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SYNTHESIS OF NOVEL TETRAHYDRONAPHTHALEN-2-YL HETEROCYCLES FOR ANALGESIC, ANTI-INFLAMMATORY AND ANTIPYRETIC EVALUATION

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Abstract: Condensation of 2-acetyltetralin with ethylcyanoacetate and/or malononitrile and some aldehydes in the presence of excess of ammonium acetate afforded the respective hydroxycyanopyridines or aminocyanopyridines **1a-f** and **2a-f**.

Treatment of 2-acetyltetralin with some sulfonylhydrazides yielded the hydrazone derivatives **3a-d**, respectively, which upon treatment with thioglycolic acid gave the corresponding thiazole derivatives **4a-d**, respectively. Compounds **4a-d** underwent cyclocondensation with different arylidene derivatives to give the corresponding pyrane derivatives **5a-d**. Upon the reaction of compounds **4a-d** with some secondary amines and paraformaldehyde the corresponding Mannich bases **6a,c**, **7b,d** and **8a,d** were obtained .

Compounds **1c**, **1d**, **1e**, **2e**, **3a** and **3d** were evaluated as analgesic, anti-iflammatory and antipyretic agents.

Keywords: 2-acetyltetralin, sulfonylhydrazide, Mannich bases, anti-inflammatory effect, analgesic effect, antipyretic effect

Various chemical and pharmaceutical activities were ascribed to 5,6,7,8-tetrahydronaphthalene derivatives especially those incorporated into heterocyclic systems (1). It has been reported that this type of compounds possess a wide variety of biological activities such as potent anti-HIV(2), antipoliovirus (3), antibacterial (4, 5), hypotensive (6), anti-arrythmic (7), moluscicidal (8), antiplatelet aggregation (9, 10), anxiolytic and antidepressant (11, 12). At the same time, different heterocyclic systems such as pyrans, pyrazolines and thiazolidines have exhibited widespread chemotherapeutic activities (13-15). Moreover, several tetralins have been developed and evaluated as analgesics and anti-inflammatory agents (16, 17). According to these findings, it was of interest to synthesize new groups of 5,6,7,8-tetrahydronaphthalene derivatives incorporated into the above mentioned heterocyles hopping to obtain more active and less toxic anti-inflammatory, analgesic and antipyretic agents.

2-Acetyltetralin prepared according to the literature method (18), was cyclocondensed with ethylcyanoacetate and/or malononitrile and the appropriate aromatic aldehydes in the presence of excess ammonium acetate in *n*-butanol, to give the corresponding: 4-substituted-2-oxo-6-(5,6,7,8-tetrahydronaphthalen-2-yl)-1,2-dihydropyridine-3-carbonitriles (**1a**-**f**) and/or 2-amino-4-substituted-6-(5,6,7,8-tetrahydronaphthalen-2-yl) nicotinonitriles (**2a**-**f**), respectively, in one pot reaction according to the reported method (19).

Also, 2-acetyltetralin was allowed to react with different prepared aromatic sulfonylhydrazides (19) to obtain the corresponding N-[1-(5,6,7,8-tetrahydro-naphthalen-2-yl)ethylidene]sulfonylhydrazide derivatives. Further treatment of these compounds (**3a**-**d**) with thioglycolic acid in dry benzene (20) afforded the corresponding 4-oxo-1,3-thiazolidin-3-yl derivatives (**4a**-**d**). Synthesis of 2H-pyrano[2,3-d]-1,3-thiazol-3(7H)-yl-sulfonamide derivatives (**5a**-**d**) was achieved by the reaction of the corresponding compounds (**4a**-**d**) with the pre-synthesized 4-chlorobenzylidene malononitrile in methanol containing 3 mL of piperidine. Mannich reaction had been carried out using the thiazolidine derivatives (**4a**-**d**) in the presence of paraformaldehyde and the appropriate secondary amines in

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absolute ethanol to afford the corresponding Mannich (20) bases (**6a**,**c**, 7**b**,**d and 8a**,**d**).

EXPERIMENTAL

All melting points are uncorrected and were determined in capillary tubes. The IR spectra were recorded in potassium bromide on a Beckman Infrared Spectrometer Model PU 9712 using KBr discs. The ^{1}H NMR spectra were obtained on Jeol EX 270 MHz Spectrometer with tetramethylsilane as an internal standard.The mass spectra (MS) were recorded on SSQ 7000 Mass Spectrometer at 70 eV. All the reactions were followed up and checked by TLC using chloroform/methanol (3:1, v/v) and spots were examined under UV lamp.

General method for preparation of 2-oxo-and/or 2-aminopyridine compounds **1a-f** and **2a-f**

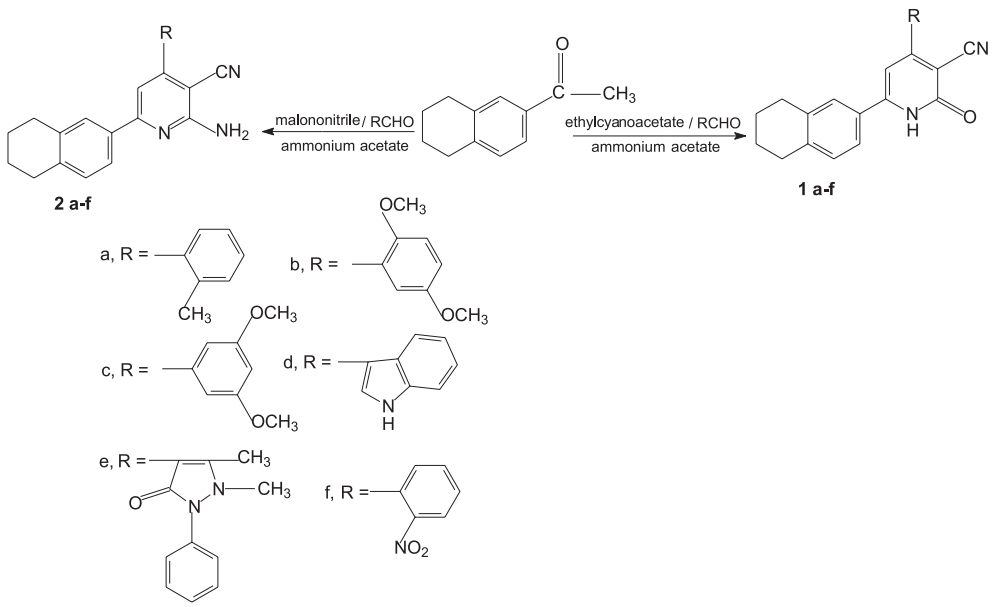
A mixture of acetyltetralin (0.003 mol), the appropriate aldehyde, namely: 2-methylbenzaldehyde, 2,5-dimethoxybenzaldehyde, 3,5-dimethoxybenzaldehyde, indole-3-carboxaldehyde, 4-antipyrinecarboxaldehyde and 2-nitrobenzaldehyde (0.003 mol), ethyl cyanoacetate and/or malononitrile (0.021 mol) and ammonium acetate (0.024 mol) in *n*-butanol (50 mL) was refluxed for 8-10 h. The reaction mixture was concentrated to half volume, then cooled and left overnight. The precipitate was filtered off, dried then crystallized from DMF/water to give tetralin-2-oxo-pyridine and tetralin-2-aminopyridine derivatives of the type **1a-f** and 2**a-f** (Scheme 1).

