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Synthesis of Some Novel Fused Substituted 3-(4-substitutedphenyl)-6,6-diphenyl-3,3a dihydroimidazo[2',1':2,3][1,3] thiazolo[4,5-*c*][1,2] isoxazoles

R. R. Dangi[a], Maya Kumari[a], Priyanka Khyaliya[a], Eduardo A Parellada[b], Adriana Neske[b] and K. L. Ameta[a]*

[a]*Department of Chemistry, College of Arts, Science and Humanities, Mody University of Science and Technology, Lakshmangarh-332311, Rajasthan, India.*
[b]*Instituto de Química Orgánica, Facultad de Bioquímica, Química y Farmacia, Universidad Nacional de Tucumán, Ayacucho 471, Tucumán-4000, Argentina.*

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Abstract: The present study describes the synthesis of some novel arylidene cyclic chalcones 2-(4-substituted benzylidene)-6,6-diphenylimidazo[2,1-*b*][1,3]thiazole-3,5-diones and their transformation to 3-(4-substitutedphenyl)-6,6-diphenyl-3,3a-dihydroimidazo[2',1':2,3][1,3]thiazolo[4,5-*c*][1,2]oxazol-7(6*H*)-ones via cyclization using hydroxylamine hydrochloride. The starting chalcones have been synthesized by the condensation of various aromatic aldehydes and methylene entity of synthesized imidazothiazole-3,5-diones which were obtained by the cyclization of 5,5-diphenyl-2-thioxoimidazolidin-4-ones and chloroacetic acid. The intermediate 5,5-diphenyl-2-thioxoimidazolidin-4-ones have been synthesized by the condensation of α-diketone (benzil) with thiourea in presence of ethanolic alkali followed by Pinacol-Pinacolone rearrangement. Structures of all the newly synthesized compounds were confirmed by chemical, analytical and spectral data.

Keywords: Chalcone, Diketone, Imidazole, Thiazole, Isoxazole.

Introduction

Nitrogen and sulphur containing heterocyles are an important class of organic compounds in medicinal chemistry, found in privileged structures (pharmacophores), thus the development of rapid synthetic routes toward focused libraries of such compounds is therefore of great importance to both medicinal and synthetic chemists. Structural frameworks have been described as privileged structures and in particular, N-containing polycyclic structures have been reported to be associated with a wide range of biological activity. Thus, fused heterocyclic derivatives with thiazole moiety are prospective objects in modern drug discovery.

Various biologically active synthetic compounds have five-membered nitrogen-containing heterocyclic ring in their core structures. In the field of five membered heterocyclic structures, imidazole nucleus shows versatile biological properties. The high therapeutic properties of the imidazole related drugs have encouraged the medicinal chemists to synthesize a large number of novel chemotherapeutic agents. Imidazole drugs have broadened scope in remedying various dispositions in clinical medicines. A lot of work on the synthesis and biological activities of the condensed imidazo [2, 1-*b*]-thiazoles has been reported. The imidazo [2, 1-*b*] [1, 3] thiazole skeleton has been used as antimicrobial agents [1] , anti-hypertensives, anti-inflammatories, immunosuppressive agents, herbicides, antitumor agents and cardiotonic agents [2-4]. The imidazo[2,1-b]thiazole derivative, was reported as a potential antitumor agent in patients with small tumor burdens [5]. In addition, numerous imidazo[2,1-b] thiazole derivatives were reported to possess antitumor activities[6-10]. Furthermore, it was found that the

*Corresponding author. Tel: +91 9414682501, Fax: +91 (1573) 225044, E-mail: klameta77@hotmail.com

incorporation of pyrazole ring into different aryl or heteroaryl ring systems was reported to exhibit significant anticancer activities [11-16]. Considering the potent bioactivities of compounds possessing an imidazothiazole core, synthesizing new imidazo [2, 1-*b*] [1, 3] thiazole derivatives efficiently attracted our attention [17-18]. In the present study we wish to report the synthesis of some novel fused imidazo [2, 1-b] [1, 3] thiazole derivatives. On the other hand thiazoles are basic class of heterocyclic moieties which possess a wide range of therapeutic interest and their importance is also very much-established in medicine [19] such as antibacterial and antifungal activities [20-21], anti-tubercular activity [22-23], anti HIV agents [24]. Among the important heterocyclic compounds 1,3,4-thiadiazoles are one of the important structural fragments in medicinal chemistry due to their various biological activities, such as Ca^{+2} channel blockers [25], anti-inflammatory agents [26], anti-tubercular activity,[27] anti-infective agents,[28] antibacterial,[29] antidepressants,[30] anti-cancer agents.[31]

