Indian Journal of Chemistry
Vol. 59B, January 2020, pp. 85-92

Efficient synthesis of new oxadiazole-thiazole hybrids using (diacetoxyiodo)benzene

Garima Sumran[a], Chinu Rani[b] & Ranjana Aggarwal*[b†]

[a] Department of Chemistry, D. A. V. College (Lahore), Ambala City 134 003, India
[b] Department of Chemistry, Kurukshetra University, Kurukshetra 136 119, India

E-mail: ranjanaaggarwal67@gmail.com

Received 30 August 2019; accepted (revised) 31 October 2019

An efficient synthesis of some new 2-aryl-5-(2'-(4-nitrophenylamino)thiazol-4'-yl)-1,3,4-oxadiazoles **7a-e**, has been accomplished through oxidative cyclization of 2-(4-nitrophenylamino)-*N'*-(substituted benzylidene) thiazole-4-carbohydrazides **6a-e** using an ecofriendly oxidant, (diacetoxyiodo)benzene at ambient temperature. The structures of the synthesized oxadiazole-thiazole hybrid compounds have been characterized by elemental and spectral (IR, ^{1}H and ^{13}C NMR, and MS) analysis. The reaction can tolerate a wide range of aldehydes to afford the corresponding unsymmetrical 2,5-disubstituted 1,3,4-oxadiazoles. The mild reaction conditions, relatively benign nonmetallic oxidant and short reaction time are noteworthy advantages of this methodology.

Keywords: 2-Aryl-5-(2'-(4-nitrophenylamino)thiazol-4'-yl)-1,3,4-oxadiazoles, 2-(4-nitrophenylamino)-*N'*-arylidenethiazole-4-carbohydrazide, (diacetoxyiodo)benzene, oxidative cyclization, oxadiazole-thiazole hybrid

Recently there has been an upsurge of interest in chemistry of 1,3,4-oxadiazole scaffold as useful synthons for the synthesis of value-added chemical entities possessing high structural diversity[1,2]. This privileged structural motif forms an integral part of various bioactive compounds and clinically important drugs such as Nesapidil, Furamizole, Zibotentan and Raltegravir (Figure 1). Compounds containing 1,3,4-oxadiazole core have extensive application in diverse areas ranging from organic light-emitting diodes, photoluminescence, liquid crystals, molecular wires, agrochemicals, polymers to medicinal chemistry[3-9]. Further, 1,3,4-oxadiazoles as bioisosteres of ester and carboxamide functionalities, can interact with a number of biological targets by forming hydrogen bonding interactions thereby enhancing the pharmacological activity of the candidate.

1,3-Thiazole and its derivatives are versatile leading molecules in medicinal chemistry due to their diverse syntheses and potential in drug design and development[10,11]. Thiazole scaffold is present naturally in vitamin B1, antibiotic Penicillin, alkaloid Bacillamide and in various synthetic pharmaceutical drugs including Fanetizole (immunomodulator), Meloxicam (anti-inflammatory), Sulfathiazole (antimicrobial), Bleomycin (anticancer), Pramipexole (antidepressant), Nizatidine (antiulcer) and Ritonavir (HIV-protease inhibitor). The integration of two or more pharmacophores in one chemical entity is a promising strategy in the search for novel therapeutic agents with higher efficacy and lower toxicity[12,13]. In this context, 2-pyridinyl substituted thiazolyl-5-aryl-1,3,4-oxadiazoles **I**, and **II** have displayed significant antitubercular activity against *Mycobacterium Bovis* BCG with MIC value of 2.65 μg/mL and 2.56 μg/mL, respectively[14]. Oxadiazole derivative **III** incorporating thiazole nucleus exhibited *in vitro* anticancer activity against two human cancer cell lines, MDA-MB231 and HT-29 and arrested cell cycle in Go/G1 phase on both cell lines[15]. In a docking study, interaction of several thiazolyl-1,3,4-oxadiazole derivatives on lanosterol 14α-demethylase (CYP51), target enzyme in the design of antifungal agents, was reported[16]. Thiazole clubbed 1,3,4-oxadiazole derivatives **IV** have found to exhibit potent antimicrobial activities[17]. Provoked by these observations, an attempt to design a series of new molecular hybrids having oxadiazole and thiazole pharmacophores using molecular hybridization approach has been put forward.

In view of significant roles of 1,3,4-oxadiazole ring in medicinal chemistry, drug design and material

† Presently at CSIR-National Institute of Science Technology and Development Studies (CSIR-NISTADS), New Delhi 110 012, India

