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Synthesis of New Chiral and Nonchiral Pyrido [3,2-*e*],[1,3,4] oxadiazine Derivatives

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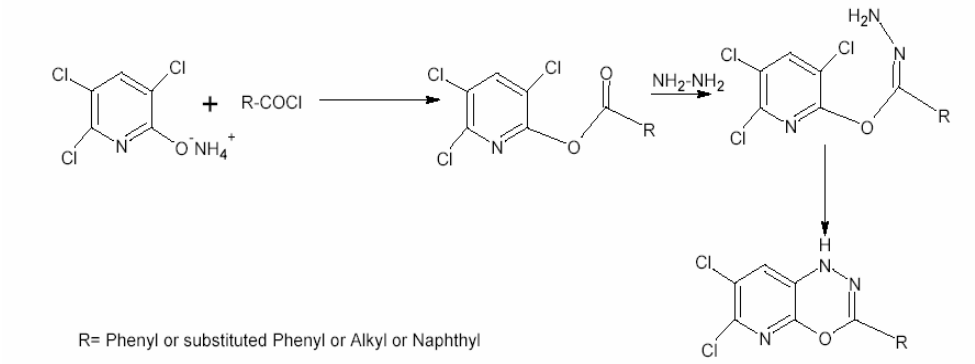
Abstract: A chiral series of 6,7-dichloro-3-[3-(2,2-dihalovinyl)-2,2-dimethylcyclopropyl] -1H-pyrido [3,2-e],[1,3,4] oxadiazines **(a-f)** and a nonchiral series of 3-substituted, 6,7-dichloro-1H-pyrido [3,2-e][1,3,4] oxadiazines **(a-g)** have been synthesized. The synthesized compounds were characterized by IR, ^{1}H-NR, HPLC and mass spectral data.

Keywords: 1H-pyrido, Chiral, Oxadiazine, Phenyl sulfanyl, Naphthyl sulfanyl.

Introduction

Oxadiazines are interesting[1] and promising heterocyclic compounds. A diversity of biological effects is associated with oxadiaxzines bearing hetero atoms at 1, 2, 4 or 1,3,4 positions. 6*H*-1, 2, 4-oxadiazine-3, 5-(2*H*, 4*H*)-dione, the 6-oxa analogue of uracil, has been shown to significantly inhibit growth in several bacterial strains while not being highly inhibitory to mammalian cells[2].

1, 3, 4-Oxadiazine derivatives exhibit cardiovascular, antibacterial, plant growth regulating, miticidal and nematocidal, acricidal, insecticidal and anticonvulsive activities[3,4]. In addition, oxadiazines are useful intermediates in the synthesis of tenidap prodrugs or β-lactam antibiotics, in particular into the synthesis of carbapenems and penems[5, 6]**.** The invention relates to an optically active form of a pyridyl-4*H*-1, 2, 4-oxadiazine derivative[7], to the therapeutical use thereof and to a pharmaceutical compositions containing the compound as active ingredient. More particularly, the invention relates to the (-) enantiomer of 5,6-dihydro-5-[(1-piperidinyl)-methyl-3-(3-pyridyl)-4*H*-1, 2, 4-oxadiazine and its acid addition salts as well as the use of these chemical compounds in the treatment of vascular diseases. It is reported in literature[8] that indoxacarb, an oxadiazine insecticide blocks insect neuronal sodium channels. Claude Bonnes and co-workers[9] reported in their invention that 3-oxo-5, 6-dihydro-1, 2, 4-oxadiazines useful as antiandrogenic agents. 4-substituted 5, 6-dihydro-2-o-hydroxyphenyl-4*H*-1, 3, 4-oxadiazine-5-ones[10] were reported in literature as potential psychopharmacological drugs. The promising therapeutic potential of this class of compounds prompted us to synthesize novel derivatives of several 1, 3, 4-oxadiazines.