Since the discovery of heterocyclic nucleus, the chemistry of isoxazole and their fused derivatives continue to draw attention of organic chemists due to their various biological activities such as antithrombotic agents [32], antitumor activity [33], antinociceptive activity activity [34], anti-inflammatory activity [35], anti-oxidants [36], antibacterial [37], antifungal [38], nematicidal agents [39], antifungal [40], anti-inflammatory and hypoglycaemic agents [41]. We planned to undertake the synthesis and characterization of some fused imidazole containing thiazolo-isoxazole derivatives carrying the above biodynamic heterocyclic systems with the hope to achieve some novel systems. All the newly synthesized compounds were characterized by IR, ^{1}H-NMR, ^{13}C-NMR spectroscopy and mass spectrometry.

Results and discussion

Simple base catalyzed condensation of α-diketone (benzil), with thiourea in absolute ethanol furnished 5,5-diphenyl-2-thioxoimidazolidin-4-one (1) followed by pinacol-pinacolone type rearrangement. Formation of this product was confirmed by IR spectrum at 3294 cm^{-1} indicates the presence of NH group of amide moiety. The other band at 3236 cm^{-1} also indicates the presence of NH in $(Ph)_2$C-NH CO. ^{1}H-NMR spectrum shows two singlet's at δ 9.9 and δ 9.1, which would be assigned for NH proton of amide. It was condensed with chloroacetic acid and glacial acetic acid in presence of anhydrous sodium acetate to yield the 6,6-diphenylimidazo[2,1-*b*][1,3]thiazole-3,5(2*H*,6*H*)-dione (2) . Its structure was confirmed by the appearance of singlet at δ 3.6 for CH_2 of thizole ring and disappearance of NH signal in ^{1}H NMR spectra. The condensation of (2) with various 4-substituted araldehydes (3) in presence of anhydrous sodium acetate and glacial acetic acid afforded corresponding 2-(4-subsituted phenyle)-6,6-diphenylimidazo[2,1-*b*][1,3]thiazole-3,5(2*H*,6*H*)-diones (4a-d). Reaction of hydroxylamine hydrochloride on these Compounds (4a-d) underwent cyclocondensation reaction afforded 3-(4-substitutedphenyl)-6,6-diphenyl-3,3a-dihydro imidazo[2',1':2,3][1,3]thiazolo[4,5-*c*][1,2] oxazol-7(6*H*)-ones **(5a-d).** The structures of these compounds were inferred by IR absorption band at 1180 (C-O) cm^{-1} and ^{1}H NMR spectra at δ 5.2 corresponding to the –CH-Ar proton of the isoxazole ring. The ^{13}C NMR spectra of compounds (**5a-d)** were recorded in DMSO-d6. The prominent signals corresponding to the carbons of thiazolo-isoxazole ring in all compounds observed nearly at 48.5, 50.1 and 154.4 ppm, are proof of further evidence of their structures (Scheme **1** and Scheme **2**).

Experimental

General Procedures

All the melting points were determined in open capillary tube and are uncorrected. The IR spectra were recorded on Perkin-Elmer spectrometer. The ^{1}H NMR spectra were scanned on a DRX-300 MHz. spectrometer (300 MHz) in $CDCl_3$/DMSO-d_6 using TMS as internal standard and chemical shifts are expressed in δ ppm. The mass spectra were recorded on Jeol SX-102 (FAB). *m*-Nitrobenzyl alcohol (NBA) was used as a matrix. Purity of synthesized compounds was checked by TLC using silica gel-G. Spots were exposed in an iodine chamber. Compound **6** was synthesized by literature method [30].

Synthesis of 5,5-diphenyl-2-thioxoimidazolidin-4-one (1):

Benzil (0.05 mol), thiourea (0.05 mol) and 15 ml of 30% aq. NaOH was refluxed in 75 ml of ethanol for 2 h. After the completion of the reaction (monitored by TLC), it was allowed to cool and poured in to crushed ice with constant stirring. Solid separated was filtered off and removed as insoluble by product. The filtrate was acidified with dil. HCl resulted solid precipitate, which was filtered, dried and recrystallized from ethanol afforded analytical samples of (**1**).

