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Design, Microwave Assisted Synthesis and Characterization of Substituted 1,2,4-Oxadiazole Analogues as Promising Pharmacological Agents

KATHARIGATTA N. VENUGOPALA

Department of Biotechnology and Food Technology, Durban University of Technology, Steve Biko Campus, Durban 4001, South Africa

*Corresponding author: Fax: +27 86 2423534; Tel: +27 31 3734887; E-mail: katharigattav@dut.ac.za

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Microwave assisted synthesis of a series of 3,5-disubstituted-1,2,4-oxadiazole analogues (**3a-j**) has been achieved between 5-(chloromethyl)-3-substituted phenyl-1,2,4-oxadiazoles (**2a-j**) and substituted benzophenone in presence of potassium carbonate in acetone medium. The structural elucidation of the newly synthesized 1,2,4-oxadiazole analogues was established by means of FT-IR, NMR, LC-MS and elemental analysis.

Keywords: Microwave assisted synthesis, 1,2,4-Oxadiazoles, Pharmacological properties.

INTRODUCTION

The oxadiazole molecular scaffolds are known for various pharmacological activities such as antitussive, anaesthetic [1], anthelmintic [2], anti-HIV [3], antiallergic [4], anticancer [5], anticonvulsant [6], anti-inflammatory [7], antimicrobial [8], antiplatelet, antithrombotic [9], insecticidal [10], monoamine oxidase inhibition [11], muscarinic receptor agonists [12] and selective H_3 receptor antagonists [13] properties.

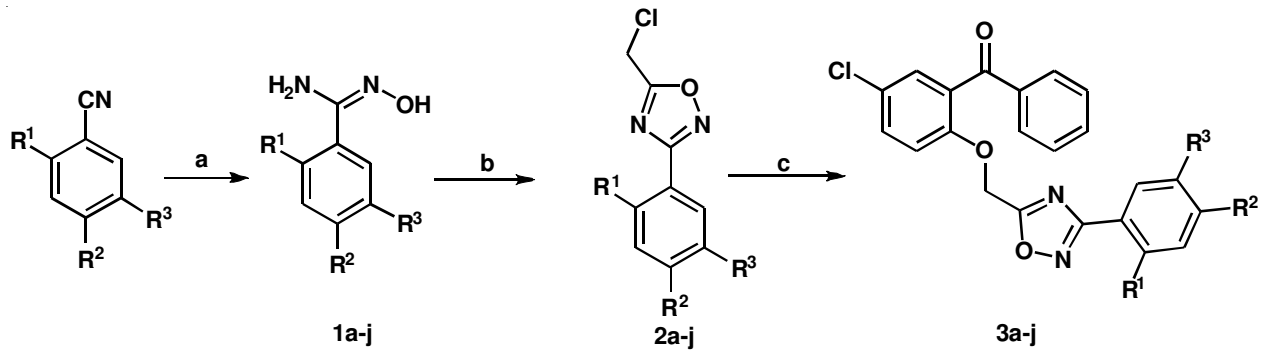
Encouraged by these observations and in continuation of our research work on the synthesis of novel heterocyclic compounds for pharmacological properties [14-17] and for the screening of polymorphic properties in heterocyclic compounds [18-20], it was decided to incorporate benzophenone moiety on 1,2,4-oxadiazole nucleus (**Scheme-I**) with the support of microwave method to study the yield and total reaction time.

EXPERIMENTAL

Commercially available chemicals were obtained from Aldrich and Merck chemical company. TLC was performed on Merck 60 F-254 silica gel plates with ethyl acetate and *n*-hexane (6:4) as solvent system and visualization with UV-light and iodine chamber. Reactions were monitored by thin layer chromatography (TLC). Melting points were determined on a Buchi melting point B-545 apparatus. The FT-IR spectra were recorded on a Nicolet 6700 FT-IR spectrometry. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AVANCE III 400 MHz instruments in $CDCl_3$ as a solvent. Chemical shifts (δ) were indicated in parts per million downfield from tetramethylsilane and the coupling constants (*J*) are recorded in Hertz. Mass spectra were recorded using LC-MS-Agilent 1100 series with MSD (Ion trap) using 0.1 % aqueous trifluoroacetic acid in acetonitrile system on C18-BDS column. Elemental analysis was performed on Thermo Finnigan FLASH EA 1112 CHN analyzer. c log P of the compounds was calculated using ChemBioDraw Ultra 13.0v.