4-(2-Methylphenyl)-2-oxo-6-(5,6,7,8-tetrahydronaphthalen-2-yl)-1,2-dihydropyridine-3-carbonitrile **1a**

Yield 75 %, m.p. 210-12^{o}C. Analysis: calc. for $C_{23}H_{20}N_2O$ (340.42): C 81.15, H 5.92 N 8.23% found: C 81.14, H 5.90, N, 8.21%. IR (cm^{-1}): 3425 (NH), 3030, 3019 (C-H aromatic), 2218 (CN), 1637 (CO). ^{1}H NMR (DMSO-d_6) δ (ppm):1.8, 2.9 (8H, m, 4CH_2), 2.5 (3H, s, CH_3), 6.5 (1H, s, H of pyridone), 7.3-8.2 (7H, m, aromatic H), 9.1 (1H, s, NH exchangeable with D_2O). MS: M^+ at m/z = 340.5 (15%).

4-(2,5-Dimethoxyphenyl)-2-oxo-6-(5,6,7,8-tetrahydronaphthalen-2-yl)-1,2-dihydropyridine-3-carbonitrile **1b**

Yield 75%, m.p. 284-86^{o}C. Analysis: calc. for $C_{24}H_{22}N_2O_3$ (386.44): C 74.59, H 5.74, N 7.25%, found: C 74.57, H 5.72, N 7.23%. IR (cm^{-1}): 3442 (NH), 3050, 3015 (C-H aromatic), 2219 (CN), 1645



Scheme 1.

(CO). ^{1}H NMR (DMSO-d_6) δ (ppm): 1.8, 2.8 (8H, m, 4CH_2), 3.6,3.8 (6H, s, 2 OCH_3), 6.6 (1H, s, H of pyridone), 7.0-7.9 (6H, m, aromatic H), 8.6 (1H, s, NH exchangeable with D_2O). MS: M^+ at m/z = 386.5 (16%).

4-(3,5-Dimethoxyphenyl)-2-oxo-6-(5,6,7,8-tetrahydronaphthalen-2-yl)-1,2-dihydropyridine-3-carbonitrile **1c**

Yield 74%, m.p. 265-67°C. Analysis: calc. for $C_{24}H_{22}N_2O_3$ (386.44): C 74.59, H 5.74, N 7.25%, found: C 74.56, H 5.71, N 7.21%. IR (cm^{-1}): 3410 (NH), 3040, 3010 (C-H aromatic), 2218 (CN), 1648 (CO). ^{1}H NMR (DMSO-d_6) δ (ppm): 1.89, 2.9 (8H, m, 4CH_2), 3.6, 3.8 (6H, s, 2 OCH_3), 6.4 (1H, s, H of pyridone), 6.8-7.8 (6H, m, aromatic H), 8.4, 9.1 (2H, s, 2 NH exchangeable with D_2O). MS: M^+ at m/z = 386.5 (9%).

4-(1*H*-Indol-3-yl)-2-oxo-6-(5,6,7,8-tetrahydronaphthalen-2-yl)-1,2-dihydropyridine-3-carbonitrile **1d**

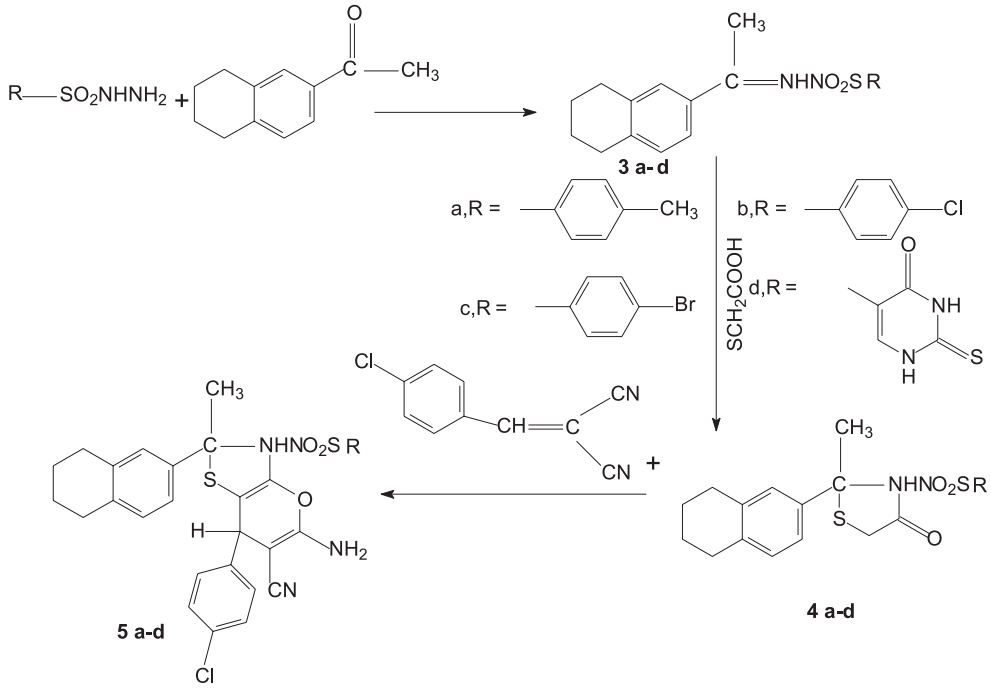
Yield 79%, m.p. 236-38°C. Analysis: calc. for $C_{24}H_{19}N_3O$ (365.43): C 78.88, H 5.24, N 11.50%, found: C 78.86, H 5.22, N 11.48%. IR (cm^{-1}): 3429 (NH), 3130, 3070 (C-H aromatic), 2220 (CN), 1648 (CO). ^{1}H NMR (DMSO-d_6) δ (ppm): 1.89, 2.9 (8H, m, 4 CH_2), 6.4 (1H, s, H of pyridone), 6.7-8.2 (8H, m, aromatic H including indole protons), 8.7, 9.1 (2H, s, 2 NH exchangeable with D_2O). MS: M^+ at m/z = 365.50 (11%).

4-(4-Antipyryl)-2-oxo-6-(5,6,7,8-tetrahydronaphthalen-2-yl)-1,2-dihydropyridine-3-carbonitrile **1e**

Yield 75%, m.p. 158-60°C. Analysis: calc. for $C_{27}H_{24}N_4O_2$ (436.52): C 74.29, H 5.54, N 12.84% found: C 74.27, H 5.52, N 12.82%. IR (cm^{-1}): 3385 (NH), 3060, 3040 (C-H aromatic), 2217(CN), 1714, 1659 (2CO). ^{1}H NMR (DMSO-d_6) δ (ppm): 1.82, 2.96 (8H, m, 4CH_2), 2.6 (3H, s, CH_3), 3.6 (3H, s, N-CH_3), 6.5 (1H, s, H of pyridone), 6.8-7.9 (8H, m, aromatic H), 9.1 (1H, s, NH exchangeable with D_2O). MS: M^+ at m/z = 436.50 (9%).

4-(2-Nitrophenyl)-2-oxo-6-(5,6,7,8-tetrahydronaphthalen-2-yl)-1,2-dihydropyridine-3-carbonitrile **1f**

Yield 76%, m.p. 205-7°C. Analysis: calc. for $C_{22}H_{17}N_3O_3$ (371.39): C 71.15, H 4.61, N 11.31%, found: C 71.13, H 4.58, N 11.29%. IR (cm^{-1}): 3453 (NH), 3160, 3050 (C-H aromatic), 2217 (CN), 1648 (CO). ^{1}H NMR (DMSO-d_6) δ (ppm): 1.9, 2.9 (8H,



Scheme 2.

m, 4CH_2), 6.6 (1H, s, H of pyridone), 6.8-7.9 (7H, m, aromatic H), 9.3(H, s, NH exchangeable with D_2O). MS: M^+ at m/z = 371.5 (11%).

