried over $MgSO_4$, filtered and evaporated in *vacuo* to yield **9** as yellow syrupy oil, which was utilized in the next step without further purification. Yield: 69%.

[2-(2-(4-chlorophenylthio)ethoxy)-3-methoxy-5-(6-(3,4,5-trimethoxyphenyl)pyridazine-3yl)benzonitrile **(10)**
A mixture of compound **9** (4.1 g, 6.2 mmol) and CuCN (0.83, 9.2 mmol) in cyclopentyl methyl ether (30 mL) was refluxed for 5 h. The reaction mixture was cooled to room temperature, diluted with water and extracted with isopropyl acetate. The organic layer was washed with water and saturated NaC1 solution, dried over $MgSO_4$, filtered and evaporated in *vacuo* to yield **10** as a yellow oily residue. The residue was purified by flash column chromatography (silica gel, 3:1 hexane/ethyl acetate) to yield **10** as a white amorphous solid. Yield: (2.21 g, 64%); m.p. 88°C; IR (neat): υ_{max} 3459, 2951, 2224, 1600, 1458, 1403, 1272, 1125, 1093, 858 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.35 (t, 2 H, *J* = 7.8 Hz), 3.92 (s, 3 H), 3.98 (s, 3 H), 4.02 (s, 6 H), 4.46 (t, 2 H, *J* = 7.8 Hz), 7.28-7.24 (m, 2 H), 7.38-7.34 (m, 2 H), 7.45 (s, 2 H), 7.68 (s, 1 H), 8.05 (br.s, 2 H), 8.29 (s, 1H). ^{13}C NMR(100MHz,$CDCl_3$): δ 38.70, 56.09 (3C), 56.20, 71.05, 102.70, 105.57 (2C), 111.70,123.8, 125.65 (3C), 137.82, 128.38 (2C), 129.10 (3C),131.70,132.20, 133.95, 134.27, 139.2,151.53, 151.87 (2C), 157.94 . EI-MS: m/z (rel.abund.%) 564 (M+, 100).

RESULTS AND DISCUSSION

The present paper describes the synthesis of the title compound, which is a hybrid scaffold of our earlier reported work on 2,5-diaryltetrahydrofuran [21-25], utilizing an in expensive commercially available vanillin as starting material. The synthesis of title compound (**Scheme 1**) was accomplished in a few high yielding steps from vanillin by modifications of the previously described procedures [21,25]. Iodination of vanillin was carried out by using a mild iodinating reagent such as benzyltrimethylammonium dichloroiodate ($BTMACl_2I$) [26] in the presence of sodium bicarbonate and methanol at room temperature for 5 hours resulted in 5-iodovanillin **2**. Alkylation of 5-iodovanillin [21] with 1,2-dibromo ethane in presence of K_2CO_3 in 2-MeTHF at 80 ^oC for 4 hours afforded compound **3**. Conversion of compound **3** to compound **4** was achieved by treatment of p-chloro-thiophenol in presence of NaOMe in 2-MeTHF at room temperature for 12 hours. Grignard reaction of compound **4** was carried out using vinyl magnesium bromide in 2-MeTHF at room temperature for 3 hours resulted in carbinol compound **5**. Oxidation of carbinol **5** with NBS/NH_4Cl [27] in acetonitrile: H_2O at 80^oC for 2.5 hours resulted in the formation of vinyl ketone **6**. 2-Methyl tetrahydrofuran was used as the choice of solvent during the conversion of compound **2** to compound **5** (in three steps), 2-Methyl tetrahydrofuran (2-MeTHF) is derived from renewable resources such as corncobs and bagasse, when used as an organometallic solvent, 2-MeTHF offers both economical and environmentally friendly advantages over tetrahydrofuran. Conversion of vinyl ketone **6** to 1,4-diketone **8** was achieved by Stetter reaction using thiazolium catalyst [21] in presence of triethyl amine in cyclopentyl methyl ether (CPME) at 70 ^oC for 6 hours. Cyclisation of the diketone **8** was carried out using hydrazine hydrate in EtOH at reflux for 3 hour resulted in compound **9,** which was utilized in the next step as such without further purification.

Displacement of the iodo group of compound **9** with CuCN in presence of tetra butyl ammonium iodide in CPME as solvent at reflux temperature gave crude compound **10,** which was purified by column chromatography using silica-gel (60 – 120) with heptane – isopropyl acetate as eluent to afford the title compound **10**. The synthesis of compound **10** is outlined in **Scheme 1**.



Scheme 1: Experimental conditions: a) $BTMACl_2I$, $NaHCO_3$, MeOH:DCM, r.t., 5 hours; b) 1,2-dibromoethane, K_2CO_3, 2-MeTHF, 80 °C, 4 hours; c) para-chlorothiophenol, NaOMe, 2-MeTHF; r.t., 12 hours; d) Vinyl magnesium bromide , 2-MeTHF, r.t., 3 hours; e) NBS/NH_4Cl, Acetonitrile/H_2O, 80 °C, 2.5 hours; f) 6, 7: 3,4,5-Trimethoxy benzaldehyde, Thiazolium catalyst, Et_3N, cyclopentyl methy ether, 70 °C, 6 hours; g) $NH_2NH_2.H_2O$, EtOH, reflux, 3 hours; h) CuCN, TBAI, cyclopentyl methyl ether, reflux.

Anti- Bacterial Activity

The anti-bacterial activity of the title compound was determined by the disc diffusion method with Amoxicillin and Cefaclor as the reference antibiotics [28]. The newly synthesized title compound was examined, respectively, against two Gram positive and Gram Negative pathogens viz., *Staphylococcus aureus*, *Staphylococcus pyogenes*, *Escherichia Coli* and *Pseudomonas aeruginosa* bacterial strains. The test results indicated that the title compound showed excellent activity towards *Escherichia Coli and Pseudomonas aeruginosa* and displayed moderate activity against *Staphylococcus aureus and Staphylococcus pyogenes.* Further structural activity relationship on the title compound to develop a lead motif is in progress in our laboratory.

Antifungal Activity

The antifungal activity of the title compound was tested against two different fungi such as *Asperigillus niger* and *Candida albicans* by disc diffusion method [28], the title compound was found to be moderately active against the fungi species tested.

CONCLUSION

We have synthesized a new pyridazine scaffold utilizing an inexpensive commercially available vanillin as starting material, in over all eight steps using milder and efficient reaction conditions. .The newly synthesized title compound showed excellent activity towards *Escherichia Coli and Pseudomonas aeruginosa* and displayed moderate activity against *Staphylococcus aureus and Staphylococcus pyogenes* and displayed moderate activity against the fungi species tested.

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