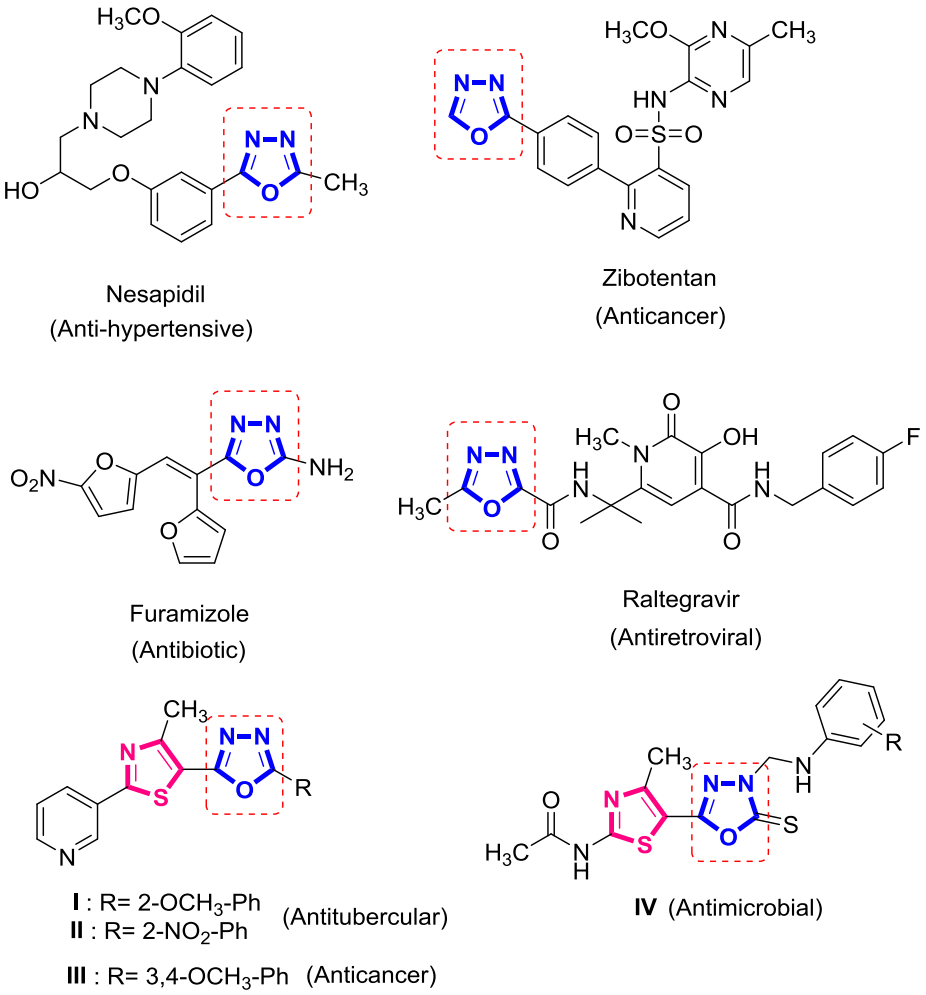
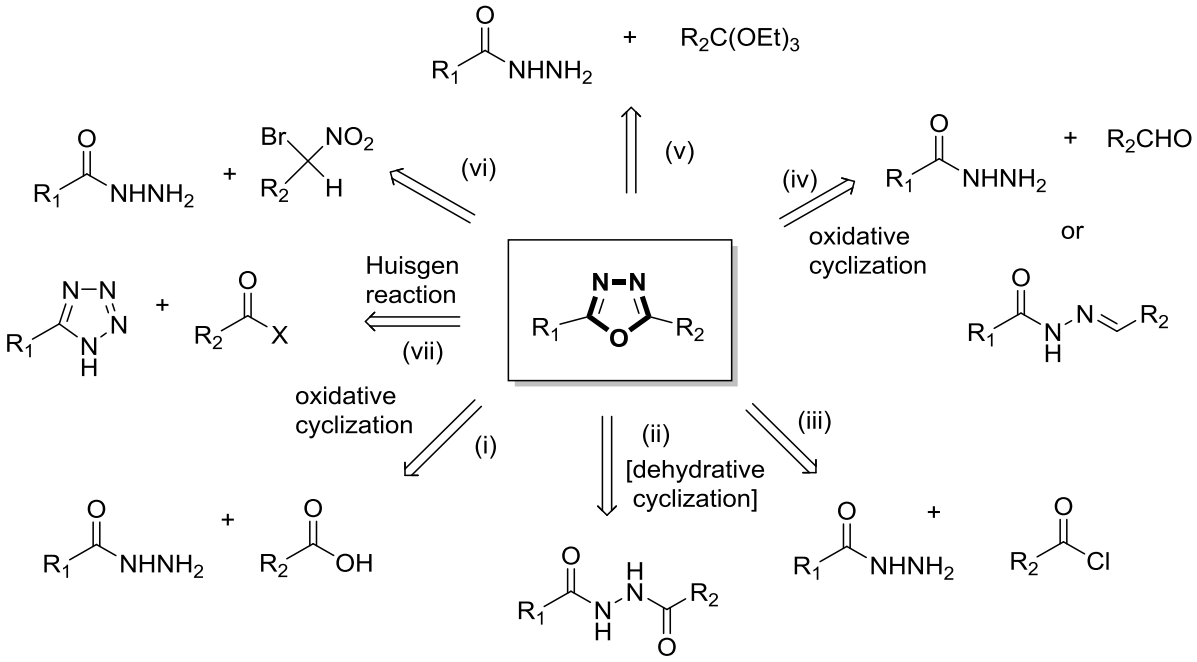


Figure 1 — Representative bioactive molecules containing 1,3,4-oxadiazole core

science, a number of synthetic approaches have been developed for symmetrical and asymmetrical 2,5-disubstituted 1,3,4-oxadiazoles (Scheme I). The commonly used synthetic routes for 1,3,4-oxadiazoles involve: (i) intermolecular condensation of acylhydrazide with carboxylic acid in presence of dehydrating reagents such as phosphorous oxychloride, polyphosohoric acid, acetic anhydride under harsh reaction conditions, (ii) cyclodehydration of *N,N'*-diacylhydrazines with thionyl chloride/ $POCl_3$/ triphenylphosphine oxide-triflic anhydride/ zirconium(IV) chloride, (iii) reaction of acylhydrazide with excess of acid chloride in hexamethyl-phosphoramide (HMPA) and then microwave irradiation, (iv) oxidative cyclization of *N*-acylhydrazones using various oxidizing agents *viz.* lead tetraacetate, lead(IV) oxide, cerric ammonium nitrate (CAN), chloroamine T, trichloroisocyanuric acid, mercuric acetate, potassium permanganate, mercury(II) oxide-iodine or through electrochemical methods, (v) reaction of arylhydrazide with orthosters using catalytic NH_4Cl, (vi) reaction of acylhydrazide with α-bromonitroalkanes, (vii) Huisgen reactions of tetrazoles with acid chlorides[7, 18-20].

The dehydrative cyclization and numerous other methods have limitations due to harsh conditions, highly toxic and corrosive reagents, longer reaction times and high temperature. On the other hand, oxidative cyclization of *N*-acylhydrazones, versatile precursors to furnish asymmetrical oxadiazoles, has also been reported by milder and environmentally sustainable reagents such as hypervalent iodine reagents ((diacetoxyiodo)benzene (DIB) and bis(trifluoroacetoxy)iodobenzene (BTI))[21] and molecular iodine[22].