Yield 94 %, m.p.136 ^{o}C ; IR (KBr) cm^{-1}: 3255 (N-H amide, CO-NH-CS); 3135 (N-H, CPh$_2$-NH-CS); 3010 (C-H Ar-H); 1749 (C=O); 1215 (C=S) ; ^{1}H NMR (DMSO d$_6$) δ: 6.9-7.6 (m, 10H, Ar-H, *J* = 9 Hz), δ 9.9 (s, 1H, NH, CO-NH-CO); δ 9.1 (s, 1H, NH, CO-NH-CPh$_2$); ^{13}C -NMR (DMSO) δ: 180.6, 174.5, 139.7, 129.1, 128.7, 126.7, 73.8; Anal.Calcd. For $C_{15}H_{12}N_2OS$: C, 67.16; N, 10.44; S,11.94 %. Found C, 67.08; N, 10.10; S,11.75%. MS: m/z 268 [M]$^{+}$.

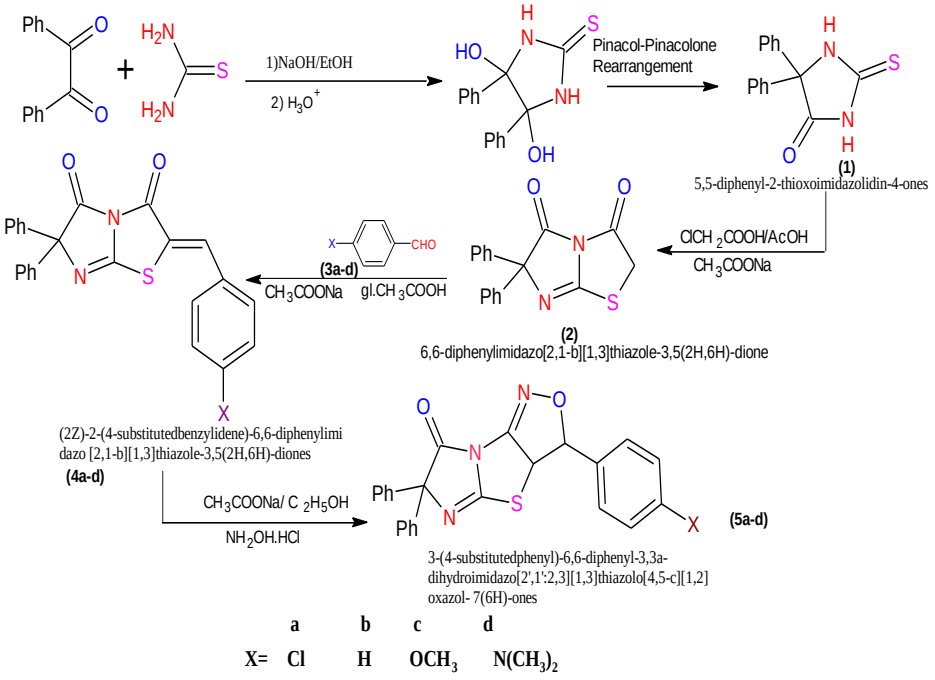
Synthesis of 6,6-diphenylimidazo[2,1-b][1,3]thiazole-3,5(2H,6H)-dione (2):

A mixture of **1** (0.01 mol) and chloroacetic acid (0.01 mol) was dissolved in gl. acetic acid and to this solution (0.02 mol) of anhydrous sodium acetate was added, and reaction mixture was refluxed for 8 h. After the completion of the reaction (monitored by TLC), the reaction mixture was cooled and poured in to ice cold water with stirring. The solid formed was filtered and crystallized from ethanol afforded analytical sample of (**2**).