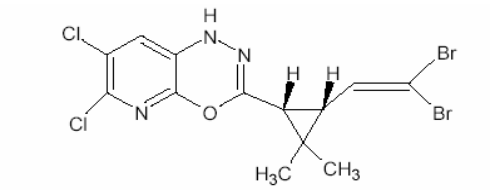
Scheme 1

Experimental

Melting points were determined on a LABINDIA MR.VIS visual melting range apparatus and are uncorrected. Reactions monitored by using Shimadzu SPD 10AV HPLC. Solvent system (mobile phase) acetonitrile –methanol-water (60:30:10) and 240 nm. HPLC column used was C-18 and flow rate maintained was 1 mL/min. IR spectra in KBR ($cm^{-1)}$ were recorded on Jasco FT/IR-410 series spectrophotometer and ^1H NMR spectra were recorded (DMSO-d_6) on a Bruker 200MHz spectrometer using TMS as internal standard (chemical shifts are expressed in δppm.). GC-MS spectra were recorded on Polaris Q mass detector.

Chiral pyrido oxadiazine derivatives

*6,7-Dichloro-3-[3-(2,2-dibromovinyl)-2,2-dimethylcyclopro- pyl]-1H-pyrido[3,2-e] [1,3,4] oxadiazine (1R, 3R isomer)(**a**)*



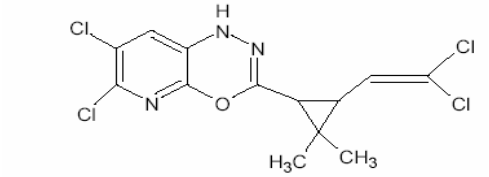
In a set up of 3 necked round bottom flask with magnetic stirrer, 150 mL methanol, 0.05 moles of 3,5,6-trichloropyridin-2-yl (1*R*, 3R)-3-(2,2-dibromovinyl)-2,2-dimethylcyclo-propanecarboxylate and 0.5 g PTSA was taken. It was slurry. This mass was cooled to 20 °C by external cooling and to this 0.055 moles of hydrazine hydrate (80.0% solution) was added. Addition was exothermic and thin slurry converted into thick white slurry. This was maintained at 20-30 °C for 4 h. Filtered the mass and washed with 50 mL of methanol. The hydrazonoate isolated yield was 97.5% **.**

In a reaction set up of single necked flask, magnetic stirring and oil heating system, 5.0 g (0.01 mole) of above prepared hydrazonoate, 25 mL dimethyl acetamide (DMAC) solvent and 0.7 g of K_2CO_3 as acid binder was taken. This was heated to 115-120 °C and maintained for 6 h. Distilled out DMAC under reduced pressure and to the left over residue added water and filtered. The filtered solid dried and crystallized with 20 mL methanol. Crystallized yield was 65.78%. Off-white crystalline solid; melting point was 180-182°C.

Spectral data

IR (KBr) ν_{max} in cm^{-1}: 3068(C-H str.), 549-662 (C-Br str.), 1462 (C=C gem. str.)

*6,7-Dichloro-3-[3-(2,2-dichlorovinyl)-2,2-dimethylcyclopro- pyl]-1H-pyrido [3,2-e] [1,3,4] oxadiazine. (55:45 cis: trans isomer)(**b**)*



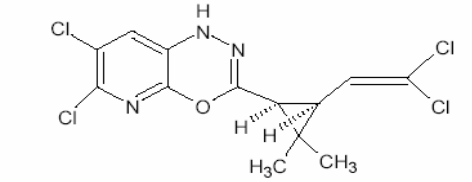
In a set up of 3 necked round bottom flask with magnetic stirrer, 150 mL methanol, 0.05 mole of 3,5,6-trichloropyridin-2-yl-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate (cis:trans - 55:45) and 0.5 g PTSA was taken. It was slurry. This mass was cooled to 18-20 °C by external cooling and to these 0.055 moles of hydrazine hydrate (80.0% solution) was added. Addition was exothermic and thin slurry converted into thick white slurry. This was maintained at 20-30 °C for 4 h. Filtered the mass and washed with 50 mL of methanol. The yield of hydrazonoate isolated was 18 g (89.5 % yield).