Immense biological activities associated with 1,3, 4-oxadiazole and 1,3-thiazole derivatives and our ongoing interest on efficacy of hypervalent iodine



Scheme I — Reterosynthetic approach to 2,5-disubstituted 1,3,4-oxadiazoles

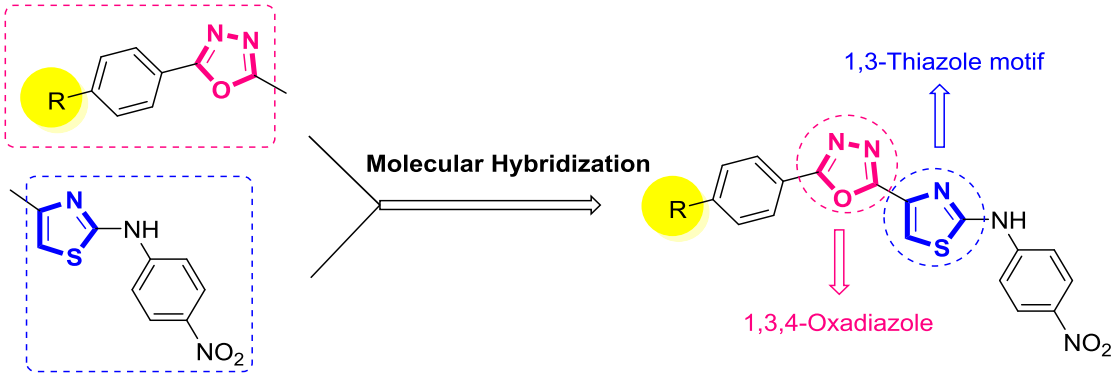
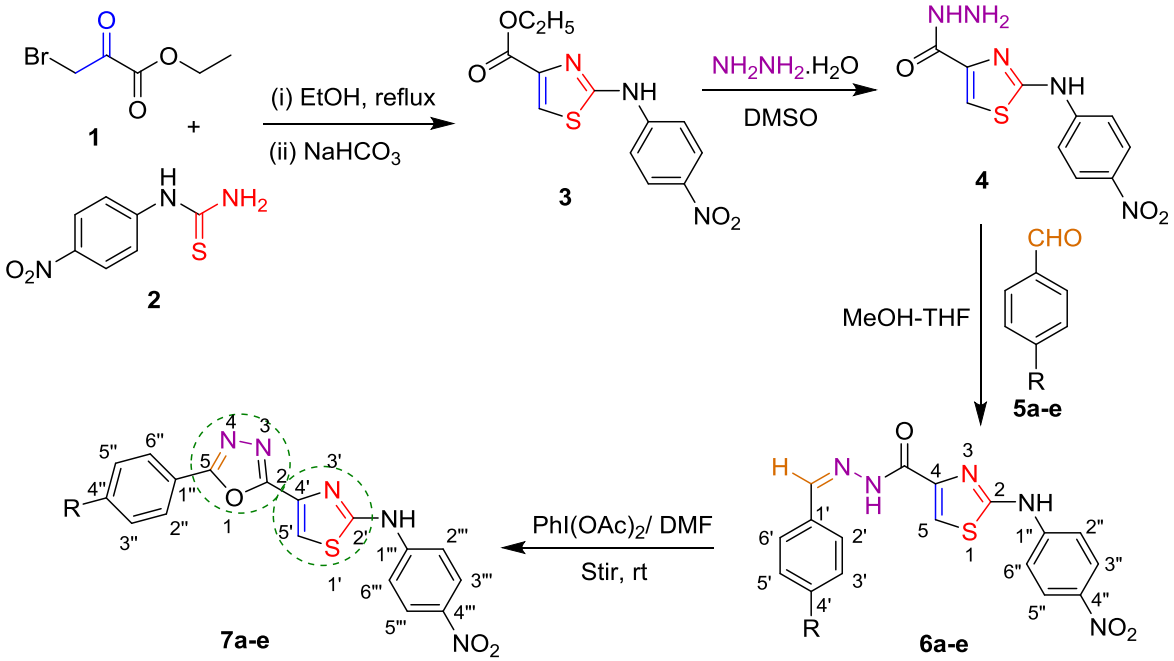


Figure 2 — Design of oxadiazole-thiazole hybrids using molecular hybridization of pharmacophores

reagents in green organic synthesis[23-28], impelled us to synthesize a series of 2-aryl-5-(2'-(4-nitrophenylamino)thiazol-4'-yl)-1,3,4-oxadiazoles **7a-e** having both thiazole and oxadiazole pharmacophores and diverse set of aromatic substitutions at position-2 of oxadiazole core in one molecular framework through a highly efficient, facile and ecofriendly route (Figure 2).

Results and Discussion

The hybrid 1,3,4-oxadiazole-1,3-thiazole compounds **7a-e** were synthesized according to the reaction sequence as framed in the Scheme II. Initially, ethyl *α*-bromopyruvate **1** obtained by bromination of ethyl pyruvate in presence of dry CO_2[29], was condensed with *p*-nitrophenylthiourea **2** in ethanol followed by neutralization with saturated sodium bicarbonate solution to afford ethyl-2-(4-nitrophenylamino)thiazole-4-carboxylate **3** *via* Hantzsch's thiazole synthesis. In the next step, compound **3** was refluxed with hydrazine hydrate in dimethylsulfoxide to obtain 2-(4-nitrophenylamino)thiazole-4-carbohydrazide **4**. A solution of **4** in MeOH-THF (1:1) was refluxed with differently substituted benzaldehydes **5a-e** in presence of two drops of acetic acid for about 2-3 h to afford 2-(4-nitrophenylamino)-*N*′-arylidenethiazole-4-carbohydrazide **6a-e** in 84-88% yields. The oxidative cyclization of **6a-e** was achieved with 1.1 equiv of DIB in dimethylformamide by stirring at RT for 2 h. The usual work up of the reaction yielded single product, 2-aryl-5-(2'-(4-nitrophenylamino)thiazol-4'-yl)-1,3,4-oxadiazoles **7a-e** in 78-85% yield (Scheme II). The structures of all the newly synthesized compounds **6a-e** and **7a-e** were