Synthesis of (5-chloro-2-((3-(substituted phenyl)-1,2,4-oxadiazol-5-yl)methoxy)phenyl)(phenyl)methanone (3a-j): A mixture of reaction intermediates (**2a-j**, 5 mmol), substituted benzophenone (5 mmol), absolute ethanol (25 mL) and K_2CO_3 (6 mmol) was exposed to microwaves in a microwave reactor for up to 10 min. After reaction completion, the reaction medium was allowed to attain room temperature. The reaction medium was filtered and the filtrate was evaporated to dryness and the residue obtained was purified by recrystallization method. The physicochemical characteristics of the characterized title compounds **3a-j** are summarized in Table-1 and details are as follows:

(5-Chloro-2-((3-(4-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)methoxy)phenyl)(phenyl)methanone (3a): Brown crystalline compound; FT-IR (KBr, ν_{max}, cm^{-1}): 3064, 1655, 1594, 1482, 1451, 1261, 738. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02-8.06 (m, 2H), 7.82-7.86 (d, *J* = 7.20 Hz, 2H), 7.55-7.63 (m, 1H), 7.43-7.51 (m, 4H), 7.12-7.22 (m, 2H), 7.07-7.02 (d, *J* = 8.61 Hz, 1H), 5.23 (s, 2H, OCH_2). ^{13}C NMR (400 MHz, $CDCl_3$): δ 194.18, 173.94, 167.65, 165.97, 163.44, 153.70, 136.99, 133.53, 129.81, 129.74, 129.64, 128.47,



Scheme-I: Reagents and conditions for the construction of 3,5-disubstituted 1,2,4-oxadiazoles (**3a-j**): (a) $NH_2OH.HCl$, sodium carbonate, ethanol; (b) chloroacetyl chloride, N,N-diisopropylethylamine (DIEA), dichloromethene (DCM); (c) potassium carbonate, 2-hydroxy-5-chloro benzophenone, ethanol

127.95, 122.43, 122.38, 116.27, 116.05, 114.90, 62.07. LC-MS (ESI, Positive): *m/z* = 459 $[M+H]^+$. CHN analysis calculated for $C_{23}H_{14}N_2O_3ClF_3$: C, 60.21; H, 3.08; N, 6.11; Found: C, 60.22; H, 3.05; N, 6.16.

(5-Chloro-2-((3-(4-fluorophenyl)-1,2,4-oxadiazol-5-yl)methoxy)phenyl)(phenyl)methanone (3b): Light yellow solid; FT-IR (KBr, ν_{max}, cm^{-1}): 3063, 1651, 1592, 1482, 1451, 1264, 742. ^1H NMR (400 MHz, $CDCl_3$): δ 8.00-8.05 (m, 2H), 7.82-7.84 (d, *J* = 7.24 Hz, 2H), 7.53-7.58 (m, 1H), 7.41-7.48 (m, 4H), 7.13-7.22 (m, 2H), 7.06-7.08 (d, *J* = 8.42 Hz, 1H), 5.25 (s, 2H, OCH_2). ^{13}C NMR (400 MHz, $CDCl_3$): δ 194.14, 173.97, 167.61, 165.98, 163.42, 153.70, 136.99, 133.53, 131.62, 131.41, 129.78, 129.71, 129.67, 128.42, 127.91, 122.42, 122.38, 116.25, 116.04, 114.89, 62.01. LC-MS (ESI, Positive): *m/z* = 410 $[M+H]^+$. CHN analysis calculated for $C_{22}H_{14}N_2O_3ClF$: C, 64.64; H, 3.45; N, 6.85; Found: C, 64.61; H, 3.47; N, 6.81.