2-Amino-4-(2-methylphenyl)-6-(5,6,7,8-tetrahydronaphthalen-2-yl) nicotinonitrile **2a**

Yield 68%, m.p. 315-17°C. Analysis: calc. for $C_{23}H_{21}N_3$ (339.43): C 81.38, H 6.24, N 12.38%, found: C 81.36, H 6.22, N 12.36%. IR (cm^{-1}): 3565 (NH_2), 3210, 3153 (C-H aromatic), 2215 (CN). ^{1}H NMR (DMSO-d_6) δ (ppm): 1.8, 2.8 (8H, m, 4CH_2), 2.5 (3H, s, CH_3),4.9 (2H, s, NH_2 exchangeable with D_2O), 6.2 (1H, s, CH of pyridine), 6.6-7.8 (7H, m, aromatic H). MS: M^+ at m/z = 339.40 (15%).

2-Amino-4-(2,5-dimethoxyphenyl)-6-(5,6,7,8-tetrahydronaphthalen-2-yl)nicotinonitrile **2b**

Yield 76%, m.p.259-61°C. Analysis: calc. for $C_{24}H_{23}N_3O_2$ (385.46): C 74.78, H 6.01, N 10.90%, found : C 74.76, H 6.00, N 10.87%. IR (cm^{-1}): 3559 (NH_2), 3167, 3093 (C-H aromatic), 2215 (CN). ^{1}H NMR (DMSO-d_6) δ (ppm): 1.7, 2.9 (8H, m, 4CH_2), 3.6, 3.9 (6H, s, 2 OCH_3), 4.9 (2H, s, NH_2 exchangeable with D_2O), 6.2 (1H, s, CH of pyridine), 6.7-7.8 (6H, m, aromatic H). MS: M^+ at m/z = 385.5 (9%).

2-Amino-4-(3,5-dimethoxyphenyl)-6-(5,6,7,8-tetrahydronaphthalen-2-yl)nicotinonitrile **2c**

Yield 81%, m.p. 195-97°C. Analysis: calc. for $C_{24}H_{23}N_3O_2$ (385.46): C 74.78, H 6.01, N 10.90%, found: C 74.99, H 5.98, N 10.88%. IR (cm^{-1}): 3557 (NH_2), 3112, 3053 (C-H aromatic), 2218 (CN). ^{1}H NMR (DMSO-d_6) δ (ppm): 1.7, 2.9 (8H, m, 4CH_2), 4.9 (2H, s, NH_2 exchangeable with D_2O), 3.6, 3.9 (6H, s, 2 OCH_3), 6.2 (1H, s, CH of pyridine), 6.7-7.8 (6H, m, aromatic). MS: M^+ at m/z = 385.5 (14%).

2-Amino-4-(1*H*-indol-3-yl)-6-(5,6,7,8-tetrahydronaphthalen-2-yl)nicotinonitrile **2d**

Yield 74%, m.p. 217-19°C, Analysis: calc. for $C_{24}H_{20}N_4$ (364.44): C 79.10, H 5.53, N 15.10%, found: C 79.08, H 5.51, N 15.08%. IR (cm^{-1}): 3450 (NH_2), 3118, 3048 (C-H aromatic), 2215 (CN). ^{1}H NMR (DMSO-d_6) δ (ppm): 1.8, 2.8 (8H, m, 4CH_2), 4.9 (2H, s, NH_2 exchangeable with D_2O), 6.3 (1H, s, CH of pyridine), 6.5-8.1 (8H, m, aromatic), 8.8 (1H, s, NH exchangeable with D_2O). MS: M^+ at m/z = 364.5 (10%).

2-Amino-4-(4-antipyryl)-6-(5,6,7,8-tetrahydronaphthalen-2-yl) nicotinonitrile **2e**

Yield 71%, m.p. 239-41°C. Analysis: calc. for $C_{27}H_{25}N_5O$ (435.52): C: 74.46, H 5.79, N 16.08%, found: C 74.44, H 5.77, N 16.06%. IR (cm^{-1}): 3440 (NH_2), 3186, 3093 (C-H aromatic), 2217 (CN), 1714, (CO). ^{1}H NMR (DMSO-d_6) δ (ppm): 1.8, 2.8 (8H, m, 4CH_2), 2.6 (3H, s, CH_3), 3.6 (3H, s, N-CH_3), 4.9 (2H, s, NH_2 exchangeable with D_2O), 6.5 (1H, s, CH of pyridine), 7.1-7.9 (8H, m, aromatic H). MS: M^+ at m/z = 435.50 (15%).

2-Amino-4-(2-nitrophenyl)-6-(5,6,7,8-tetrahydronaphthalen-2-yl)nicotinonitrile **2f**

Yield 71%, m.p. 225-27°C. Analysis: calc. for $C_{22}H_{18}N_4O_2$ (370.40): C 71.34, H 4.90, N 15.13%, found: C 71.32, H 4.88, N 15.11%. IR (cm^{-1}): 3450 (NH_2), 3150, 3083 (C-H aromatic), 2217 (CN). ^{1}H NMR (DMSO-d_6) δ (ppm): 1.8- 2.8 (8H, m, 4CH_2), 4.9 (2H, s, NH_2 exchangeable with D_2O), 6.4 (1H, s, CH of pyridine), 6.8-7.9 (7H, m, aromatic H), MS: M^+ at m/z = 370.0 (9%).

General method for preparation of 5,6,7,8-tetrahydronaphthalenesulfonylhydrazide compounds **3a-d**

A mixture of acetyltetralin (0.01 mol), the appropriate sulfonylhydrazide, namely: p-methylphenylsulfonylhydrazide, p-chlorophenylsulfonylhydrazide, p-bromophenyl sulfonylhydrazide and 5-thiouracilsulfonylhydrazide (0.01 mol) in (50 mL) ethanol was refluxed for 7-9 h. The solid separated on cooling was filtered off, dried and crystallized from DMF/water giving **3a-d** (Scheme 2).

4-Methyl-*N*-[1-(5,6,7,8-tetrahydronaphthalen-2yl)-ethylidene]benzenesulfonylhydrazide **3a**

Yield 68%, m.p. 166-68°C, Analysis: calc. for $C_{19}H_{22}N_2O_2S$ (342.46): C, 66.64, H 6.48, N 8.18%, found: C 66.62, H 6.47, N 8.16% . IR (cm^{-1}): 3245 (NH), 3116, 3083 (C-H aromatic), 1327, 1220 (-N-SO_2-).^{1}H NMR (DMSO-d_6) δ (ppm): 1.9, 2.8 (8H, m, 4CH_2), 2.4 (3H, s, CH_3), 2.6 (3H, s, ph-CH_3), 7.1-7.5 (7H, m aromatic H), 9.1 (1H, s, NH exchangeable with D_2O). MS: M^+ at m/z = 342.5 (9%).

4-Chloro-*N*-[1-(5,6,7,8-tetrahydronaphthalen-2-yl)ethylidene]benzenesulfonylhydrazide **3b**

Yield 65%, m.p. 161-63°C, Analysis: calc. for $C_{18}H_{19}ClN_2O_2S$ (362.87): C 59.58, H 5.28, N 7.72%, found: C 59.56, H 5.26, N 7.70%. IR (cm^{-1}): 3245 (NH), 3206, 3083 (C-H aromatic), 1327, 1220 (-N-SO_2-).^{1}H NMR (DMSO-d_6) δ (ppm): 1.9, 2.8 (8H, m, 4CH_2), 2.5 (3H, s, CH_3), 7.1-7.8 (7H, m aromatic H), 9.3 (1H, s, NH exchangeable with D_2O). MS: M^+ at m/z = 362.5 (5%), M^+ at m/z = 364.5 (15 %).