5, 6, 7	a	b	c	d	e
R	H	CH_3	Cl	Br	F

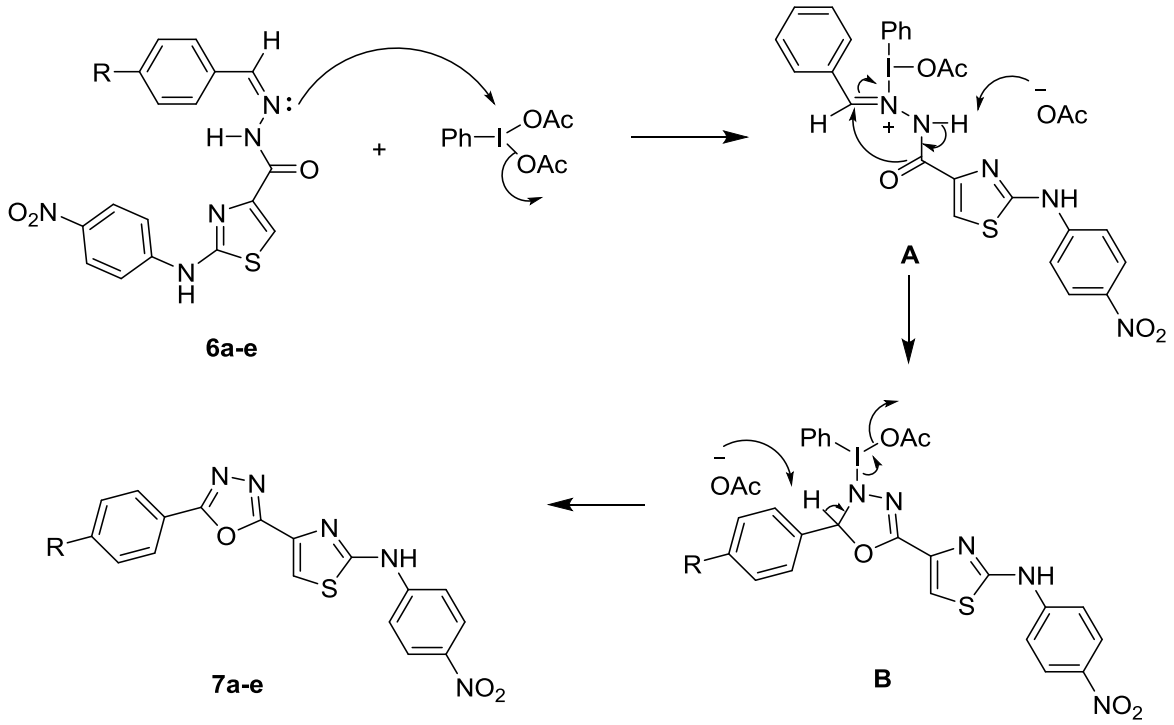
Scheme II — Synthesis of 2-aryl-5-(2'-(4-nitrophenylamino)thiazol-4'-yl)-1,3,4-oxadiazoles **7a-e**

characterized by spectral data such as IR, NMR (^{1}H and ^{13}C), mass and elemental analyses.

The IR spectra of 2-(4-nitrophenylamino)-*N'*-arylidenethiazole-4-carbohydrazides **6a-e** displayed absorption bands in the range 3374-3397 cm^{-1} and 3270-3285 cm^{-1} which were attributed to the –NH stretch and –NH stretch of secondary amide, respectively. The absorption band for –C=O stretch was observed in the range 1662-1685 cm^{-1}. The ^{1}H NMR spectra of **6a-e** displayed two characteristic singlets of one proton intensity each at δ 7.86-7.99 attributed to the thiazole-5-H and at δ 8.59-8.65 attributed to imine group (N=CH) proton, besides the signals for phenyl groups in the aromatic region. Two more singlets of one proton intensity have also been observed at δ 11.11-11.20 and at δ 11.37-11.49, corresponding to secondary amino (-NH) and secondary amide (–CONH) groups, respectively. The ^{13}C NMR spectra of carbohydrazides **6a-e** displayed characteristic signal for C_5 carbon of thiazole ring in the range at δ 116.47-116.82. Two signals ranging from δ 156.91-160.54 and δ 140. 52-140.55 have been assigned to carbonyl group of amide and carbon of imino group, respectively.

The IR spectra of 2-aryl-5-(2'-(4-nitrophenylamino)thiazol-4'-yl)-1,3,4-oxadiazoles **7a-e** displayed one absorption band ranging from 3378-3394 cm^{-1} for –NH stretch. Disappearance of absorption bands for –NH and –C=O stretch of secondary amide indicated the cyclization of carbohydrazides **6a-e** to oxadiazoles **7a-e**. In the ^{1}H NMR spectra of **7a-e**, one proton corresponding to thiazole-5-H resonated at δ 7.96-8.12 *i.e.* somewhat deshielded compared to that observed at δ 7.86-7.99 in **6a-e**. Disappearance of two singlets at δ 8.59-8.65 and at δ 11.37-11.49 of **6a-e** confirmed the oxidative cyclization of carbohydrazides **6a-e** to oxadiazoles **7a-e**. Also, **7a-e** displayed a singlet of one proton intensity at δ 11.18-11.22 due to –NH group besides the signals for phenyl groups in the aromatic region. In the ^{13}C NMR spectrum of **7a**, characteristic signals for C_2 and C_5 carbons of oxadiazole ring appeared at δ 163.54 and δ 163.07, respectively. The signal at δ 116.39 has been assigned to C_5 carbon of thiazole ring.

The plausible mechanism of this transformation is outlined in Scheme III. First step involves the electrophilic attack of IBD on hydrazone **6a-e** followed



Scheme III — A plausible mechanism for formation of 2-aryl-5-(2'-(4-nitrophenylamino)thiazol-4'-yl)-1,3,4-oxadiazoles **7a-e** from reaction of **6a-e** with DIB

by exchange of an acetoxy ligand of IBD to form another hypervalent iodine intermediate **A**. The cyclization of intermediate **A** occurred by intramolecular attack of carbonyl oxygen to form the intermediate **B**, which undergoes acetate catalyzed intramolecular reductive elimination of iodobenzene and loss of one molecule of acetic acid to give the product **7a-e**.

Material and Methods

p-Nitroaniline and ethyl pyruvate were purchased from Spectrochem Pvt. Ltd. *p*-Nitrophenylthiourea was prepared by heating *p*-nitroaniline with ammonium thiocyanate in acidic medium following the reported procedure[30]. Melting points were determined in open capillaries in electrical apparatus and are uncorrected. Infrared spectra were recorded on IR M-500 spectrophotometer (Buck Scientific Inc, Norwalk, CT) in KBr pellets (ν_{max} in cm^{-1}). ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO on a Bruker instrument at 300 MHz and 75 MHz, respectively. Chemical shifts were recorded as δ values and expressed in parts per million (ppm) downfield from TMS as an internal reference. Coupling constants (*J*) are given in Hertz (Hz). Mass spectra were measured in ESI^+ mode on a Kratos MS-50 spectrometer at MS Facilities at SAIF, Panjab University, Chandigarh, India. The compounds gave satisfactory analytical results (within ± 0.5 of the theoretical values). The reactions were monitored by TLC carried out on precoated silica gel plates.