(5-Chloro-2-((3-(3-chloro-4-fluorophenyl)-1,2,4-oxadiazol-5-yl)methoxy)phenyl)(phenyl)methanone (3c): Light yellow crystalline compound; FT-IR (KBr, ν_{max}, cm^{-1}): 3058, 1662, 1594, 1480, 1443, 1261, 742. ^1H NMR (400 MHz, $CDCl_3$): δ 8.06-8.10 (m, 1H), 7.91-7.97 (m, 1H), 7.79-7.84 (m, 2H), 7.54-7.58 (m, 1H), 7.30-7.46 (m, 4H), 7.21-7.28 (m, 1H), 7.04-7.09 (d, *J* = 8.42 Hz, 1H), 5.24 (s, 2H, OCH_2). ^{13}C NMR (400 MHz, $CDCl_3$): δ 194.07, 174.25, 166.81, 161.27, 158.74, 153.63, 133.97, 131.66, 131.43, 130.05, 129.79, 128.48, 128.05, 127.57, 127.49, 123.44, 123.38, 122.12, 121.96, 117.42, 117.19, 114.92, 62.05. LC-MS: (ESI, Positive) *m/z* = 444 $[M+H]^+$. CHN analysis calculated for $C_{22}H_{13}N_2O_3Cl_2F$: C, 59.61; H, 2.96; N, 6.32. Found C, 59.58; H, 3.02; N, 6.30.

(5-Chloro-2-((3-(4-fluoro-3-methylphenyl)-1,2,4-oxadiazol-5-yl)methoxy)phenyl)(phenyl)methanone (3d): Light yellow solid; FT-IR (KBr, ν_{max}, cm^{-1}): 3051, 2935, 1659, 1617, 1484, 1450, 1258, 748. ^1H NMR (400 MHz, $CDCl_3$): δ 7.81-7.89 (m, 4H), 7.54-7.58 (m, 1H), 7.41-7.45 (m, 4H), 7.03-7.12 (m, 2H), 5.26 (s, 2H, OCH_2), 2.32 (s, 3H, CH_3). ^{13}C NMR (400 MHz, $CDCl_3$): δ 194.15, 173.80, 167.79, 164.59, 162.05, 153.72, 136.98, 133.51, 131.41, 131.33, 130.88, 130.83, 129.79, 128.44, 127.89, 127.02, 126.93, 125.95, 125.77, 121.98, 121.94, 115.83, 115.62, 114.87, 62.05, 14.52. LC-MS (ESI, Positive): *m/z* = 424 $[M+H]^+$. CHN analysis calculated for $C_{23}H_{16}N_2O_3ClF$: C, 65.33; H, 3.81; N, 6.63. Found C, 65.30; H, 3.89; N, 6.58.

(5-Chloro-2-((3-(4-fluoro-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)methoxy)phenyl)(phenyl)methanone (3e): Light yellow solid; FT-IR (KBr, ν_{max}, cm^{-1}): 3068, 2981, 1651, 1630, 1498, 1441, 1253, 743. ^1H NMR (400 MHz, $CDCl_3$): δ 7.80-7.83 (m, 2H), 7.54-7.65 (m, 3H), 7.42-7.47 (m, 4H), 7.14-7.21 (m, 1H), 7.03-7.10 (d, *J* = 8.42 Hz, 1H), 5.27 (s, OCH_2), 3.93 (s, OCH_3). ^{13}C NMR (400 MHz, $CDCl_3$): δ 193.97, 173.89, 167.67, 167.60, 156.08, 153.69, 152.67, 148.18, 147.92, 136.95, 133.47, 131.58, 131.30, 129.68, 128.42, 127.87, 122.51, 122.41, 120.62, 120.52, 116.52, 116.39, 114.85, 112.19, 112.09, 62.04, 56.21. LC-MS (ESI, Positive): *m/z* = 440 $[M+H]^+$. CHN analysis calculated for $C_{23}H_{16}N_2O_4ClF$: C, 62.95; H, 3.67; N, 6.38. Found: C, 62.98; H, 3.70; N, 6.35.