4-Bromo-*N*-[1-(5,6,7,8-tetrahydronaphthalen-2-yl)ethylidene]benzenesulfonylhydrazide **3c .**

Yield 69%, m.p.195-97şC. Analysis: calc. for $C_{18}H_{19}BrN_2O_2S$ (407.33): C 53.08, H 4.70, N

6.88%, found: C 53.06, H 4.68, N 6.86%. IR (cm^{-1}): 3245 (NH), 3116, 3083 (C-H aromatic), 1327, 1220 (-N-SO_2-). ^{1}H NMR (DMSO-d_6) δ (ppm): 1.8, 2.9 (8H, m, 4CH_2), 2.5 (3H, s, CH_3), 7.1-7.5 (7H, m, aromatic), 9.3 (1H, s, NH exchangeable with D_2O), MS: M^+ at m/z = 407 (9%), 409 (9%).

4-Oxo-2-thioxo-*N*-[1-(5,6,7,8-tetrahydronaphthalen-2-yl)ethylidene]-1,2,3,4-tetrahydropyrimidine-5-sulfonylhydrazide **3d** .

Yield 69%, m.p. 233-35°C. Analysis: calc. for $C_{16}H_{18}N_4O_3S_2$ (378.47): C 50.78, H 4.79, N 14.80%, found: C 50.76, H 4.77, N 14.78%. IR (cm^{-1}): 3245 (NH), 3206, 3083 (C-H aromatic), 1712 (CO of thiouracil), 1327, 1220 (-N-SO_2-), 1270 (C=S of thiouracil). ^{1}H NMR (DMSO-d_6) δ (ppm): 1.8, 2.9 (8H, m, 4CH_2), 2.5 (3H, s, CH_3), 7.1-7.5 (3H, m, aromatic H), 8.1 (1H, s, H of thiouracil), 9.2, 10.1, 10.4 (3H, s, 3 NH exchangeable with D_2O), MS: M^+ at m/z = 378.47 (12%).

General method for preparation of 5,6,7,8-tetrahydronaphthalene-4-oxothiazolidine compounds **4a-d**

A solution of thioglycolic acid (0.15 mol) in dry benzene (10 mL) was added to a solution of **3a-d** (0.01 mol) in 40 mL of dry benzene and then the mixture was refluxed on a water bath for 9-12 h . The formed product was filtered off and crystallized from dimethylformamide (DMF)/water to give compounds **4a-d** (Scheme 2).

4-Metyl-*N*-[2-methyl-4-oxo-2-(5,6,7,8-tetrahydronaphthalen-2-yl)-1,3-thiazolidin-3-yl]benzenesulfonamide **4a**

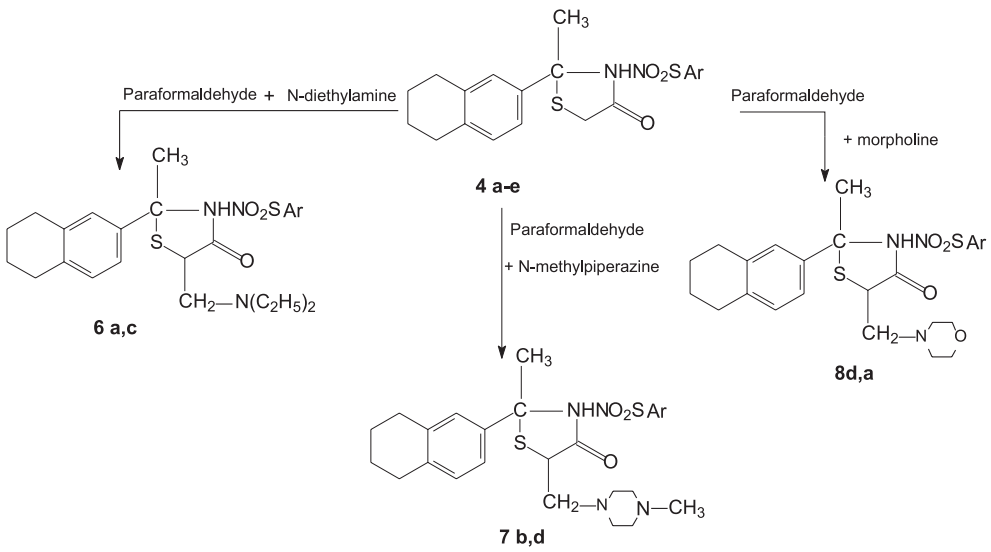
Yield 65%, m.p. 142-44°C. Analysis: calc. for $C_{21}H_{24}N_2O_3S_2$ (416.56): C 60.55, H 5.81, N 6.72%, found: C 60.53, H 5.79, N 6.70%. IR (cm^{-1}) 3245 (NH), 3116, 3083 (C-H aromatic), 1680 (CO), 1327, 1220 (-N-SO_2-). ^{1}H NMR (DMSO-d_6) δ (ppm): 1.7, 2.8 (8H, m, 4CH_2), 2.6 (3H, s, C-CH_3), 2.8 (3H, s, ph-CH_3), 4.4, 4.6 (2H, dd, CH_2), 7.1-7.8 (7H, m aromatic H) , 10.4 (1H, s, NH exchangeable with D_2O). MS: M^+ at m/z = 416.5 (9%).

4-Chloro-*N*-[2-methyl-4-oxo-2-(5,6,7,8-tetrahydronaphthalen-2-yl)-1,3-thiazolidin-3-yl]benzenesulfonamide **4b**

Yield 68%, m.p. 140-42°C. Analysis: calc. for $C_{20}H_{21}ClN_2O_3S_2$ (436.98): C 54.97, H 4.84,N 6.41%, found: C 54.95, H 4.82, N 6.39%. IR (cm^{-1}): 3245 (NH), 3110, 3083 (C-H aromatic), 1675 (CO), 1327, 1220 (-N-SO_2-).^{1}H NMR (DMSO-d_6) δ (ppm): 1.8, 2.9 (8H, m, 4CH_2), 2.5 (3H, s, CH_3), 4.2, 4.6 (2H, dd, CH_2),7.0-7.8 (7H, m, aromatic H), 9.4 (1H, s, NH exchangeable with D_2O). MS: M^+ at m/z = 436.8 (12%), 438 (4%).

4-Bromo-*N*-[2-methyl-4-oxo-2-(5,6,7,8-tetrahydronaphthalen-2-yl)-1,3-thiazolidin-3-yl]benzenesulfonamide **4c**

Yield 62%, m.p. 182-30°C, Analysis: calc. for $C_{20}H_{21}BrN_2O_3S_2$ (481.43): C 49.90, H 4.40, N



Scheme 3.

5.82%, found: C 49.88, H 4.38, N 5.80%. IR (cm^{-1}): 3245 (NH), 3159, 3083(C-H aromatic), 1682 (CO), 1327, 1220 (-N-SO_2-). ^{1}H NMR (DMSO-d_6) δ (ppm): 1.7, 2.9 (8H, m, 4CH_2), 2.6 (3H, s, CH_3), 4.1, 4.6 (2H, dd, CH_2), 6.9-7.8 (7H, m, aromatic H), 9.3 (1H, s, NH exchangeable with D_2O). MS: M^+ at m/z = 481.5 (11%), 483.5 (11 %).