Experimental Section

Preparation of ethyl-2-(4-nitrophenylamino)thiazole-4-carboxylate, 3

To an ethanolic solution (30 mL) of α-bromoethyl pyruvate **1** (2.14 g, 11 mmol), *p*-nitrophenylthiourea **2** (1.97 g, 10 mmol) was added and the mixture was allowed to reflux for 5-6 h. The solvent was distilled off and the reaction mixture was poured in water followed by neutralization with saturated sodium bicarbonate solution. The solid so obtained was filtered, washed with water and recrystallized with ethanol to afford the desired product **3**. m.p. 194-195ºC. Yield 76%. IR (KBr): 3270 (N-H), 1730 cm^{-1} (C=O ester); ^1H NMR (300 MHz, DMSO-d_6): δ 1.31 (t, 3H, *J* = 7.2 Hz, $-CH_3$), 4.29 (q, 2H, *J* = 7.2 Hz, $-CH_2$), 7.83-7.88 (m, 2H, Ph), 7.97 (s, 1H, thiazole-5-H), 8.23-8.28 (m, 2H, Ph), 11.16 (s, 1H, NH).

Preparation of 2-(4-nitrophenylamino)thiazole-4-carbohydrazide, 4

To a solution of ethyl-2-(4-nitrophenylamino) thiazole-4-carboxylate **3** (2.93 g, 10 mmol) in DMSO

(25 mL), hydrazine hydrate (0.6 mL, 11 mmol) was added. The mixture was allowed to reflux for 2 h. The solvent was distilled off and reaction mixture was poured in water. The solid thus obtained was filtered, washed with water and dried in air to afford compound **4**. m.p. 178-180ºC. Yield 72%. IR (KBr): 3386, 3374, 3285, 1656 cm^{-1} (C=O); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.74 (s, 1H, thiazole-5-H), 7.96-8.03 (m, 2H, Ph), 8.16-8.23 (m, 2H, Ph), 9.63 (s, 1H, NH), 11.12 (s, 1H, NH).

General procedure for the synthesis of 2-(4-nitrophenylamino)-*N′*-(substituted benzylidene) thiazole-4-carbohydrazides, **6a-e**

A solution of 2-(4-nitrophenylamino)thiazole-4-carbohydrazide **4** (2.79 g, 10 mmol) and appropriately substituted benzaldehyde **5a-e** (11 mmol) in 20 mL MeOH-THF (1:1) was refluxed in the presence of two drops of acetic acid for 2-3 h. The solvent was evaporated in vacuum to half of its volume and cooled to RT. The solid thus obtained was filtered, washed with ethanol and dried in air to afford **6a-e**.

2-(4-Nitrophenylamino)-*N′*-(benzylidene)thiazole-4-carbohydrazide, 6a: m.p. >280ºC. Yield 84%. IR (KBr): 3386 (N-H), 3274 (N-H amide), 1685 cm^{-1} (C=O); ^{1}H NMR (300 MHz, DMSO-d_6): 7.44-7.48 (m, 3H, Ph-3', 4', 5'-H), 7.78 (d, 2H, *J* = 8.1 Hz, Ph-2", 6"-H), 7.86 (s, 1H, thiazole-5-H), 7.99-8.03 (m, 2H, Ph-2′, 6′-H), 8.23 (d, 2H, *J* = 8.1 Hz, Ph-3", 5"-H), 8.65 (s, 1H, CH), 11.11 (s, 1H, NH, exchangeable with D_2O), 11.37 (s, 1H, NH, exchangeable with D_2O); ^{13}C NMR (75 MHz, DMSO-d_6): δ 116.73 (C-5), 125.21 (2C, Ph-2′, 6′), 127.11 (2C, Ph-2″, 6″), 128.61 (2C, Ph-3′, 5′), 129.03 (Ph-4′), 129.95 (Ph-1′), 134.20 (Ph-1″), 140.55 (CH=N), 144.82 (2C, Ph-3″, 5″), 146.28 (Ph-4″), 148.92 (C-4), 156.91 (C=O), 162.05 (C-2); MS: (*m/z*) 368.04 ($[M+H]^+$). Anal. Calcd for $C_{17}H_{13}N_5O_3S$: C, 55.58; H, 3.57; N, 19.06. Found: C, 55.24; H, 3.59; N, 19.12%.

2-(4-Nitrophenylamino)-*N′*-(*p*-methylbenzylidene) thiazole-4-carbohydrazide, 6b: m.p. >280ºC. Yield 84%. IR (KBr): 3374 (N-H), 3270 (N-H amide), 1674 cm^{-1} (C=O); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.36 (s, 3H, 4'-CH_3), 7.30 (d, 2H, *J* = 7.8 Hz, Ph-3′, 5′-H), 7.66 (d, 2H, *J* = 8.1 Hz, Ph-2", 6"-H), 7.90 (s, 1H, thiazole-5-H), 8.00 (d, 2H, *J* = 7.8 Hz, Ph-2′, 6′-H), 8.25 (d, 2H, *J* = 8.1 Hz, Ph-3", 5"-H), 8.59 (s, 1H, CH), 11.19 (s, 1H, NH, exchangeable with D_2O), 11.38 (s, 1H, NH, exchangeable with D_2O); ^{13}C NMR (75 MHz, DMSO-d_6): δ 25.62 (CH_3), 116.47 (C-5), 124.68 (2C, Ph-2′, 6′), 127.74 (2C, Ph-3′, 5′), 128.95 (2C, Ph-2″, 6″), 130.34 (Ph-1′), 134.61 (Ph-1″), 137.62 (Ph-4′), 140.55 (CH=N), 143.57 (2C, Ph-3″, 5″), 146.82 (Ph-4″), 148.65 (C-4), 158.92 (C=O), 162.42 (C-2); MS: (*m/z*) 382.10 ($[M+H]^+$). Anal. Calcd for $C_{18}H_{15}N_5O_3S$: C, 56.68; H, 3.96; N, 18.36. Found: C, 56.72; H, 4.09; N, 18.61%.