(5-Chloro-2-((3-(2,5-difluoro-4-methylphenyl)-1,2,4-oxadiazol-5-yl)methoxy)phenyl)(phenyl)methanone (3f): Yellow crystalline compound; FT-IR (KBr, ν_{max}, cm^{-1}): 3055, 2938, 1659, 1598, 1481, 1459, 1260, 743. ^1H NMR (400 MHz, $CDCl_3$): δ 7.83-7.89 (d, *J* = 7.20 Hz, 2H), 7.55-7.68 (m, 2H), 7.44-7.49 (m, 4H), 7.04-7.12 (m, 2H), 5.29 (s, 2H, OCH_2), 2.33 (s, 3H, CH_3). ^{13}C NMR (400 MHz, $CDCl_3$): δ 194.11, 173.58, 164.73, 164.69, 164.65, 164.61, 158.28, 158.23, 157.59, 157.54, 155.88, 155.83, 155.08, 154.88, 153.61, 136.98, 133.57, 131.67, 131.38, 130.87, 130.81, 130.69, 130.60, 129.79, 128.49, 127.97, 119.32, 119.28, 119.11, 119.02, 116.37, 116.33, 116.09, 116.01, 114.76, 112.83, 112.78, 112.72, 112.63, 61.86, 14.92, 14.81. LC-MS (ESI, Positive): *m/z* = 442 $[M+H]^+$. CHN analysis calculated for $C_{23}H_{15}N_2O_3ClF_2$: C, 62.67; H, 3.43; N, 6.35. Found: C, 62.62; H, 3.51; N, 6.39.

(5-Chloro-2-((3-(4-iodophenyl)-1,2,4-oxadiazol-5-yl)methoxy)phenyl)(phenyl)methanone (3g): Light brown crystalline compound; FT-IR (KBr, ν_{max}, cm^{-1}): 3056, 1650, 1591, 1476, 1452, 1268, 747, 521. ^1H NMR (400 MHz, $CDCl_3$): δ 7.76-7.85 (m, 6H), 7.55-7.58 (m, 1H), 7.42-7.48 (m, 4H), 7.05-7.08 (d, *J* = 8.42 Hz, 1H), 5.22 (s, 2H, OCH_2). ^{13}C NMR (400 MHz, $CDCl_3$): δ 194.11, 174.12, 167.94, 153.66, 138.22, 136.95, 133.57, 131.62, 131.43, 129.81, 128.96, 128.47, 128.06, 125.63, 114.94, 98.33, 62.05. LC-MS (ESI, Positive): *m/z* = 518 $[M+H]^+$. CHN analysis calculated for $C_{22}H_{14}N_2O_3ClI$: C, 51.14; H, 2.73; N, 5.42. Found: C, 51.17; H, 2.71; N, 5.49.

(5-Chloro-2-((3-phenyl-1,2,4-oxadiazol-5-yl)methoxy)-phenyl)(phenyl)methanone (3h): White amorphous compound;

FT-IR (KBr, ν_{max}, cm^{-1}): 3061, 1655, 1591, 1484, 1451, 1247, 738. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89-8.06 (m, 2H), 7.71-7.78 (m, 2H), 7.28-7.58 (m, 8H), 7.04-7.08 (d, *J* = 8.42 Hz, 1H), 5.23 (s, 2H, OCH_2). ^{13}C NMR (400 MHz, $CDCl_3$): δ 194.10, 174.08, 167.94, 153.71, 138.25, 136.81, 133.50, 131.59, 131.38, 129.81, 128.91, 128.51, 128.12, 125.63, 125.60, 114.93, 98.36, 62.09. LC-MS (ESI, Positive): *m/z* = 392 $[M+H]^+$. CHN analysis calculated for $C_{22}H_{15}N_2O_3Cl$: C, 67.61; H, 3.87; N, 7.17; Found: C, 67.62; H, 3.91; N, 7.22.