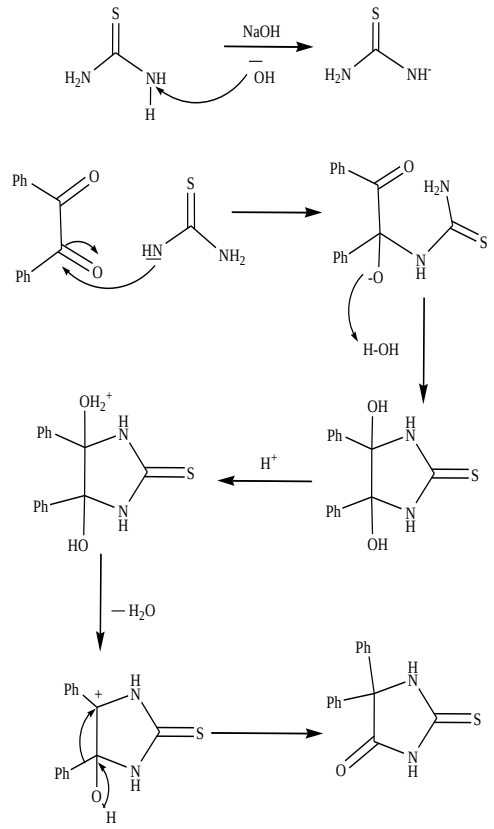
Yield 89%, m.p.162 ^{o}C ; IR (KBr) cm^{1}: 3045 (C-H Ar-H); 2952 (C-H,CH$_2$), 1695 (C=O), 1594 (C=N); ^{1}H NMR (DMSO d$_6$) δ: 7.8-7.2 (m, 10H, Ar-H, *J* = 8.7 Hz),3.6 (s,CH$_2$, thizole); ^{13}C -NMR (DMSO d$_6$) δ: 167.2, 170.0, 162.5, 143.1, 129.2, 128.1, 126.1, 73.0, 32.7 : Anal.Calcd. For $C_{17}H_{12}N_2O_2S$: C, 66.32; N, 9.09; S, 10.38 %. Found C, 66.02; N, 10.08; S, 10.05 %. MS: m/z 308 [M] $^{+}$.

Synthesis of (2Z)-2-(4-substitutedbenzylidene)-6,6-diphenylimidazo[2,1-b][1,3]thiazole-3,5(2H,6H)-diones (4a-d):

An equimolar mixture of 2 (0.01mol) and 4-chlorobenzaldehyde 3a (0.01mol) in glacial acetic acid was taken in a round bottom flask and anhydrous sodium acetate (0.02 mol) was added and refluxed for 8 h. After completion of the reaction, (progress of the reaction was accessed by TLC) reaction mixture was allowed to cool and solid separated was recrystallized from ethanol afforded (**4a-d)** in good yields.



Scheme1: Synthesis of the title compounds



Scheme 2: Mechanism of Thiohydentoin Synthesis

Synthesis of 2-(4-chlorobenzylidene)-6,6-diphenylimidazo[2,1-b][1,3]thiazole-3,5(2H,6H)-dione (4a):

Yield 84%, m.p.189 ^{o}C ; IR (KBr) cm^{-1}: 3025 (C-H, Ar-H), 1691 (C=O), 1590 (C=N), 758 (C-Cl) ; ^{1}H NMR (DMSO d_6) δ: 7.6-7.7 (m, 14H, Ar-H, *J* = 8.4 Hz), 6.1 (s, 1H,=CH-Ar); ^{13}C -NMR (DMSO d_6) δ: 171.0, 166.3, 163.0, 142.0, 140.1, 132.2, 129.2, 128.8,127.1, 126.3, 124.2,122.5,121.3, 120.6, 80.0; Anal.Calcd.For $C_{24}H_{15}ClN_2O_2S$; C,66.97; N,6.51, S ,7.44 %. Found C, 66.54; N, 6.45; S, 7.24 %. MS:m/z 430 [M]$^{+}$. 432 [M +2]$^{+}$.

Synthesis of 2-benzylidene-6,6-diphenylimidazo[2,1-b][1,3]thiazole-3,5(2H,6H)-dione (4b):

Yield 81%, m.p.180 ^{o}C ; IR (KBr) cm^{-1}: 3027 (C-H, Ar-H), 1693 (C=O), 1594 (C=N); ^{1}H NMR (DMSO d_6) δ: 7.5-7.6 (m, 14H, Ar-H, *J* = 8.4 Hz), 6.0 (s, 1H,=CH-Ar). ^{13}C -NMR (DMSO d_6) δ: 170.6, 165.9, 162.8, 142.1, 139.6, 132.1, 129.0, 128.6, 127.1,126.1,123.4,121.9,121.2, 120.2, 78.3. Anal.Calcd.For $C_{24}H_{15}N_2O_2S$; C,72.72; N,7.07; S, 8.08 %. Found C,72.54 ; N, 6.90 ; S, 7.89 %. MS: m/z 396 [M]$^{+}$.