In a reaction set up of single necked flask, magnetic stirring and oil heating system, 5.0 g (0.012 mole) of above prepared hydrazonoate, 25 mL dimethyl acetamide (DMAC) solvent and 0.7 g of K_2CO_3 as acid binder was taken. This was heated to 115-125 °C and maintained for 7 h. DMAC was distilled out under reduced pressure and to the left over residue, water was added and filtered. The filtered solid dried and crystallized with 25 mL methanol. Crystallized yield was 22.7 %. Off-white crystalline solid; melting point was 258-259 °C.

*6, 7-Dichloro-3-[3-(2,2-dichlorovinyl)-2,2-dimethylcyclopro- pyl]-1H-pyrido [3,2-e] [1,3,4] Oxadiazine (Trans isomer)(**c**)*

Procedure followed for this compound is same as compound (**b**), but staring ester for this synthesis was 3, 5, 6-trichloropyridin-2-yl -3-(2, 2-dichlorovinyl)-2, 2-dimethyl cyclopropane-carboxylate (99.0 % trans isomer). The yield was off-white crystalline solid (12.0 %); melting point was 236-237 °C.

*6,7-Dichloro-3-[3-(2,2-dichlorovinyl)-2,2-dimethylcyclopro- pyl]-1H-pyrido [3,2-e][1,3,4] oxadiazine (SS isomer)(**d**)*



Procedure followed for this compound was exactly same as compound (**b**), but staring ester for this synthesis was 3, 5, 6-trichloropyridin-2-yl (1*S*, 3S)-3-(2, 2- dichlorovin-yl)-2, 2-dimethyl cyclopropanecarboxylate (99.0 % SS isomer). The yield of off-white crystalline solid was 22.0%, melting point was 179-181°C.

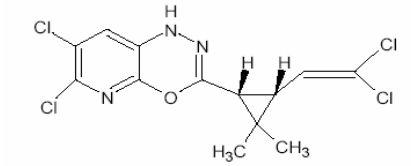
Spectral data

IR (KBr) ν_{max} in cm^{-1}: 3068 (-NH str.), 2969 (C-H str.), 1627(C=C aromatic.), 818-847 (C-Cl str.)

^{1}H NMR (DMSO-d_6):δ, 1.24(3H,s, CH_3), 1.28(3H,s, CH_3), 1.73 (1H,d,), 2.01(1H,d), 6.31(1H,d, - vinyl), 7.27 (1H, aromatic**),** 6.35(1H, s, NH)

GC-MS: 368 (M + 1 peak).

*6,7-Dichloro-3-[3-(2,2-dichlorovinyl)-2,2-dimethylcyclo-propyl]-1H-pyrido[3,2-e] [1,3,4]oxadiazine (RR isomer)(**e**)*



In a set up of 3 necked round bottom flask with magnetic stirrer, 150 mL methanol, 0.05 moles of 3,5,6-trichloropyridin-2-yl (1*R*, 3R)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-carboxylate and 0.5 g PTSA was taken. It was slurry. This mass was cooled to 15-20 °C by external cooling and to these 0.055 moles of hydrazine hydrate (80.0% solution) was added. Addition was exothermic and thin slurry converted into thick white slurry. This was maintained at 20-30 °C for 4 h. Filtered the mass and washed with 50 mL of methanol. The yield of hydrazonoate isolated was 89%

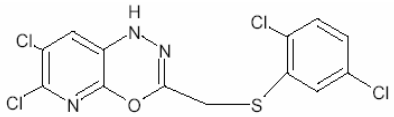
In a reaction set up of single necked flask, magnetic stirring and oil heating system, 5.0 g (0.012 mole) of above prepared hydrazonoate and 25 mL pyridine was taken and heated to reflux at 115-116 °C and maintained for 6 h. Pyridine was distilled out under reduced pressure and to the left over residue 50 mL dichloromethane solvent +50 mL water was added. Separated layers and organic layer washed with 25 mL of dilute sodium carbonate solution followed by water. Organic layer concentrated and crystallized with 10 mL of isopropyl alcohol. The yield of off-white crystalline solid was 34%, melting point was 160-162 °C.