2-(4-Nitrophenylamino)-*N′*-(*p*-chlorobenzylidene) thiazole-4-carbohydrazide, 6c: m.p. 253-255ºC. Yield 88%. IR (KBr): 3397 (N-H), 3278 (N-H amide), 1682 cm^{-1} (C=O); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.55 (d, 2H, *J* = 8.4 Hz, Ph-3′, 5′-H), 7.79 (d, 2H, *J* = 8.1 Hz, Ph-2", 6"-H), 7.92 (s, 1H, thiazole-5-H), 8.03 (d, 2H, *J* = 8.4 Hz, Ph-2′, 6′-H), 8.25 (d, 2H, *J* = 8.1 Hz, Ph-3", 5"-H), 8.63 (s, 1H, CH), 11.20 (s, 1H, NH, exchangeable with D_2O), 11.49 (s, 1H, NH, exchangeable with D_2O); ^{13}C NMR (75 MHz, DMSO-d_6): δ 116.82 (C-5), 121.47 (2C, Ph-2′, 6′), 126.52 (2C, Ph-3′, 5′), 128.49 (Ph-4′), 128.88 (2C, Ph-2″, 6″), 130.62 (Ph-1′), 134.92 (Ph-1″), 140.54 (CH=N), 142.82 (2C, Ph-3″, 5″), 146.28 (Ph-4″), 147.54 (C-4), 160.54 (C=O), 161.92 (C-2); MS: (*m/z*) 402.05 ($[M+H]^+$)/404.04 ($[M+H+2]^+$), (3:1). Anal. Calcd for $C_{17}H_{12}ClN_5O_3S$: C, 50.81; H, 3.01; N, 17.43. Found: C, 50.97; H, 3.30; N, 17.33%.

2-(4-Nitrophenylamino)-*N′*-(*p*-bromobenzylidene) thiazole-4-carbohydrazide, 6d: m.p. 220-222ºC. Yield 85%. IR (KBr): 3386 (N-H), 3285 (N-H amide), 1662 cm^{-1} (C=O); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.69 (d, 2H, *J* = 8.1 Hz, Ph-3′, 5′-H), 7.87 (d, 2H, *J* = 8.1 Hz, Ph-2", 6"-H), 7.99 (s, 1H, thiazole-5-H), 8.01 (d, 2H, *J* = 8.1 Hz, Ph-2′, 6′-H), 8.24 (d, 2H, *J* = 8.1 Hz, Ph-3", 5"-H), 8.62 (s, 1H, CH), 11.13 (s, 1H, NH, exchangeable with D_2O), 11.44 (s, 1H, NH, exchangeable with D_2O); ^{13}C NMR (75 MHz, DMSO-d_6): δ 116.75 (C-5), 120.28 (2C, Ph-2′, 6′), 123.40 (Ph-4′), 125.28 (2C, Ph-3′, 5′), 128.91 (2C, Ph-2″, 6″), 130.06 (Ph-1′), 133.48 (Ph-1″), 140.52 (CH=N), 142.47 (2C, Ph-3″, 5″), 146.42 (Ph-4″), 147.65 (C-4), 160.45 (C=O), 161.75 (C-2); MS: (*m/z*) 445.99 ($[M+H]^+$)/447.98 ($[M+H+2]^+$), (1:1). Anal. Calcd for $C_{17}H_{12}BrN_5O_3S$: C, 45.75; H, 2.71; N, 15.69. Found: C, 45.49; H, 2.51; N, 15.86%.

2-(4-Nitrophenylamino)-*N′*-(p-fluorobenzylidene) thiazole-4-carbohydrazide, 6e: m.p. >280ºC. Yield 85%. IR (KBr): 3394 (N-H), 3280 (N-H amide), 1668 cm^{-1} (C=O); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.30-7.35 (m, 2H, Ph-3′, 5′-H), 7.82 (d, 2H, *J* = 8.1 Hz, Ph-2", 6"-H), 7.91 (s, 1H, thiazole-5-H), 7.99-8.02 (m, 2H, Ph-2′, 6′-H), 8.25 (d, 2H, *J* = 8.1 Hz, Ph-3", 5"-H), 8.63 (s, 1H, CH), 11.20 (s, 1H, NH, exchangeable with D_2O), 11.46 (s, 1H, NH, exchangeable with D_2O); ^{13}C NMR

(75 MHz, DMSO-d_6): δ 116.82 (C-5), 120.44 (2C, Ph-3′, 5′), 128.68 (2C, Ph-2′, 6′), 128.94 (2C, Ph-2″, 6″), 131.74 (Ph-1′), 134.47 (Ph-1″), 140.55 (CH=N), 143.55 (2C, Ph-3″, 5″), 146.28 (Ph-4″), 148.82 (C-4), 159.54 (C=O), 161.35 (C-2), 163.54 (Ph-4′); MS: (*m/z*) 386.05 ($[M+H]^+$). Anal. Calcd for $C_{17}H_{12}FN_5O_3S$: C, 52.98; H, 3.14; N, 18.17. Found: C, 52.75; H, 3.27; N, 18.43%.

General procedure for the synthesis of 2-aryl-5-(2'-(4-nitrophenylamino)thiazol-4'-yl)-1,3,4-oxadiazoles, 7a-e

To a solution of 2-(4-nitrophenylamino)-*N*′-(substituted benzylidene)thiazole-4-carbohydrazide **6a-e** (10 mmol) in dimethylformamide (20 mL) was added (diacetoxyiodo)benzene (11 mmol) and the solution was stirred for 2 h. The excess solvent was evaporated in vacuum and the reaction mixture was poured in water. The solid so obtained was filtered and washed with petroleum ether to afford the pure compound **7a-e**.