(5-Chloro-2-((3-(4-ethoxyphenyl)-1,2,4-oxadiazol-5-yl)methoxy)phenyl)(phenyl)methanone (3i): Light yellow crystalline compound; FT-IR (KBr, ν_{max}, cm^{-1}): 3088, 2978, 1652, 1591, 1482, 1449, 1272, 745. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91-7.96 (m, 2H), 7.83-7.94 (m, 2H), 7.54-7.57 (m, 1H), 7.40-7.45 (m, 4H), 7.03-7.06 (d, *J* = 8.42 Hz, 1H), 6.92-6.98 (m, 2H), 5.29 (s, 2H, OCH_2), 4.05-4.14 (q, 2H, OCH_2), 1.42-1.48 (t, 3H, CH_3). ^{13}C NMR (400 MHz, $CDCl_3$): δ 194.07, 173.52, 168.08, 161.51, 153.61, 136.94, 133.41, 131.54, 131.32, 129.82, 129.68, 129.11, 128.39, 127.75, 119.00, 114.74, 114.67, 63.60, 61.90, 14.63. LC-MS (ESI, Positive): *m/z* = 436 $[M+H]^+$. CHN analysis calculated for $C_{24}H_{19}N_2O_4Cl$: C, 66.29; H, 4.40; N, 6.44. Found: C, 66.32; H, 4.39; N, 6.47.

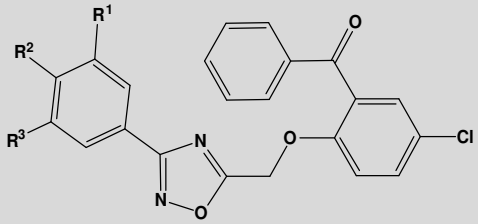
(5-Chloro-2-((3-(4-isopropylphenyl)-1,2,4-oxadiazol-5-yl)methoxy)phenyl)(phenyl)methanone (3j): Light yellow crystalline compound; FT-IR (KBr, ν_{max}, cm^{-1}): 3051, 2972, 1657, 1598, 1481, 1453, 1268, 747. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95-7.99 (m, 2H), 7.80-7.87 (m, 2H), 7.51-7.59 (m, 1H), 7.44-7.48 (m, 4H), 7.34-7.36 (d, *J* = 8.16 Hz, 2H), 7.05-7.09 (m, 1H), 5.31 (s, 2H, OCH_2), 2.95-2.97 (q, *J* = 6.84 Hz, 1H), 1.27-1.31 (d, 6H, 2 X CH_3). ^{13}C NMR (400 MHz, $CDCl_3$): δ 194.18, 173.57, 168.40, 153.69, 152.81, 137.08, 133.55, 131.72, 131.29, 129.98, 129.82, 128.61, 127.84, 127.61, 127.09, 123.64, 114.83, 62.00, 34.26, 23.71. LC-MS (ESI, Positive): *m/z* = 434 $[M+H]^+$. CHN analysis calculated for $C_{25}H_{21}N_2O_3Cl$: C, 69.36; H, 4.89; N, 6.47. Found: C, 69.42; H, 4.99; N, 6.51.

RESULTS AND DISCUSSION

Synthetic route for the formation of 1,2,4-oxadiazole analogues (**3a-j**) by microwave method is depicted in **Scheme-I**. The title compounds **3a-j** were synthesized from substituted benzophenone and reaction intermediates 5-(chloromethyl)-3-substituted phenyl-1,2,4-oxadiazoles (**2a-j**) in absolute ethanol medium. Intermediates **2a-j** were synthesized from equimolar ratios of *N'*-hydroxybenzimidamides (**1a-j**) and chloroacetyl chloride in presence of DIPEA in dichloro methanol medium. The synthesis of *N'*-hydroxybenzimidamides (**1a-j**) was accomplished from the corresponding hydroxylamine hydrochloride and substituted benzonitriles in presence of sodium carbonate in methanol medium. The reaction intermediates **1a-j** and **2a-j** were synthesized and characterized by FT-IR, ^{1}H NMR, LC-MS and the characterization details matched with our previous communication [8]. The title compounds **3a-j** were characterized by FT-IR, NMR, LC-MS and CHN analysis. The yields of intermediates **1a-j** and **2a-j** were in the range of 58-79 and 56-75 %, respectively. The yield of title compounds 3,5-disubstituted 1,2,4-oxadiazoles (**3a-j**) was 87-93 % and the physicochemical constants of the title compounds are summarized in Table-1.