N-[2-Methyl-4-oxo-2-(5,6,7,8-tetrahydronaphthalen-2-yl)-1,3-thiazolidin-3-yl]-4-oxo, 2-thioxo-1,2,3,4-tetrahydropyrimidine-5-sulfonamide **4d** .

Yield 69%, m.p. 210-12°C. Analysis: calc. for $C_{18}H_{20}N_4O_4S_3$ (452.57): C 47.77, H 4.45, N 12.38%, found: C 47.75, H 4.43, N 12.36. IR (cm^{-1}): 3245 (NH), 3178, 3083 (C-H aromatic), 1680 1712 (2CO), 1327, 1220 (-N-SO_2-), 1270 (C=S of thiouracil). ^{1}H NMR (DMSO-d_6) δ (ppm): 1.8, 2.8 (8H, m, 4CH_2), 2.5 (3H, s, CH_3), 4.2, 4.5 (2H, dd, CH_2), 7.3-7.9 (3H, m, aromatic H), 8.3 (1H, s, H of thiouracil), 9.4, 10.6, 11.4 (3H, s, 3NH exchangeable with D_2O). MS: M^+ at m/z = 452.5 (17%).

General method for prepararion of 5,6,7,8-tetrahydronaphthalene-pyrano[2,3-*d*]-1,3-thiazole compounds **5a-d** .

A solution mixture of **4a-d** (0.01 mol) and 4-chlorobenzylidene malononitrile (0.01 mol) in methanol (40 mL) containing piperidine (3 mL) was refluxed for 8-12 h . The formed product was filtered off and crystallized from DMF/water to give compounds **5a-d** (Scheme 2).

N-[5-Amino-7-(4-chlorophenyl)-6-cyano-2-methyl-2-(5,6,7,8-tetrahydronaphthalen-2-yl)-2*H*-pyrano[2,3-*d*]-1,3-thiazol-3(7*H*)-yl]-4-methylbenzenesulfonamide **5a**

Yield 65%, m.p. 215-17°C. Analysis: calc. for $C_{31}H_{29}ClN_4O_3S_2$ (605.17): C 61.52, H 4.83, N 9.26%, found: C 61.50, H 4.81, N 9.24%. IR (cm^{-1}): 3455 (NH_2), 3245 (NH), 3116, 3083 (C-H aromatic), 2218 (CN), 1327, 1220 (-N-SO_2-).^{1}H NMR (DMSO-d_6) δ (ppm): 1.8, 2.9 (8H, m, 4CH_2), 2.6 (3H, s, CH_3), 2.8 (3H, s, ph-CH_3), 4.7 (2H, s, NH_2 exchangeable with D_2O),7.1-7.8 (12H, m aromatic H), 10.4 (1H, s, NH exchangeable with D_2O). MS: M^+ at m/z = 605.5 (12%), 607.5 (4 %).

N-[5-Amino-7-(4-chlorophenyl)-6-cyano-2-methyl-2-(5,6,7,8-tetrahydronaphthalen-2-yl)-2*H*-pyrano[2,3-*d*]-1,3-thiazol-3(7*H*)-yl]-4-chlorobenzenesulfonamide **5b**

Yield 65%, m.p. 225-27°C. Analysis: calc. for $C_{30}H_{26}Cl_2N_4O_3S_2$ (625.59): C 57.60, H 4.19, N 8.96%, found: C 57.57, H 4.17, N 8.94%. IR (cm^{-1}): 3445 (NH_2), 3235 (NH), 3183, 3020 (C-H aromatic), 2220 (CN), 1327, 1220 (-N-SO_2-). ^{1}H NMR (DMSO-d_6) δ (ppm): 1.7, 2.8 (8H, m, 4CH_2), 2.7 (3H, s, CH_3), 4.6 (2H, s, NH_2 exchangeable with D_2O), 7.2-7.8 (12H, m, aromatic H), 10.4 (1H,s, NH exchangeable with D_2O), MS: M^+ at m/z = 625.5 (9%), 627 (3%).

Table 1. Anti-inflammatory effects of selected investigated compounds

Group	Dose mg/100 g b. wt.	1 h	2 h	3 h	4 h
Control		68.2 ± 5	78.6 ± 3.0	88.7 ± 5.0	92.6 ± 6.0
1c	10	37.7 ± 2.2* (-57.0)	50.1 ± 2.2* (-36.3)	56.8 ± 3.4* (-36.0)	71.7 ± 3.1* (-22.6)
1d	10	26.0 ± 1.3* (-61.9)	42.3 ± 2.8* (-46.2)	51.5 ± 1.7 (-41.9)	62.3 ± 3 (-32.7)
1e	10	39.1 ± 2.7* (-42.7)	48.04 ± 2.5* (-38.2)	53.6 ± 3.0* (-39.6)	59.1 ± 1.9* (-36.2)
2e	10	27.7 ± 2.4* (-59.4)	32.4 ± 2.6* (-58.8)	51.2 ± 0.48* (-42.3)	55.8 ± 3.1* (-39.7)
3a	10	36.2 ± 2.2* (-46.9)	52.9 ± 2.0* (-32.7)	60.3 ± 3.5* (-32.0)	64.4 ± 2.4* (-31.4)
3d	10	29.3 ± 1.9* (-57.0)	43.8 ± 2.8* (-44.3)	50.5 ± 2.1* (-43.1)	64.3 ± 2.0* (-30.6)
Indo.	2	28.8 ± 2.5* (-57.8)	44 ± 2.7* (-44.0)	56.9 ± 2.0* (-35.9)	63.5 ± 2.4* (-30.8)

Each group represents the mean ± S-E of six animals. Significant *vs*. control group at the corresponding hour * $p < 0.05$. Indo. – indomethacin, % of inhibition in parentheses.

Table 2. Analgesic effect of selected investigated compounds
a) Hot-plate test

Group	Dose mg/100 g b. wt.	Pre-drug value	1 h		2 h	
		$X^- \pm$ S.E	$X^- \pm$ S.E	% of change[a]	$X^- \pm$ S.E	% of change[a]
Control	1 ml	saline	9.4 ± 0.8	9.4 ± 0.76	-	9.1 ± 0.8
1c	10	11.5 ± 0.9	18.6 ± 1.3**	61.7	17.7 ± 1.2**	53.9
1d	10	12.8 ± 1.1	13.8 ± 1.2	7.8	14.2 ± 1.1	10.9
1e	10	9.4 ± 0.4	10.2 ± 0.8	8.5	10.8 ± 1.1	14.9
2e	10	11.3 ± 0.8	13.5 ± 1.0	19.5	8.4 ± 1.0	-26.3
3a	10	10.1 ± 0.9	15.8 ± 0.3***	56.4	15.3 ± 0.5***	51.5
3d	10	10.4 ± 0.34	15.4 ± 1.0**	48.1	14.6 ± 1.1*	44.6
Indo**.**	2	9.0 ± 0.3	13.6 ± 1.0**	51.1	16.1 ± 0.9**	78.9

Data are presented as the mean ± S.E. [a] % of change from basal (pre-drug) value for each group
* p < 0.05, ** p < 0.01, ***p < 0.001. Indo. – indomethacin

b) Acetic acid-induced writhing

Group	Dose mg/100 g b. wt.	Number of contractions $X^- \pm$ S.E	% of change[a]
Control	1 ml saline	44.0 ± 1.5	-
1c	10	38.0 ± 1.3	-13.6
1d	10	37.8 ± 2.9	-14.1
1e	10	30.8 ± 1.3***	-30
2e	10	27.0 ± 2.1***	-38.6
3a	10	23.2 ± 1.3***	47.3
3d	10	18.8 ± 0. ***	-57.3
Indomethacin	2	22.0 ± 1.2***	50