2-Phenyl-5-(2'-(4-nitrophenylamino)thiazol-4'-yl)-1,3,4-oxadiazole, 7a: m.p. 250-252ºC. Yield 78%. IR (KBr): 3385 cm^{-1} (N-H); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.61-7.65 (m, 3H, Ph-3", 4", 5"-H), 7.95 (d, 2H, *J* = 8.1 Hz, Ph-2"', 6"'-H), 8.12 (s, 1H, thiazole-5'-H), 8.13-8.15 (m, 2H, Ph-2", 6"-H), 8.25 (d, 2H, *J* = 8.1 Hz, Ph-3"', 5"'-H), 11.21 (s, 1H, NH, exchangeable with D_2O); ^{13}C NMR (75 MHz, DMSO-d_6): δ 116.39 (C-5′), 124.65 (2C, Ph-2‴, 6‴), 125.12 (2C, Ph-2″, 6″), 126.55 (2C, Ph-3″, 5″), 126.95 (Ph-4″), 129.07 (Ph-1″), 131.57 (Ph-1‴), 140.55 (CH=N), 140.57 (C-4′), 141.86 (2C, Ph-3‴, 5‴), 146.25 (Ph-4‴), 156.91 (C=O), 159.92 (C-2′), 163.07 (C-5), 163.54 (C-2); MS: (*m/z*) 366.06 ($[M+H]^+$). Anal. Calcd for $C_{17}H_{11}N_5O_3S$: C, 55.89; H, 3.03; N, 19.17. Found: C, 56.02; H, 3.15; N, 19.49%.

2-(4-Methylphenyl)-5-(2'-(4-nitrophenylamino) thiazol-4'-yl)-1,3,4-oxadiazole, 7b: m.p. 208-210ºC. Yield 85%. IR (KBr): 3378 cm^{-1} (N-H); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.44 (s, 3H, CH_3), 7.38 (d, 2H, *J* = 7.8 Hz, Ph-3", 5"-H), 7.93 (d, 2H, *J* = 8.1 Hz, Ph-2"', 6"'-H), 7.96 (s, 1H, thiazole-5'-H), 8.02 (d, 2H, *J* =7.8 Hz, Ph-2", 6"-H), 8.24 (d, 2H, *J* = 8.1 Hz, Ph-3"', 5"'-H), 11.19 (s, 1H, NH, exchangeable with D_2O); ^{13}C NMR (75 MHz, DMSO-d_6): δ 21.19 (CH_3), 116.86 (C-5′), 124.59 (2C, Ph-2‴, 6‴), 126.45 (2C, Ph-3″, 5″), 127.09 (Ph-4″), 129.58 (Ph-1″), 129.73 (2C, Ph-2″, 6″), 135.45 (Ph-1‴), 140.55 (CH=N), 140.67 (C-4′), 141.94 (2C, Ph-3‴, 5‴), 146.20 (Ph-4‴), 158.92 (C=O), 159.72 (C-2′), 163.04 (C-5), 163.58 (C-2); MS: (*m/z*) 380.05 ($[M+H]^+$). Anal. Calcd for $C_{18}H_{13}N_5O_3S$: C, 56.99; H, 3.45; N, 18.46. Found: C, 56.67; H, 3.17; N, 18.68%.

2-(4-Chlorophenyl)-5-(2'-(4-nitrophenylamino) thiazol-4'-yl)-1,3,4-oxadiazole, 7c: m.p. 220-222ºC. Yield 82%. IR (KBr): 3394 cm^{-1} (N-H); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.62 (d, 2 H, *J* = 8.4 Hz, Ph-3", 5"-H), 7.95 (d, 2H, *J* = 8.1 Hz, Ph-2"', 6"'-H), 8.08 (s, 1H, thiazole-5'-H), 8.01 (d, 2H, *J* = 8.4 Hz, Ph-2", 6"-H), 8.22 (d, 2H, *J* = 8.1 Hz, Ph-3"', 5"'-H), 11.18 (s, 1H, NH, exchangeable with D_2O); ^{13}C NMR (75 MHz, DMSO-d_6): δ 116.36 (C-5′), 121.89 (2C, Ph-3″, 5″), 125.03 (2C, Ph-2‴, 6‴), 128.11 (2C, Ph-2″, 6″), 129.26 (Ph-4″), 135.21 (Ph-1‴), 137.08 (Ph-1″), 140.54 (CH=N), 140.94 (C-4′), 141.92 (2C, Ph-3‴, 5‴), 146.19 (Ph-4‴), 160.04 (C-2′), 160.54 (C=O), 162.03 (C-5), 162.80 (C-2); MS: (*m/z*) 400.02 ($[M+H]^+$)/402.01 ($[M+H+2]^+$), (3:1). Anal. Calcd For $C_{17}H_{10}ClN_5O_3S$: C, 51.07; H, 2.52; N, 17.52. Found: C, 51.33; H, 2.41; N, 17.81%.

2-(4-Bromophenyl)-5-(2'-(4-nitrophenylamino) thiazol-4'-yl)-1,3,4-oxadiazole, 7d: m.p. 243-245ºC. Yield 80%. IR (KBr): 3382 cm^{-1} (N-H); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.79 (d, 2H, *J* = 8.1 Hz, Ph-3", 5"-H), 7.93 (d, 2H, *J* = 8.1 Hz, Ph-2"', 6"'-H), 7.99 (s, 1H, thiazole-5'-H), 8.05 (d, 2H, *J* = 8.1 Hz, Ph-2", 6"-H), 8.24 (d, 2H, *J* = 8.1 Hz, Ph-3"', 5"'-H), 11.21 (s, 1H, NH, exchangeable with D_2O); ^{13}C NMR (75 MHz, DMSO-d_6): δ 116.39 (C-5′), 122.33 (2C, Ph-3″, 5″), 125.08 (2C, Ph-2‴, 6‴), 125.72 (2C, Ph-2″, 6″), 128.32 (Ph-4″), 132.26 (Ph-1″), 132.70 (2C, Ph-3‴, 5‴), 135.17 (Ph-1‴), 140.52 (CH=N), 140.70 (C-4′), 146.22 (Ph-4‴), 160.10 (C-2′), 160.45 (C=O), 162.81 (C-5), 163.12 (C-2); MS: (*m/z*) 443.98 ($[M+H]^+$)/445.96 ($[M+H+2]^+$), (1:1). Anal. Calcd For $C_{17}H_{10}BrN_5O_3S$: C, 45.96; H, 2.27; N, 15.76. Found: C, 45.94; H, 2.25; N, 15.78%.