In the FT-IR spectra of 3,5-disubstituted 1,2,4-oxadiazole analogues (**3a-j**), carbon-chlorine and carbonyl group (C=O) peaks were found in the ranges of 725-760 and 1646-1668 cm^{-1}, respectively. In the ^{1}H NMR spectra singlet peak in the range of 5.22-5.31 corresponds to -OCH_2- group in molecular scaffolds **3a-j**. In ^{13}C NMR spectra, alkyl carbon (-CH_2-) and carbonyl carbon peaks are observed in the range of δ 61.86-62.09 and 193.97-194.18, respectively. In LC-MS spectra,

TABLE-1
PHYSICO-CHEMICAL CHARACTERISTICS OF 3,5-DISUBSTITUTED 1,2,4-OXADIAZOLES (**3a-j**)



Compd. No.	R^1	R^2	R^3	m.f.	m.w.	Reaction time (min)	Yield (%)	m.p. (°C) reported [Ref. 8]	m.p. (°C) found	Crystal solvent	c log P^b
3a	H	CF_3	H	$C_{23}H_{14}N_2O_3ClF_3$	458	4	91	–	102-103	Ethanol	6.2627
3b	H	F	H	$C_{22}H_{14}N_2O_3ClF$	408	6	88	96-97	97-98	Methanol	5.5197
3c	H	F	Cl	$C_{22}H_{13}N_2O_3Cl_2F$	442	5	93	85-86	86-87	Methanol	6.2332
3d	H	F	CH_3	$C_{23}H_{16}N_2O_3ClF$	422	6	84	73-74	73-74	Ethanol	6.0187
3e	H	F	OCH_3	$C_{23}H_{16}N_2O_4ClF$	438	7	89	84-85	85-86	Ethanol	5.4184
3f	F	CH_3	F	$C_{23}H_{15}N_2O_3ClF_2$	440	5	92	87-89	88-89	Ethanol	6.1622
3g	H	I	H	$C_{22}H_{14}N_2O_3ClI$	516	6	87	124-126	125-126	Methanol	6.4997
3h	H	H	H	$C_{22}H_{15}N_2O_3Cl$	390	8	83	108-110	109-110	Methanol	5.3727
3i	H	OC_2H_5	H	$C_{24}H_{19}N_2O_4Cl$	434	7	88	80-82	81-82	Ethanol	5.9437
3j	H	$CH(CH_3)_2$	H	$C_{25}H_{21}N_2O_3Cl$	432	8	86	110-112	111-112	Ethanol	6.7997

[a]All the yields are on isolated basis. Compound purification is by recrystallization method.
[b]c log *P* of the compounds is calculated by ChemBioDraw Ultra 13.0v.

molecular ion peaks (M^{+1}) of the tittle compounds **3a-j** were in good agreement with proposed molecular weight. The elemental analysis results were within ± 0.05 % of the calculated values of the 3,5-disubstituted 1,2,4-oxadiazole analogues (**3a-j**). The ChemBioDraw calculated partition coefficient values of the title compounds **3a-j** were in the range of p = 5.3727-6.7997. Compound with aliphatic group (isopropyl) on phenyl ring which is on third place of 1,2,4-oxadiazole nucleus exhibited highest partition value of p = 6.7997 compared to other analogoues in the series.

Conclusion

In the present investigation, synthesis of 3,5-disubstitued 1,2,4-oxadiazole molecular scaffolds was achieved by microwave method. The functional groups such as halogens and alkoxy groups on 1,2,4-oxadiazole moiety favoured good yields and were found in the range of 87-93 % after purification by recrystallization method. It was confirmed from the present investigation that, microwave method favoured to enhance the yield of the product and reduce the reaction time to obtain the title compounds **3a-j**. The Title compounds are proposed to test for suitable pharmacological properties.

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