*6,7-Dichloro-3-[3-(2,2-dichlorovinyl)-2,2-dimethylcyclopro- pyl]-1H-pyrido[3,2-e][1,3,4] oxadiazine (RR + SS - isomer)(**f**)*

Synthesis procedure remains same as compound (**e**), but only change is that starting ester is 3, 5, 6-trichloropyridin-2-yl-3- (2,2-dichlorovinyl)-2,2-dimeth- yl cyclopropane carboxylate (RR + SS isomer). The yield of off-white crystalline solid was 35%, melting point was 147-148 °C.

Nonchiral pyrido oxadiazine derivatives

*6,7-Dichloro-3-{[(2,5-dichlorophenyl)sulfanyl]methyl}-1H-pyrido [3,2-e][1,3,4] oxadiazine(**a**)*



In a set up of single necked round bottom flask with magnetic stirrer, 50 mL of methanol, 0.006 moles of 3,5,6-trichloropyridin-2-yl [(2,5-dichlorophenyl) sulfanyl] acetate and 0.1g PTSA was taken. It was slurry. This mass was cooled to 18-20 °C by external cooling and to these 0.007 moles of hydrazine hydrate (80.0% solution) was added. Addition was exothermic and thin slurry converted into thick white slurry. This was maintained at 20-30 °C for 4 h. Filtered the mass and washed with 50 mL of methanol. The yield of hydrazonoate yield was 93.0 %.

In a reaction set up of single necked flask, magnetic stirrer and oil heating system, 2.0 g (0.005 mole) of above prepared hydrazonoate, 25 mL DMAC solvent and 0.23 g of K_2CO_3 was added as acid binder. This was heated to 140-145 °C and maintained for 4 h.

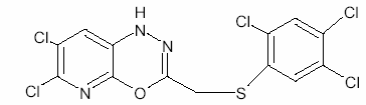
DMAC was distilled out under reduced pressure and to the left over residue water was added and filtered. The filtered solid dried and crystallized with 100 mL methanol, as solubility is very poor. The yield of buffer-white crystalline solid was 74%, melting point was 211-212 °C.

Spectral data

IR (KBr) ν_{max} in cm^{-1}: 3209 (-NH str.), 3045 (C-H str.), 1607(C=C aromatic.), 801-843 (C-Cl str.)

^{1}H NMR(DMSO-d_6): δ, 3.31(2H, s, CH_2), 6.95(1H, s, NH) 7.21-7.59 (4H, aromatic).

*6,7-Dichloro-3-{[(2,4,5-trichlorophenyl)sulfanyl]methyl}-1H -pyrido [3,2-e][1,3,4] oxadiazine (**b**)*



Synthesis procedure remains same as compound (**a**), but starting ester is 3, 5, 6-trichloropyridin-2-yl [(2, 4, 5-trichlorophenyl) sulfanyl] acetate. The yield of crystalline solid was 70%, melting point was 212-213 °C.

Spectral data

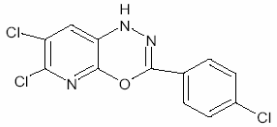
IR (KBr) ν_{max} in cm^{-1}: 3205 (-NH str.), 3038 (C-H str.), 1605(C=C aromatic.), 804-841 (C-Cl str.)

^{1}H NMR(DMSO-d_6):δ, 3.01 (2*H*, s, CH_2), 7.41(1H, s, NH) 7.21-7.59 (3*H*, aromatic)

*6,7-Dichloro-3-[(naphthalene–1-yl-sulfanyl)methyl]-1H-pyrido[3,2-e][1,3,4] oxadiazine(**c**)*

Synthesis procedure remains same as compound (**a**) above but starting ester is 3, 5, 6-trichloropyridin-2-yl (1-naphthylthio) acetate. The yield of crystalline solid was 65%, melting point was 133-134 °C.