Data are presented as the mean ± S.E. [a] % of change from control value; significant change from control group
*** p < 0.001.

c) Plantar test

Group	Dose mg/100 g b.wt.	1 h $X^- \pm$ S.E	2 h $X^- \pm$ S.E
Control	1 ml saline	6.8 ± 0.8	7.1 ± 0.7
1c	10	11.3 ± 2.0	14.0 ± 2.4
1d	10	11.4 ± 1.6	5.5 ± 0.9
1e	10	10.3 ± 0.4**	16.3 ± 1.7*
2e	10	12.8 ± 0.7**	13.4 ± 0.9**
3a	10	8.5 ± 0.7	17.2 ± 1.2***
3d	10	11.7 ± 1.2*	14.8 ± 1.6**
Indomethacin	2	14.6 ± 1.8**	16.9 ± 2.2**

Data are presented as the mean ± S.E. % of change from control value; significant change from control group is denoted by * p < 0.05, ** p < 0.01, ***p < 0.001

Table 3. The effect of compounds **1c**, **1d**, **1e**, **2e**, **3a**, and **3d** (10 mg/100 g b.wt.) and paracetamol (10 mg/100 g b. wt.) on hyperthermia induced by yeast in rats

Group	Dose 10 mg/100 g b.wt	Mean change in body temperature ± S.E (°C)		
		0 min	30 min	60 min
Control	Mean + S.E	2.95 ± 0.2	2.87 ± 0.09	2.5 ± 0.2
1 mL saline	% of change from initial	-	2.7	15.3
1c	Mean + S.E	3.8 ± 0.1	3.3 ± 0.15	3.1 ± 0.2*
	% of change	-	-13.2	- 18.4
1d	Mean + S.E	2.8 ± 0.1	2.7 ± 0.2	1.98 ± 0.2*
	% of change	-	-3.7	-29.3
1e	Mean + S.E.	2.1 ± 0.17	1.9 ± 0.1	1.48 ± 0.18*
	% of change	-	9.5	-29.5
2e	Mean + S.E	2.9 ± 0.2	2.3 ± 0.16	2.2 ± 0.2
	% of change	-	-20.7	-24.1
3a	Mean + S.E	3.3 ± 0.12	3.15 ± 0.1	2.4 ± 0.26*
	% of change	-	-4.5	-27.3
3d	Mean + S.E	3.2 ± 0.17	2.7 ± 0.1*	1.9 ± 0.2**
	% of change	-	-15.6	-40.6
Paracetamol	Mean ± S.E	2.9 ± 0.1	2.25 ± 0.2*	1.5 ± 0.16**
	% of change	-	22.4	-48.3

% of changes are calculated *vs.* 0 time; * significantly different from control at p = 0.05
** significantly different from control at p = 0.01

N-[5-Amino-7-(4-chlorophenyl)-6-cyano-2-methyl-2-(5,6,7,8-tetrahydronaphthalen-2-yl)-2*H*-pyrano[2,3-*d*]-1,3-thiazol-3(7*H*)-yl]-4-bromobenzenesulfonamide **5c**

Yield 65%, m.p. 265-67°C. Analysis: calc. for $C_{30}H_{26}BrClN_4O_3S_2$ (670.04): C 53.78, H 3.91, N 8.36%, found: C 53.76, H 3.89, N 8.34%. IR (cm^{-1}): 3448 (NH_2), 3245 (NH), 3116, 3083(C-H aromatic), 2217 (CN), 1327, 1220 (-N-SO_2-).^{1}H NMR (DMSO-d_6) δ (ppm): 1.8, 2.9 (8H, m, 4CH_2), 2.6 (3H,s, CH_3), 4.8 (2H, s, NH_2 exchangeable with D_2O), 7.0-7.8 (12H, m, aromatic H), 9.4 (1H, s, NH exchangeable with D_2O). MS: M^+ at m/z = 670.5 (9%), 672 (9 %).

N-[5-Amino-7-(4-chlorophenyl)-6-cyano-2-methyl-2-(5,6,7,8-tetrahydronaphthalen-2-yl)-2*H*-pyrano[2,3-*d*]-1,3-thiazol-3(7*H*)-yl]-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-sulfonamide **5d**

Yield 65%, m.p. 310-12°C. Analysis: calc. for $C_{28}H_{25}ClN_6O_4S_3$ (641.19): C 52.45, H 3.93, N 13.11%, found: C 52.43, H 3.91, N 13.09. IR (cm^{-1}): 458 (NH_2), 3255 (NH), 3136, 3079 (C-H aromatic), 2219 (CN), 1712 (CO of thiouracil), 1327, 1220 (-N-SO_2-), 1270 (C=S of thiouracil). ^{1}H NMR (DMSO-d_6) δ (ppm): 1.8, 2.8 (8H, m, 4CH_2), 2.8 (3H, s, CH_3), 4.6 (2H, s, NH_2),7.1-7.9 (8H, m aromatic), 8.3 (1H, s, CH of thiouracil), 9.2, 10.4, 11.3 (3H, s, 3NH exchangeable with D_2O). MS: M^+ at m/z = 641 (9%), 643 (3 %).

General method for preparation of Mannich bases **6a,c, 7b,d and 8a,d**

A mixture of (0.003 mol) of paraformaldehyde and the appropriate amine, namely: diethylamine, N-methylpiperazine and/or morpholine (0.006 mol) in 25 mL of absolute ethanol, was refluxed for 0.5 h till complete solubility of paraformaldehyde. Then a warmed solution of **4a-e** (0.001 mol) in 30 mL of ethanol was added to the reaction mixture. The whole mixture was refluxed for 9-12 h and left at room temperature for three days, then the volatile material was evaporated. The dry residue was extracted with chloroform and crystallized from methanol to give **6a,c**, **7b,d** and **8a,d**, respectively (Scheme 3).

N-{5-[(diethylamino)methyl]-2-methyl-2-(5,6,7,8-tetrahydronaphthalen-2-yl)-4-oxo-1,3-thiazolidin-3-yl]-4-methylbenzenesulfonamide **6a**

Yield 65%, m.p. 215-17°C. Analysis: calc. for $C_{26}H_{35}N_3O_3S_2$ (501.72): C 62.24, H 7.03, N 8.38%,

Table 4. Effect of newly synthesized compounds **1c**, **1d**, **1e, 2e**, **3a**, and **3d** on gastric mucosal injury induced by indomethacin (IND.) in rats

Treatment group	Dose mg/100 g b. wt.	Number of lesions/rat $X^- \pm$ S.E.	% of change	Severity of lesions/rat $X^- \pm$ S.E.	% of change
IND. control	5 mg/100 g b.wt.	8.2 ± 0.3	-	12.0 ± 0.2	-
1c	10	6.1 ± 0.4**	-25.6	7.5 ± 0.3***	-37.5
1d	10	6.0 ± 0.2 ***	-26.8	10.1 ± 0.5*	-15.8
1e	10	6.5 ± 0.5*	-20.7	8.5 ± 0.4***	-29.2
2e	10	3.3 ± 0.3 ***	-59.8	9.0 ± 0.3 ***	-25
3a	10	6.5 ± 0.3**	-20.7	7.5 ± 0.4**	-37.5
3d	10	6.3 ± 0.2**	-23.2	9.0 ± 0.6**	-25

Statistical comparison of the difference between the control group (IND.) and treated groups is indicated by asterisks * $p < 0.05$, ** $p < 0.001$, *** $p < 0.001$ (Student's *t*-test)

found: C 62.22, H 7.01, N 8.36%. IR (cm^{-1}): 3245 (NH), 3116, 3083 (C-H aromatic), 1680 (CO), 1327, 1220 (-N-SO_2-). ^{1}H NMR (DMSO-d_6) δ (ppm): 1.5 (6H, t, of 2 CH_3 from 2 C_2H_5), 1.7, 2.8 (8H, m, 4CH_2 of tetralin), 2.6 (3H, s, CH_3), 2.8 (3H, s, CH_3-ph), 3.3 (1H, s, CH of thiazolidine), 4.4-4.8 (6H, m, 2CH_2, CH_2-N), 7.1-7.8 (7H, m aromatic H), 10.4 (1H, s, NH exchangeable with D_2O). MS: M^+ at m/z = 516.5 (9%).