2-(4-Fluorophenyl)-5-(2'-(4-nitrophenylamino) thiazol-4'-yl)-1,3,4-oxadiazole, 7e: m.p. 228-230ºC. Yield 82%. IR (KBr): 3392 cm^{-1} (N-H); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.65-7.71 (m, 2H, Ph-3", 5"-H), 7.93 (d, 2H, *J* = 8.1 Hz, Ph-2"', 6"'-H), 7.99 (s, 1H, thiazole-5'-H), 8.03-8.07 (m, 2H, Ph-2", 6"-H), 8.24 (d, 2H, *J* = 8.1 Hz, Ph-3"', 5"'-H), 11.22 (s, 1H, NH, exchangeable with D_2O); ^{13}C NMR (75 MHz, DMSO-d_6): δ 116.36 (C-5′), 120.87 (2C, Ph-3″, 5″), 125.07 (2C, Ph-2‴, 6‴), 128.34 (2C, Ph-2″, 6″), 131.46 (Ph-1″), 134.42 (Ph-1‴), 140.55 (CH=N), 140.72 (C-4′), 141.94 (2C, Ph-3‴, 5‴), 146.25 (Ph-4‴), 159.54 (C=O), 160.04 (C-2′), 163.08 (C-5), 163.37 (Ph-4″), 163.55 (C-2); MS: (*m/z*) 384.05 ($[M+H]^+$). Anal. Calcd for $C_{17}H_{10}FN_5O_3S$: C, 53.26; H, 2.63; N, 18.27. Found: C, 53.39; H, 2.69; N, 18.52%.

Conclusion

In abridgement, an efficient and ecofriendly route has been developed for the synthesis of some new 2-aryl-5-(2'-(4-nitrophenylamino)thiazol-4'-yl)-1,3,4-oxadiazoles *via* oxidative cyclization of 2-(4-nitrophenylamino)-*N'*-arylidenethiazole-4-carbohydrazides using DIB at ambient temperature. This approach worked well with a wide variety of carbohydrazides and offered operational simplicity, easy work-up and efficient yields of unsymmetrical 1,3,4-oxadiazoles thereby extending the versatility of DIB in organic synthesis.

Acknowledgements

The authors are grateful to the Council of Scientific and Industrial Research, New Delhi, India, for providing financial assistance and Senior Research Fellowship to Chinu Rani. Thanks are also due to Sophisticated Analytical Instrumentation Facility, Panjab University, Chandigarh, India for providing elemental analyses and mass spectra.

References

1 Zarudnitskii E V, Pervak I I, Merkulov A S, Yurchenko A A & Tolmachev A A, *Tetrahedron*, 64 (2008) 10431.
2 Linganna N & Rai K M L, *Synth Commun*, 28 (1998) 4611.
3 Kostyuchenko A S, Yurpalov V L, Kurowska A, Domagala W, Pron A & Fisyuk A S, *Beilstein J Org Chem*, 10 (2014) 1596.
4 Kostyuchenko A S, Zheleznova T Y, Stasyuk A J, Kurowska A, Domagala W, Pron A & Fisyuk A S, *Beilstein J Org Chem*, 13 (2017) 313.
5 Higashihara T, Wu H C, Mizobe T, Lu C, Ueda M & Chen W C, *Macromolecules*, 45 (2012) 9046.
6 Zhiqiang J H, Wang X F & Wang L B Y, *Dyes Pigm*, 154 (2018) 234.
7 Salahuddin, Mazumder A, Shahar Y M, Mazumder R, Chakraborthy G S, Ahsan M J & Rahman M U, *Synth Commun*, 47 (2017) 1805.
8 Pitasse-Santos P, Sueth-Santiago V & Lima M E F, *J Braz Chem Soc*, 29 (2018) 435.
9 Bajaj S, Asati V, Singh J & Roy P P, *Eur J Med Chem*, 97 (2015) 124.
10 Aggarwal R, Kumar S, Kaushik P, Kaushik D & Gupta G K, *Eur J Med Chem*, 62 (2013) 508.
11 Chhabria M T, Patel S, Modi P & Brahmkshatriya P S, *Curr Top Med Chem*, 16 (2016) 2841.
12 Desai N, Trivedi A, Pandit U, Dodiya A, Rao V K & Desai P, *Mini Rev Med Chem*, 16 (2016) 1500.
13 Fan Y L, Ke X & Liu M, *J Heterocycl Chem*, 55 (2018) 791.
14 Dhumal S T, Deshmukh A R, Bhosle M R, Khedkar V M, Nawale L U, Sarkar D & Mane R A, *Bioorg Med Chem Lett*, 26 (2016) 3646.
15 Santosh R, Prabhu A, Selvam M K, Krishna P M, Nagaraja G K & Rekha P D, *Heliyon*, 5 (2019) e01255.
16 Stoica C I, Marc G, Pîrnău A, Vlase L, Araniciu C, Oniga S, Palage M & Oniga O, *Farmacia*, 64 (2016) 390.
17 Desai N C, Bhatt N, Somani H & Trivedi A, *Eur J Med Chem*, 67 (2013) 54.
18 Oliveira C S D, Lira B F, Barbosa-Filho J M, Fernandez Lorenzo J G & Athayde-Filho P F D, *Molecules*, 17 (2012) 10192.
19 Patel K D, Prajapati S M, Panchal S N & Patel H D, *Synth Commun*, 44 (2014) 1859.
20 Tokumaru K & Johnston J N, *Chem Sci*, 8 (2017) 3187.
21 Paraschivescu C, Matache M, Dobrotă C, Nicolescu A, Maxim C, Deleanu C, Fărcășanu I C & Hădade N D, *J Org Chem*, 78 (2013) 2670.
22 Guin S, Rout S K, Ghosh T, Khatun N & Patel B K, *RSC Adv*, 2 (2012) 3180.
23 Aggarwal R, Sumran G, Saini A & Singh S P, *Tetrahedron Lett*, 47 (2006) 4969.
24 Aggarwal R, Rani C & Sumran G, *Synth Commun*, 44 (2014) 923.
25 Sumran G & Aggarwal R, *J Sulfur Chem*, 36 (2015) 170.
26 Sumran G, Aggarwal R, Hooda M, Sanz D & Claramunt R M, *Synth Commun*, 48 (2018) 439.
27 Mamta, Aggarwal R, Sadana R, Ilag J & Sumran G, *Bioorg Chem*, 86 (2019) 288.
28 Sumran G, Aggarwal R, Mittal A, Aggarwal A & Gupta A, *Bioorg Chem*, 88 (2019) 102932.
29 Ward C F, *J Chem Soc Trans*, 123 (1923) 2207.
30 Mathur N, Jain N & Sharma A. K, *Open Chem J*, 5 (2018) 182.