*6,7-Dichloro-3-(4-chlorophenyl)-1H-pyrido[3,2-e][1,3,4] oxadiazine (**d**)*



Synthesis of 3,5,6-trichloropyridin-2-yl 4-chlorobenzoate

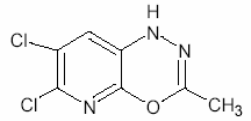
To 1 necked 250 mL round bottom flask, 50 mL dichloromethane solvent and TBAB catalyst was taken and then to this 21.5 g (0.1 mole) of ammonium salt of 3,5,6-trichloro –pyridine-2-ol was added. It was stirred using magnetic stirrer. It was thin white slurry. To this, 19.25 g (0.11 moles) of 4-chloro benzoyl chloride was added slowly over 15 minutes. The addition of acid chloride was exothermic and hence temperature was controlled at 30-42 °C. After addition of acid chloride, reaction mass becomes thin with fine salt (ammonium chloride) precipitation. Further reaction was maintained at 40-42 °C for 4 h. To this mass 100 mL of water was added and stirred. Separated layers and organic layer washed with 50 mL of 5% Na_2CO_3 solution to remove any unreacted acid part. Organic layer further washed with water and dried over $CaCl_2$. Product in dichloromethane solvent was concentrated to below 50 °C to remove solvent part and crude product re-slurried with 100 mL methanol was filtered. The yield of white crystalline solid was 92%, melting point was 118-119 °C.

The reaction with hydrazine hydrate to hydrazonoate was remains same as compound (**a**). Cyclization of hydrazonate intermediate to 6, 7-dichloro-3-(4-chlorophenyl)-1*H*-pyrido [3,2-e][1,3,4] oxadiazine remains same as that we followed in the compound (**a**)**.** The yield of white crystalline solid was 61%, melting point was 173-175 °C.

Spectral data

IR (KBr) ν_{max} in cm^{-1}: 3283 (-NH str.), 2983 (C-H str.), 1595(C=C aromatic.), 827-855 (C-Cl str.).
^{1}H NMR(DMSO-d_6):δ, 7.27(1H, s, NH) 7.43-7.78 (5H, aromatic)**.**
GC-MS: 317 (M + 1 peak).

*6,7-Dichloro-3-methyl-1H-pyrido [3,2-e][1,3,4] oxadiazine(**e**)*



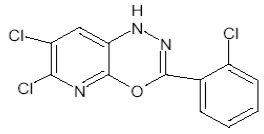
Synthesis of 3,5,6-trichloropyridin-2-yl acetate

To 1 necked 100 mL round bottom flask, 50 mL dichloromethane solvent, DMAP catalyst was taken and then to this 16.0 g. (0.075 mole) of ammonium salt of 3,5,6-trichloro – pyridine-2-ol was added . It was stirred using magnetic stirrer. It was thin white slurry. To this 7.06 g (0.09 moles) of acetyl chloride was slowly added over 5 minutes. The addition of acid chloride was exothermic and hence temperature controlled between 30-42 °C. After addition of acid chloride, reaction mass becomes thin with fine salt (ammonium chloride) precipitation. Further reaction was maintained between 40-42 °C for 4 h. To this mass 50 mL water was added and stirred. Separated layers and organic layer washed with 25 mL of 5% Na_2CO_3 solution to remove any unreacted acid part.

Organic layer further washed with water and dried over $CaCl_2$. Product in dichloromethane solvent was concentrated to below 50 °C to remove solvent part and crude product was re-slurried with 50 mL methanol and filtered. The yield of white crystalline solid product was 77.7%.

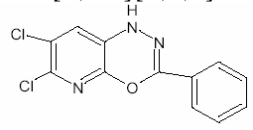
The reaction with hydrazine hydrate to hydrazonoate remains same as compound (**a**). In a reaction set up of single necked flask, magnetic stirring and oil heating system, 5.0 g (0.02 mole) of above prepared hydrazonoate, 25 mL pyridine was added heated to reflux at 115-116 °C and maintained for 6 h. Pyridine was distilled out under reduced pressure and to the left over residue 50 mL dichloromethane solvent + 50 mL water was added. Separated layers and organic layer washed with 25 mL of dilute sodium carbonate solution followed by water. Organic layer concentrated and crystallized with 10 mL of isopropyl alcohol. The yield of off-white crystalline solid was 68.8%, melting point was 173-174 °C.