N-{5-[(Diethylamino)methyl]-2-methyl-2-(5,6,7,8-tetrahydronaphthalen-2-yl)-4-oxo-1,3-thiazolidin-3-yl}-4-bromobenzenesulfonamide **6c**

Yield 65%, m.p. 187-89°C. Analysis: calc. for $C_{25}H_{32}BrN_3O_3S_2$ (566.58): C 53.00, H 5.69, N 7.42%, found: C 52.98, H 5.67, N 7.40%. IR (cm^{-1}): 3245 (NH), 3216, 3083 (C-H aromatic), 1680 (CO), 1327, 1220 (-N-SO_2-). ^{1}H NMR (DMSO-d_6) δ (ppm): 1.5 (6H, t, 2 CH_3 from 2 C_2H_5), 1.7, 2.7 (8H, m, 4CH_2), 2.6 (3H, s, CH_3), 3.2 (1H, s, CH of thiazolidine), 4.5- 4.7 (6H, m, 2CH_2 of 2 C_2H_5, CH_2-N), 7.1-7.8 (7H, m, aromatic H), 10.2 (1H, s, NH exchangeable with D_2O). MS: M^+ at m/z = 566.5 (11%), m/z = 568.5 (11%).

N-{2-Methyl-2-(5,6,7,8-tetrahydronaphthalen-2-yl)-5-[(4-methylpiperazin-1-yl)methyl]-4-oxo-1,3-thiazolidin-3-yl}-4-chlorobenzenesulfonamide **7b**

Yield 65%, m.p. 289-91°C. Analysis: calc. for $C_{26}H_{33}ClN_4O_3S_2$ (549.15): C 56.87, H 6.06, N 10.20%, found: C 56.85, H 6.04, N 10.18%. IR (cm^{-1}): 3245 (NH), 3116, 3083 (C-H aromatic), 1680 (CO), 1327, 1220 (-N-SO_2-). ^{1}H NMR (DMSO-d_6) δ (ppm): 1.7, 2.8 (8H, m, 4 CH_2 of tetralin), 2.6 (3H, s, CH_3), 2.9 (3H, s, N-CH_3), 3.4-3.9 (9H, m, H of piperazine and CH of thiazolidinone ring), 4.4 (2H, d, CH_2), 7.1-7.8 (7H, m, aromatic H), 9.4 (1H, s, NH exchangeable with D_2O). MS: M^+ at m/z = 549.5 (8%), 551 (2.6%).

N-[2-Methyl-2-(5,6,7,8-tetrahydronaphthalen-2-yl)-4-oxo-1,3-thiazolidin-3-yl]-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-sulfonamide **7d**

Yield 65%, m.p. 324-26°C. Analysis: calc. for $C_{24}H_{32}N_6O_4S_3$ (564.75): C 51.04, H 5.71, N 14.88%, found: C 51.02, H 5.69, N 14.86%. IR (cm^{-1}) 3245 (NH), 3116, 3083 (CH-aromatic), 1710, 1680 (2CO), 1327, 1220 (-N-SO_2-), 1270 (C=S of thiouracil). ^{1}H NMR (DMSO-d_6) δ (ppm): 1.7, 2.8 (8H, m, 4CH_2), 2.6 (3H, s, CH_3), 2.9 (3H, s, CH_3), 3.4-3.6 (9H, m, H of piperazine and CH of thiazolidine ring), 4.4 (2H, d, CH_2), 7.1-7.8 (3H, m, aromatic H), 8.1 (1H, s, CH of thiouracil), 9.1, 9.8, 10.1 (3H, s, 3NH exchangeable with D_2O). MS: M^+ at m/z = 564.5 (14%).

N-[2-Methyl-2-(5,6,7,8-tetrahydronaphthalen-2-yl)-5-(morpholin-4-ylmethyl)-4-oxo-1,3-thiazolidin-3-yl]-4-methylbenzenesulfonamide **8a**

Yield 65%, m.p. 250-52°C. Analysis: calc. for $C_{26}H_{33}N_3O_4S_2$ (515.69): C 60.56, H 6.45, N 8.15%, found: C 60.54, H 6.43, N 8.15%. IR (cm^{-1}): 3245 (NH), 3116, 3083 (C-H aromatic), 1680 (CO), 1327, 1220 (-N-SO_2-). ^{1}H NMR (DMSO-d_6) δ (ppm): 1.7, 2.8 (8H, m, 4 CH_2 of tetralin), 2.4-2.5(4H, m, CH_2-N-CH_2), 2.6 (3H, s, CH_3), 2.9 (3H, s, CH_3-ph), 3.2 (1H, s, CH of thiazolidine), 3.5-3.7 (4H, m, CH_2-N-CH_2), 4.4 (2H, d, CH_2), 7.1-7.8 (7H, m, aromatic), 10.4 (1H, s, NH exchangeable with D_2O). MS: M^+ at m/z = 515.5 (9%).

N-[2-Methyl-2-(5,6,7,8-tetrahydronaphthalen-2-yl)-5-(morpholin-4-ylmethyl)-4-oxo-1,3-thiazolidin-3-yl]-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-sulfonamide **8d**

Yield 65%, m.p. 315-17°C. Analysis: calc. for $C_{23}H_{29}N_5O_5S_3$ (551.71): C 50.07, H 5.30, N 12.69%, found: C 50.05, H 5.28, N 12.67%. IR (cm^{-1}): 3245 (NH), 3116, 3083 (C-H aromatic), 1712, 1680 (2 CO), 1327, 1220 (-N-SO_2-), 1270 (C=S of thiouracil). ^{1}H NMR (DMSO-d_6) δ (ppm): 1.7, 2.8 (8H, m, 4CH_2), 2.4-2.5 (4H, m, CH_2-N-CH_2), 2.6 (3H, s, CH_3), 2.9 (3H, s, CH_3), 3.3 (1H, s, CH of thiazolidine) 3.5-3.7 (4H, m, CH_2-O-CH_2), 4.4 (2H, s, CH_2), 7.1-7.8 (3H, m aromatic H), 8.3 (1H, s, CH of thiouracil), 9.2, 10.4, 10.7 (3H, s, 3NH exchangeable with D_2O). MS: M^+ at m/z = 551.5 (12%).