Synthesis of 2-(4-methoxybenzylidene)-6,6-diphenylimidazo[2,1-b][1,3]thiazole-3,5 (2H,6H)-dione (4c):

Yield 83%, m.p.184 ^{o}C ; IR (KBr) cm^{-1}: 3028 (C-H, Ar-H), 1687(C=O), 1589 (C=N), 1098 (C-O); ^{1}H NMR (DMSO d_6) δ :7.6-7.7 (m, 14H, Ar-H, *J* = 8.8 Hz), 6.0 (s,1H,=CH-Ar) 3.6 (3H,s,OCH_3). ^{13}C - NMR (DMSO d_6) δ: 170.4, 166.1, 163.1,141.3, 139.1, 132.2, 128.16, 127.9, 127.3, 125.9,123.2,122.6,121.3, 120.2, 56.7, 78.1, Anal.Calcd.For $C_{25}H_{18}N_2O_3S$; C,70.40; N,6.27; S,7.05 %. Found C, 70.12; N, 6.05;S, 7.16 %.MS: m/z 446 [M]$^{+}$.

Synthesis of 2-[4-(N,N dimethylamino) benzylidene]-6,6-diphenylimidazo[2,1-b][1,3] thiazole-3,5(2H,6H)-dione (4d):

Yield 87%, m.p.182 ^{o}C ; IR (KBr) cm^{-1}: 3043 (C-H, Ar-H), 1681 (C=O), 1584 (C=N); ^{1}H NMR (DMSO d_6) δ: 7.3-7.5 (m, 14H, Ar-H, *J* = 8.5 Hz), 6.1 (s, 1H,=CH-Ar), 3.1 (6H,s,$N(CH_3)_2$; ^{13}C -NMR (DMSO d_6) δ:171.1, 166.1,162.9, 141.4, 139.2, 132.5, 128.3, 127.8, 127.1, 125.6, 119.9, 56.4, 78.3, 43.7;

Anal.Calcd.For $C_{26}H_{21}N_3O_2S$; C,71.07; N,9.56; S,7.28 %. Found C, 69.98; N, 9.35; S, 7.02 %.MS: m/z 439 $[M]^+$.

Synthesis of 3-(4-substitutedphenyl)-6,6-diphenyl-3,3a-dihydroimidazo[2',1':2,3][1,3] thiazolo [4,5-c][1,2]oxazol-7(6H)-ones (5a-d):

Anhydrous sodium acetate (0.02mole) was dissolved in hot acetic acid. Compound (**4a,** 0.01 mole) and hydroxylamine hydrochloride (0.01 mole) were taken in absolute alcohol (20 mL). The solution of sodium acetate in acetic acid was transferred to the reaction mixture and refluxed for 8-10 h. After completion of the reaction (monitored by TLC), the reaction mixture was cooled, diluted with water and kept under refrigeration. The resulting compounds were filtered and recrystallized from ethanol afforded analytical samples of **5a-d** in good yields.

Synthesis of 3-(4-chlorophenyl)-6,6-diphenyl-3,3a-dihydroimidazo[2',1':2,3][1,3] thiazolo[4,5-c][1,2]oxazol-7(6H)-one (5a):

Yield 53 %, m.p.223 ^oC;IR (KBr) cm^{-1}: 3048 (C-H, Ar-H), 1726 (C=O), 1524 (C=N), 1180 (C-O),747 (C-Cl); ^1H NMR (DMSO d_6) δ : 7.1-7.8 (m, 14H, Ar-H, *J* = 8.8 Hz), 5.2 (d,1H,-CH-Ar, *J* = 3.2 Hz) 3.6 (1H,-CH-S, *J* = 3.2 Hz); ^{13}C -NMR (DMSO d_6) δ: 212.4, 164.0, 154.4,144.0, 140.5, 139.2, 132.8, 129.2, 128.4, 128.8, 128.0, 122.9, 80.1,48.5,50.1; Anal.Calcd. For $C_{24}H_{16}ClN_3O_2S$; C, 64.71; N, 9.43; S, 7.17 %. Found C, 63.53; N, 8.80; S, 7.01 %. MS: m/z 445 $[M]^+$. 447 $[M+2]^+$.