*6,7-Dichloro-3-(2-chlorophenyl)-1H-pyrido[3,2-e][1,3,4] oxadiazine (**f**)*



Synthetic procedure was remains same as (**d**). The yield of off-white crystalline solid was 65.5%, melting point was 175-177 °C.

*6,7-Dichloro-3-phenyl -1H-pyrido[3,2-e][1,3,4] oxadiazine (**g**)*



In a one necked 250 mL round bottom flask, 50 mL of dichloromethane solvent, TBAB catalyst was taken and then to this 10.8 g (0.05 mole) of ammonium salt of 3,5,6-trichloro – pyridine-2-ol was added. It was stirred using magnetic stirrer. It was thin white slurry. To this 7.8 g (0.55 moles) of benzoyl chloride was added slowly over 15 minutes. The addition of acid chloride was exothermic and hence temperature controlled between 30-42 °C. After addition of acid chloride, reaction mass was becomes thin with fine salt (ammonium chloride) precipitation. Further reaction was maintained between 40-42 °C for 4 h. To this mass 100 mL water was added and stirred. Separated layers and organic layer washed with 40 mL of 5% Na_2CO_3 solution to remove any unreacted acid part. Organic layer further washed with water and dried over $CaCl_2$. Product in dichloromethane solvent was concentrated to below 50 °C to remove solvent part and crude product re-slurried with 100 mL methanol and filtered. The yield of white crystalline solid was 93.9%.

In a set up of one necked 50 mL round bottom flask with magnetic stirrer, 25 mL methanol, 0.013 moles of 3,5,6-trichloropyridin-2-yl benzoate and 0.1 g PTSA was added. It was slurry. This mass was cooled to 18-20 °C by external cooling and to these 0.015 moles of hydrazine hydrate (80.0% solution) was added. Addition was exothermic and thin slurry converted into thick white slurry. This was maintained at 20-30 °C for 4 h. Reaction mass concentrated under reduced pressure at 45-50 °C. To this concentrated product 25 mL of pyridine was added and refluxed for 6 h. Then pyridine was distilled out under vacuum at 100-105 °C. To the residual part, water was added and filtered the product. The isolated crude product purified in 25 mL of methanol. The yield of buffer white solid was 62%, melting point was 175-177 ^{o}C. **GC-MS:** 283 (M + 1 peak).

Results and Discussion

The chiral acid mixture (3-(2, 2-dihalovinyl)-2,2-dimethyl cyclopropane carboxylic acid) used in the synthetic process was obtained from M/s Gharda Chemicals Ltd. The chiral mixture was resolved to get single isomer as well as recemic mixture for experimental purpose. The isolated acid was converted into acid chloride by reacting with thionyl chloride under controlled condition to preserve chiral purity. The input raw material *i.e.* 3,5,6-trichloropyrine-2-ol was obtained from M/S Gharda Chemicals Ltd. This 3,5,6-trichloropyrine-2-ol (198.5 g, 1.0 mole) was taken in 500 mL methanol solvent and dry ammonia gas at 30-35 °C was passed till ammonical pH. This was further refluxed for 1.0 h and then filtered at 30 °C to get ammonium salt. 3,5,6-trichloropyridin-2-yl-3-(2,2-dihalovinyl)-2,2-dimethylcyclopropanecarboxylate was prepared by reacting corresponding acid chloride with 3,5,6-trichloropyrine-2-ol ammonium salt in dichloromethane solvent in presence of DMAP catalyst at 40 °C. The quantity of ammonium salt taken was 10 mL excess than acid chloride and dichloromethane solvent was 100 mL per 0.05 mole scale. Similarly other carboxylates and sulfanyl acetates were prepared. Reacting 0.05 moles of these intermediate in 50 mL methanol and 0.055 moles of 80% hydrazine hydrate at 20 °C using PTSA catalyst, prepared the corresponding hydrazonoates. The novel derivatives of synthesized oxadiazine likely to show diverse biological activity.

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