Biological activity

Animals

Adult rats of both sexes weighing 150-200 g and adult mice weighing 20-25 g were used in the experiments. Animals were housed under standardized conditions for light and temperature and received standard rat chow and tap water *ad libitum*. Animals were randomly assigned to different experimental groups, each kept in separate cage. All animal procedures were performed after approval from the Ethics Committee of the National Research Centre and in accordance with the recommendations for the proper care and use of laboratory animals (NIH publication No. 85-23, revised 1985).

Drugs and chemicals

Carrageenan lambda from Sigma–Aldrich Chemical Co. (USA), indomethacin from Khahira Pharmaceutical and Chemical Co. (Cairo, Egypt), paracetamol (acetaminophen) from BDH Chemicals, England, dried yeast from Matroh Co.

Determination of median lethal dose (LD_{50})

The approximate LD_{50} of the different compounds were determined using mice. Compounds were dissolved in distilled water and given orally to groups of 6 mice each. Each group was given different doses of each compound. Animals were observed for any toxic signs and the percentage mortality for each group was recorded after 24 h.

Anti-inflammatory effect

The carrageenan rat paw edema model of inflammation was used to evaluate the anti-inflammatory properties of the tested compounds (21). Rats were randomly assigned to treatment groups and sterile carrageenan lambda (100 mL of a 1% solution in saline) was injected sub-plantar into the right hind paw of the rat. The contralateral hind paw received the same volume of saline and served as a control. Carrageenan caused visible redness and pronounced swelling that was well developed by 4 h and persisted for more than 48 h (22). Hind foot-pad thickness was measured with a micrometer caliber (23, 24) before, and at 1, 2, 3 and 4 h after carrageenan injection. Eight groups of rats, each of six animals, were administered either saline (1 mL) and served as control or the tested compounds (10 mg/100 g b.wt. orally) or indomethacin (2 mg/100 g b.wt.) given 1 h before carrageenan injection.

Tests on analgesia

Hot-plate test

The hot-plate test was performed on rats by using an electronically controlled hot-plate (Ugo Basile, Italy) heated to 52°C (± 0.1°C), for possible centrally mediated analgesic effect of the drugs (25). Eight groups of 6 rats each were given vehicle and/or tested compounds and the last group received indomethacin (2 mg/100 g b.wt.) 60 min prior to testing. Latency to lick a hind paw or jumping (26) was recorded sequentially before and at 1 and 2 h after treatment.

Acetic acid-induced writhing

Eight separate groups of 6 rats each were administered the vehicle and/or the tested compounds (10 mg/100 g b. wt.). After 60 min interval, an *i.p.* injection of 0.6% acetic acid was administered (27, 28). Each rat was then placed in an individual clear plastic observational chamber and the total number of writhes made by each rat was counted for 20 min.

Plantar test

This model has gained favor as an analgesic drug bioassay for several technical reasons: (i) it permits independent testing of either hind paw (ii) testing can be undertaken with minimum handling (iii) the end point (paw withdrawal) can be automatically detected in unrestrained animals. Utilization of this model as a drug bioassay merits consideration of model properties that contribute to response variability and sensitivity (29).

Animals were allowed to accommodate in 10 cm × 17 cm enclosure of 7371 – plantar test, Ugo Basile, Comerio, Italy. An infrared beam, (Halogen 64607 OSRAM, 8 V-50 W-IR movable bulb, Ugo Basile, Comerio, Italy) was applied through the transparent surface of the enclosure to the plantar

surface of the right hind paw of each animal and time needed to produce a response is calculated in order to reflect the analgesic effect of the tested drugs.

Time required for the animal to withdraw its paw was recorded by a photocell sensitive system linked to a time recorder. Paw licking was used as the end point for the withdrawal latency.

Antipyretic activity

Hyperthermia was induced in 8 groups, each of 6 rats. Their body temperature was recorded before, 1.5 h following the treatment (30). Six groups received the tested compounds (10 mg/100 g b.wt.). The positive control groups received paracetamol (10 mg/100 g b.wt.) while the control group received saline.

A febrile reaction was induced in rats by *i.m.* injection of 44% yeast suspension (1 mg/100 g b.wt.). Five hours later, when the fever has reached a constant level, the drugs were administered orally into the febrile animals. The antipyretic effect was determined on the basis of difference in mean temperature between the control and treated groups.

Gastric ulcerogenic studies

Gastric mucosal damage was evoked in rats by the administration of indomethacin (5 mg/100 g b.wt. *s.c.*). The effect of different compound (10 mg/100 mg b.wt.) administered at time of indomethacin injection was studied. Food and water were provided *ad libitum*. Rats were sacrificed 24 h after drug administration, stomachs were excised and examined for gastric mucosal lesions (31).

Statistical analysis

Results are expressed as the mean $\pm$ S.E. Differences between vehicle control and treated groups were tested using one-way ANOVA followed by the least significant difference (L.S.D.). Methods of statistical analysis were done according to (32).

RESULTS

Toxicological study: oral administration of different doses of compounds **1e**, **1c, 1d, 2e, 3a, and 3d** up to 1 g/kg b.wt. to mice induced no obvious toxic effects and all the treated animals were still alive after 24 h.

Effect of the tested compounds on carrageenan induced paw edema

Administration of the tested compounds 60 min prior to carrageenan injection at a dose of 10 mg/100 g b.wt. significantly inhibited the paw edema response (Table 1). The percentages of inhibition were for **1c** – 57.0; **1d –** 61.9, **1e –** 42.7, **2e –** 59.4, **3a –** 46.9 and **3d –** 57.0, after 1 h of treatment, respectively, in comparison to control group. The positive control, indomethacin, markedly and significantly inhibited the paw edema response by 57.8%, after 1 h of carrageenan injection. All compounds showed anti-inflammatory activity, compound **1d** ,**1c** and **2e** were as potent as indomethacin. (Table 1).

Effect on analgesia

Hot plate test

The mean reaction time on the hot plate was significantly delayed after the administration of compounds **1c**, **3a** and **3d** with percent of change 61.7, 56.4 and 48.1 after 1 h, respectively, and by 53.9, 51.5 and 44.6 after 2 h, whereas indomethacin showed a significant delay by 51.1% and 78.9% change after 1 and 2 h, respectively, indicating a central analgesic effect (Table 2a).

Acetic acid induced writhing

Acetic acid induced writhing was significantly reduced in rats receiving all tested compounds except compound **1c** and **1d**. The antinociceptive activity of the tested compounds yielded maximal reduction of the writhing score by 47.3% and 57.3% for compounds **3a** and **3d**, respectively, indicating peripheral analgesic effect. The positive control, indomethacin, inhibited the writhing response by 50%, i.e. the analgesic effect of compound **3d** was significantly higher than that of indomethacin (Table 2b).

Plantar test

The results presented in Table 2c for compounds **1e**, **2e**, **3a** and **3d** showed a significant effect in comparison to control after 1 and 2 h. These compounds increased the time required for the rats to respond to the thermal stimulation.

Antipyretic effect

The results shown in Table 3 revealed that the intramuscular injection of 44% yeast suspension in rats resulted in an increase in body temperature that ranged from 2.5 to 2.9^{o}C. Compound **3d** revealed a significant antipyretic activity after 30 and 60 min while compound **1e**, **1d** and **3a** showed a significant antipyretic activity after 60 min. Compound **2e** have no antipyretic effect.

Gastric ulcerogenic studies

In the indomethacin control group, the number and severity of gastric mucosal lesions rate were 8.2

± 0.3 and 12.0 ± 0.2, respectively. This was significantly reduced by the newly synthesized compounds and compounds **1d** and **2e** produced the most potent reducing effect of 26.8 and 59.8%, respectively, as shown in Table 4.

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