Synthesis of 3,6,6-triphenyl-3,3a-dihydroimidazo[2',1':2,3][1,3]thiazolo[4,5-c][1,2]oxazol-7(6H)-one (5b):

Yield 58 %, m.p.205 ^oC; IR (KBr) cm^{-1} 3042 (C-H, Ar-H), 1724 (C=O), 1528 (C=N); ^1H NMR (DMSO d_6) δ : 6.9-7.6 (m, 15, Ar-H, *J* = 8.4 Hz), 4.5 (d,1H,-CH-Ar**,** *J* = 3.1 Hz), 3.4 (d,1H,-CH-S, *J* = 3.1 Hz) ; ^{13}C-NMR (DMSO d_6) δ: 205.0, 161.3, 151.3, 143.8, 140.2, 139.4, 131.4, 128.3, 128.8, 127.0, 127.8, 126.0, 79.9, 47.1, 49.1; Anal.Calcd.For $C_{24}H_{17}N_3O_2S$; C,70.71; N,10.21; S ,7.79%. Found C,69.72; N,12.40; S, 7.57 %. MS:m/z 411 $[M]^+$.

Synthesis of 3-(4-methoxyphenyl)-6,6-diphenyl-3,3a-dihydroimidazo[2',1':2,3][1,3] thiazolo[4,5-c][1,2]oxazol-7(6H)-one (5c):

Yield 52 %, m.p.228 ^oC ; IR (KBr) cm^{-1} 3047 (C-H Ar-H), 1731 (C=O), 1532 (C=N), 1103 (C-O) ; ^1H NMR (DMSO d_6) δ : 6.7-7.1 (m, 14H, Ar-H, *J* = 8.9 Hz), 6.6 (s, 1H,NH),4.5 (d,1H,-CH-Ar, *J* = 3.4 Hz), 3.3 (d,1H,-CH-S, *J* = 3.6 Hz), 3.6 (3H,s,OCH_3);^{13}C-NMR (DMSO d_6) δ: 208.3, 154.2, 164.0, 143.8, 140.4, 139.2, 132.1, 130.3, 128.6, 129.1, 127.7, 126.7, 79.1, 55.9, 47.6, 49.3; Anal.Calcd.For $C_{25}H_{19}N_3O_3S$; C,68.18; N,9.52; S ,7.27 %. Found C, 67.80; N, 12.34; S, 6.87 %. MS:m/z 441 $[M]^+$.

Synthesis of 3-(4-(N,N dimethylamino phenyl)-6,6-diphenyl-3,3a-dihydroimidazo [2',1':2,3] [1,3] thiazolo[4,5-c][1,2]oxazol-7(6H)-one (5d):

Yield 48 %, m.p.219 ^oC ; IR (KBr) cm^{-1} 3039 (C-H, Ar-H), 1724 (C=O), 1562 (C=N) ; ^1H NMR (DMSO d_6) δ : 6.9-7.4 (m, 14H, Ar-H, *J* = 9.0 Hz), 6.5 (s, 1H,NH), 4.3 (d,1H,-CH-Ar, *J* = 3.5 Hz), 3.4 (d,1H,-CH-S, *J* = 3.4 Hz), 3.1 (6H, s, $N(CH_3)_2$; ^{13}C -NMR (DMSO d_6) δ:173.2, 154.5, 164.7, 143.6, 140.2, 139.1, 132.1, 130.4, 128.5, 129.5, 127.7, 126.1, 79.3, 55.6, 47.8; Anal.Calcd.For $C_{26}H_{22}N_4O_2S$; C, 68.72 ; N,12.33 ; S , 7.06 %. Found C, 67.56; N, 12.23 ; S ,6.78 %. MS:m/z 454 $[M]^+$.

Conclusion

In the present paper our aim has been verified by the synthesis of some novel fused 3-(4-substitutedphenyl)-6,6-diphenyl-3,3a-dihydroimidazo [2',1': 2,3] [1,3] thiazolo [4,5-*c*] [1,2] isoxazoles, in which imidazole and thiazolo-isoxazole moieties are present as the part of same molecular framework.

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